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# Reduction in saturated fat intake for cardiovascular disease (Review)

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[Intervention Review]

# Reduction in saturated fat intake for cardiovascular disease

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## ABSTRACT

### Background

Reducing saturated fat reduces serum cholesterol, but effects on other intermediate outcomes may be less clear. Additionally it is unclear whether the energy from saturated fats that are lost in the diet are more helpfully replaced by polyunsaturated fats, monounsaturated fats, carbohydrate or protein. This review is part of a series split from and updating an overarching review.

### Objectives

To assess the effect of reducing saturated fat intake and replacing it with carbohydrate (CHO), polyunsaturated (PUFA) or monounsaturated fat (MUFA) and/or protein on mortality and cardiovascular morbidity, using all available randomised clinical trials.

### Search methods

We updated our searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid) and EMBASE (Ovid) on 5 March 2014. We also checked references of included studies and reviews.

### Selection criteria

Trials fulfilled the following criteria: 1) randomised with appropriate control group; 2) intention to reduce saturated fat intake OR intention to alter dietary fats and achieving a reduction in saturated fat; 3) not multifactorial; 4) adult humans with or without cardiovascular disease (but not acutely ill, pregnant or breastfeeding); 5) intervention at least 24 months; 6) mortality or cardiovascular morbidity data available.

### Data collection and analysis

Two review authors working independently extracted participant numbers experiencing health outcomes in each arm, and we performed random-effects meta-analyses, meta-regression, subgrouping, sensitivity analyses and funnel plots.

### Main results

We include 15 randomised controlled trials (RCTs) (17 comparisons, ~59,000 participants), which used a variety of interventions from providing all food to advice on how to reduce saturated fat. The included long-term trials suggested that reducing dietary saturated fat reduced the risk of cardiovascular events by 17% (risk ratio (RR) 0.83; 95% confidence interval (CI) 0.72 to 0.96, 13 comparisons, 53,300 participants of whom 8% had a cardiovascular event, $I^2$ 65%, GRADE moderate quality of evidence), but effects on all-

cause mortality (RR 0.97; 95% CI 0.90 to 1.05; 12 trials, 55,858 participants) and cardiovascular mortality (RR 0.95; 95% CI 0.80 to 1.12, 12 trials, 53,421 participants) were less clear (both GRADE moderate quality of evidence). There was some evidence that reducing saturated fats reduced the risk of myocardial infarction (fatal and non-fatal, RR 0.90; 95% CI 0.80 to 1.01; 11 trials, 53,167 participants), but evidence for non-fatal myocardial infarction (RR 0.95; 95% CI 0.80 to 1.13; 9 trials, 52,834 participants) was unclear and there were no clear effects on stroke (any stroke, RR 1.00; 95% CI 0.89 to 1.12; 8 trials, 50,952 participants). These relationships did not alter with sensitivity analysis. Subgrouping suggested that the reduction in cardiovascular events was seen in studies that primarily replaced saturated fat calories with polyunsaturated fat, and no effects were seen in studies replacing saturated fat with carbohydrate or protein, but effects in studies replacing with monounsaturated fats were unclear (as we located only one small trial). Subgrouping and meta-regression suggested that the degree of reduction in cardiovascular events was related to the degree of reduction of serum total cholesterol, and there were suggestions of greater protection with greater saturated fat reduction or greater increase in polyunsaturated and monounsaturated fats. There was no evidence of harmful effects of reducing saturated fat intakes on cancer mortality, cancer diagnoses or blood pressure, while there was some evidence of improvements in weight and BMI.

**Authors' conclusions**

The findings of this updated review are suggestive of a small but potentially important reduction in cardiovascular risk on reduction of saturated fat intake. Replacing the energy from saturated fat with polyunsaturated fat appears to be a useful strategy, and replacement with carbohydrate appears less useful, but effects of replacement with monounsaturated fat were unclear due to inclusion of only one small trial. This effect did not appear to alter by study duration, sex or baseline level of cardiovascular risk. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturated fats. The ideal type of unsaturated fat is unclear.

## PLAIN LANGUAGE SUMMARY

**Effect of cutting down on the saturated fat we eat on our risk of heart disease**

**Review question**

We wanted to find out the effects on health of cutting down on saturated fat in our food (replacing animal fats with plant oils, unsaturated spreads and more starchy foods).

**Background**

Health guidance suggests reducing the amount of saturated fat we eat, by cutting down on animal fats, is good for our health. We wanted to combine all available evidence to see whether following this advice leads to a reduced risk of dying or getting cardiovascular disease (heart disease or stroke).

**Study characteristics**

We assessed the effect of cutting down the amount of saturated fat we eat on health outcomes including dying, heart disease, stroke and cancer for at least two years. We only looked at studies of adults (18 years or older). This included men and women with and without cardiovascular disease. We did not include studies of acutely ill people or pregnant or breastfeeding women.

**Key results**

We found 15 studies with over 59,000 participants. The evidence is current to March 2014. The review found that cutting down on saturated fat led to a 17% reduction in the risk of cardiovascular disease (including heart disease and strokes), but no effects on the risk of dying. The review found no clear health benefits of replacing saturated fats with starchy foods or protein. Changing the type of fat we eat, replacing saturated fats with polyunsaturated fats, seems to protect us better, reducing our risk of heart and vascular problems. The greater the decrease in saturated fat, and the more serum total cholesterol is reduced, the greater the protection. People who are currently healthy appear to benefit as much as those at increased risk of heart disease or stroke (people with high blood pressure, high serum cholesterol or diabetes, for example), and people who have already had heart disease or stroke. There was no clear difference in effect between men and women.

**Quality of the evidence**

There is a large body of evidence, including almost 60,000 people who have been in studies assessing effects of reducing saturated fat for at least two years each. Together the studies provide moderate-quality evidence that reducing saturated fat and replacing it with polyunsaturated fats reduces our risk of cardiovascular disease.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

**Low saturated fat compared with usual saturated fat for CVD risk**

**Patient or population: people at any baseline risk of CVD**
**Intervention: reduction of saturated fat intake**
**Comparison: usual saturated fat intake**

| Outcomes | Relative effect (95% CI) | Absolute effects (per 10,000) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|
| **All-cause mortality** follow-up mean duration 56 months[1] | **RR 0.97** (0.90 to 1.05) | **17 fewer** (from 57 fewer to 29 more) | 55,858 (12) | ⊕⊕⊕◯ **moderate**[2,3,4,5,6] | Critical importance |
| **Cardiovascular mortality** follow-up mean duration 53 months[1] | **RR 0.95** (0.80 to 1.12) | **10 fewer** (from 39 fewer to 23 more) | 53,421 (12) | ⊕⊕⊕◯ **moderate**[2,3,4,5,6] | Critical importance |
| **Combined cardiovascular events** follow-up mean duration 52 months[1] | **RR 0.83** (0.72 to 0.96) | **138 fewer** (from 33 fewer to 228 fewer) | 53,300 (13) | ⊕⊕⊕◯ **moderate**[2,4,6,7,8] | Critical importance |
| **Myocardial infarctions** follow-up mean duration 55 months | **RR 0.90** (0.80 to 1.01) | **32 fewer** (from 63 fewer to 3 more) | 53,167 (11) | ⊕⊕⊕◯ **moderate**[2,3,4,5,6] | Critical importance |
| **Non-fatal MI** follow-up mean duration 55 months[1] | **RR 0.95** (0.80 to 1.13) | **13 fewer** (from 51 fewer to 33 more) | 52,834 (9) | ⊕⊕⊕◯ **moderate**[2,3,4,5,9] | Critical importance |
| **Stroke** follow-up mean duration 59 months[1] | **RR 1.00** (0.89 to 1.12) | **0 fewer** (from 25 fewer to 25 more) | 50,952 (8) | ⊕⊕⊕◯ **moderate**[2,3,4,5,9] | Critical importance |

| | | | | | |
|---|---|---|---|---|---|
| **CHD mortality** follow-up mean duration 65 months[1] | **RR 0.98** (0.84 to 1.15) | **3 fewer** (from 25 fewer to 23 more) | 53,159 (10) | ⊕⊕⊕◯ **moderate**[2,3,4,5,6] | Critical importance |
| **CHD events** follow-up mean duration 59 months[1] | **RR 0.87** (0.74 to 1.03) | **80 fewer** (from 160 fewer to 19 more) | 53,199 (12) | ⊕⊕◯◯ **low**[2,4,5,6,10] | Critical importance |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio; CHD: coronary heart disease.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Minimum study duration was 24 months
[2]These large RCTs of relatively long duration were well randomised but fewer than half had good allocation concealment (the rest were unclear). Blinding was only well-conducted in 1 RCT, however blinding is very difficult in trials of dietary fat intake. Incomplete outcome data were variable, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group). We noted no other biases. We downgraded each study once for a combination of these issues around validity and issues around precision. The level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[3]No important heterogeneity; $I^2 \leq 30\%$
[4]These RCTs directly assessed the effect of lower vs usual saturated fat intake on health outcomes of interest. Participants included men and women with and without CVD at baseline (also some participants with CVD risk factors like diabetes, or at risk of cancers).
[5]The 95% CI crosses 1.0 and does not exclude important benefit or harm.
[6]The funnel plot did not suggest any small-study (publication) bias.
[7]Potentially important heterogeneity was identified; $I^2 = 65\%$. However, the heterogeneity was partly explained by the degree of saturated fat reduction, and the degree of cholesterol lowering achieved (in subgrouping and in meta-regression). For this reason we did not downgrade the study for inconsistency.
[8]The 95% CI does not cross 1.0 or a threshold of important harm.
[9]Too few studies to reliably assess small-study bias (<10 RCTs)
[10]Important heterogeneity; $I^2 = 66\%$.

## BACKGROUND

In 1949 Ryle and Russell in Oxford documented a dramatic increase in coronary heart disease (CHD), and the Registrar General's Statistical Tables of 1920 to 1955 showed that there had been a 70-fold increase in coronary deaths during this 35-year period (Oliver 2000; Ryle 1949). This sudden surge in coronary heart disease sparked research into its causes. A case-control study published in 1953 of 200 post-myocardial infarction patients and age-matched controls established that those with disease had higher low density lipoprotein (LDL) cholesterol levels (Oliver 1953).

Meanwhile in 1949 in the US Gofman had separated lipids into lipoprotein classes through ultra centrifugation, describing the LDL as 'atherosclerogenic' (Gofman 1949). The following year Keys 1950 proposed that the concentration of plasma cholesterol was proportional to dietary saturated fatty acids (SFA) intake, and this relationship was confirmed in work by Hegsted (Hegsted 1965; Hegsted 2000), who published an equation explaining the relationship in 1965 and subsequently in 2000, suggesting that dietary saturated fat increases serum cholesterol and so increases cardiovascular (CV) risk, while polyunsaturated fats (PUFA) reduce both. This has since been further refined:

Δ serum cholesterol (in mg/dl) = 2.16 * Δ dietary saturated fat intake (as percentage of energy) - 1.65 * Δ dietary PUFA intake (as percentage of energy, %E) + 6.77 * Δ dietary cholesterol intake (in units of 100mg/day) - 0.53

The Seven Countries Study compared CHD mortality in 12,000 men aged 40 to 59 in seven countries, and found positive correlations between CHD mortality and total fat intake in 1970, then in 1986 between CHD mortality and saturated fat intake (Keys 1986; Thorogood 1996). A migrant study of Japanese men living in different cultures confirmed in 1974 that men in California had the diet richest in saturated fat and cholesterol, and the highest CHD rates, those in Hawaii had intermediate saturated fat and CHD rates, and those in Japan had a diet lowest in saturated fat and cholesterol, and the least CHD (Kagan 1974; Robertson 1977). However, more recent systematic reviews of the observational data have not confirmed these early studies. Skeaff 2009 included 28 US and European cohorts (including 6600 CHD deaths among 280,000 participants) investigating the effects of total, saturated, monounsaturated, trans and omega-3 fats on CHD deaths and events. They found no clear relationship between total, saturated or monounsaturated fat (MUFA) intake and coronary heart disease events or deaths. There was evidence that trans fats increased both coronary heart disease events and deaths, and that total PUFAs and omega-3 fats decreased them. Intervention studies are needed to clarify cause and effect, to ensure that confounding is not hiding true relationships, or suggesting relationships where they do not exist. Trials also directly address the issue of whether altering dietary saturated fat in adults is helpful in reducing the risk of CVD in the general population and in those at high risk. Intervention trials are crucial in forming the basis of evidence-based practice in this area.

Most intervention studies have assessed the effect of dietary interventions on risk factors for heart disease, and separate work ties the effect of altering these risk factors to changes in disease incidence and mortality. Systematic reviews in this area follow the same pattern, so that there are systematic reviews of the effect of dietary fat advice on serum lipid levels (Brunner 1997; Clarke 1997; Denke 1995; Kodama 2009; Malhotra 2014; Mensink 1992; Mensink 2003; Rees 2013; Weggemans 2001; Yu-Poth 1999), suggesting that dietary changes cause changes in serum lipids and reviews on the effect of lipid level alterations on CV morbidity and mortality (Briel 2009; De Caterina 2010; Law 1994; Robinson 2009; Rubins 1995; Walsh 1995), suggesting that changes in lipids do affect CVD risk. Other risk factors dealt with in a similar way are blood pressure (Bucher 1996; Law 1991; Shah 2007), body weight or fatness (Astrup 2000; Hession 2009; SIGN 1996), angiographic measurements (Marchioli 1994), antioxidant intake (Ness 1997), metabolic profile (Kodama 2009) and alcohol intake (Rimm 1996). A problem with this two-level approach is that any single dietary alteration may have effects over a wide range of risk factors for CVD. An example of this is the choice of substitution of saturated fats by carbohydrate, PUFAs or MUFAs in the diet. This choice may alter lipid profile, and may also affect blood pressure, body weight, oxidative state, rate of cholesterol efflux from fibroblasts, insulin resistance, post-prandial triacylglycerol response, blood clotting factors, and platelet aggregation. There may also be further risk factors of which we are not yet aware. Evidence of beneficial effect on one risk factor does not rule out an opposite effect on another unstudied risk factor, and therefore an overall null (or harmful) effect of intervention. While understanding the effects of dietary advice on intermediate risk factors helps to ensure diets are truly altered by advice, and illuminates mechanisms, the best way of combining the effects on all of these risk factors is to not study risk factors, but to study the effects of dietary change on important outcomes, on CV morbidity and mortality, and on total mortality.

Substantial randomised controlled trial data on the effects of dietary fat on mortality and morbidity do exist and have been previously reviewed (Hooper 2012). A recent very large study, the Women's Health Initiative, that included over 2000 women with, and over 48,000 women without, CVD at baseline for over eight years (WHI with CVD 2006; WHI without CVD 2006)) has raised many questions about both the effects of fat on health and on how we best conduct research to understand the relationship (Astrup 2011; Michels 2009; Prentice 2007; Stein 2006; Yngve 2006). We incorporated these findings into an update of a Cochrane review on dietary fat and CVD risk with a search in 2010 (Hooper 2012), finding reductions in cardiovascular events in studies that modified dietary fat, and in studies of at least two years' duration, but not in studies of fat reduction or studies with

less than two years' follow-up.

### Why it is important to do this review

Public health dietary advice on prevention of cardiovascular disease (CVD) has changed over time, with a focus on fat modification during the 1960s and fat reduction during the 1990s following the introduction of US and UK dietary guidance on fat reduction, limiting saturated fat intake to 10% of energy (Harcombe 2015). In 2006 recommendations by the American Heart Association suggested that, among other dietary measures, Americans should "limit intake of saturated fat to 7% of energy, trans fat to 1% of energy, and cholesterol to 300 mg/day by choosing lean meats and vegetable alternatives, fat-free (skim) or low-fat (1% fat) dairy products and minimize intake of partially hydrogenated fats" (Lichtenstein 2006). The most recent American Heart Association guidelines suggest that Americans should "Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat" and "Reduce percent of calories from saturated fat" (both graded as strong evidence on the basis of effects on serum lipids - trials with cardiovascular outcomes are not referenced or discussed, Eckel 2013). European guidance on the treatment of dyslipidaemia is similarly based on dietary effects on lipids, recommending reduction in saturated fats (ESC/EAS 2011) and referencing Mensink 2003, while the Joint British Societies' guidance on preventing CVD recommends changing "Intake of saturated fat to <10% of total fat intake (preferably in lean meat and low fat dairy products)" and "Replace saturated fat with polyunsaturated fat where possible" (JBS3 2014), referencing a variety of evidence including several recent systematic reviews. Recent UK National Institute for Health and Care Excellence(NICE) guidance suggests that for people at high risk of or with CVD "to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by monounsaturated and polyunsaturated fats" and "replace their saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils" (based on long-term randomised controlled trials reporting hard outcomes, they separately assessed effects of high polyunsaturated diets, including only four of the trials included in this review, NICE 2014).

We were interested in assessing the direct evidence from trials of the effects of reducing saturated fats, and considering what the saturated fats were replaced by. Instead of updating the Cochrane review on dietary fat (Hooper 2012) as a whole again, the review has been split into smaller, more manageable reviews. As well as this review, the series will address the effect of modified fat intake (compared to usual fat intake) on cardiovascular disease, the effect of reduced total fat on cardiovascular disease, the effect of reduced and modified fat on cardiovascular disease, the effect of reduced total fat compared to modified fat on cardiovascular disease, and the effect of reduced total fat on weight and fatness. This also supports the request from the World Health Organization Nutrition Guidance Expert Advisory Group (WHO NUGAG) to more accurately assess effects of reducing saturated fats on all-cause mortality, CV morbidity and other health outcomes, and to consider the differential effects on health outcomes of replacement of the energy from saturated fat by other fats, carbohydrates or protein.

## OBJECTIVES

To assess the effect of reducing saturated fat intake and replacing it with carbohydrate (CHO), polyunsaturated (PUFA) or monounsaturated fat (MUFA) and/or protein on mortality and cardiovascular morbidity, using all available randomised clinical trials.

Additional World Health Organization Nutrition Guidance Expert Advisory Group (WHO NUGAG) specific questions included:

1. In adults what is the effect in the population of reduced percentage of energy (%E) intake from saturated fatty acids (SFA) relative to higher intake for reduction in risk of non-communicable diseases (NCDs)?

2. What is the effect on coronary heart disease mortality and coronary heart disease events?

3. What is the effect in the population of replacing SFA with polyunsaturated fats (PUFAs), monounsaturated fats (MUFAs), carbohydrates (CHO) (refined versus unrefined), protein or trans fatty acids (TFAs) relative to no replacement for reduction in risk of NCDs?

4. What is the effect in the population of consuming < 10%E as SFA relative to > 10%E as SFA for reduction in risk of NCDs?

5. What is the effect in the population of a reduction in %E from SFA from 10% in gradual increments relative to higher intake for reduction in risk of NCDs?

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials only. We accepted randomisation of individuals, or of larger groups (clusters) where there were at least six of these groups randomised. We excluded studies where allocation was not truly randomised (e.g. divisions based on days of the week or first letter of the family name), or where allocation

was not stated as randomised, and no further information was available from the authors.

### Types of participants

We accepted studies of adults (18 years or older, no upper age limit) at any risk of cardiovascular disease, with or without existing cardiovascular disease, using or not using lipid-lowering medication. Participants could be of either gender, but we excluded those who were acutely ill, pregnant or lactating.

### Types of interventions

The overarching Cochrane review (Hooper 2012) that served as the origin of this review included studies that compared a low-fat diet (which aimed to reduce total fat intake to < 30% of energy) or a modified fat diet (that aimed to include over 30% of energy from total fats, but that increased the proportions of PUFAs or MUFAs or both) compared with a usual diet or with each other. For this review we include the subset of these randomised controlled trials stating an intention to reduce saturated fat (SFA) intake (by suggesting appropriate nutrient-based or food-based aims) OR which provided a general dietary aim, such as improving heart health or reducing total fat, that also achieved a statistically significant saturated fat reduction ($P < 0.05$) during the trial in the intervention arm compared with the control arm. The intervention had to be dietary advice, supplementation of fats, oils or modified or low-fat foods, or a provided diet, and the control group usual diet, placebo or a control diet. Intended duration of the dietary intervention was at least two years (24 months or 104 weeks).

### Types of outcome measures

#### Primary outcomes

- All-cause mortality (deaths from any cause)
- Cardiovascular (CVD) mortality (deaths from myocardial infarction, stroke, or sudden death)
- Combined CVD events. These included data available on any of the following: cardiovascular deaths, cardiovascular morbidity (non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events, atrial fibrillation) and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty

#### Secondary outcomes

- Additional health events; the outcomes CHD mortality and CHD events are added at the request of the WHO NUGAG group, and were not present in the original overarching systematic review:
    - Myocardial infarction, total (fatal and non-fatal) and non-fatal
    - Stroke including stroke incidence (type of stroke), stroke mortality, and stroke morbidity
    - CHD mortality, which includes death from myocardial infarction or sudden death
    - CHD events, which include any of the following: fatal or non-fatal myocardial infarction, angina or sudden death
    - type II diabetes incidence
- Blood measures including serum blood lipids
    - total cholesterol (TC)
    - low-density lipoprotein (LDL) cholesterol
    - high-density lipoprotein (HDL) cholesterol
    - triglyceride (TG)
    - TG/HDL ratio
    - LDL/HDL ratio
    - total/HDL ratio
    - lipoprotein (a) (Lp(a))
    - insulin sensitivity including glucose tolerance (homeostatic model assessment (HOMA), intravenous glucose tolerance test (IV-GTT), clamp, glycosilated haemoglobin (HbA1C))
- Other outcomes including adverse effects reported by study authors
    - cancer diagnoses
    - cancer deaths
    - body weight
    - body mass index (BMI)
    - systolic blood pressure (sBP)
    - diastolic blood pressure (dBP)
    - quality of life

We only included trials where we could collect data on at least one primary outcome, by communication with authors if necessary. We excluded studies where we knew that no primary outcome events occurred.

## Search methods for identification of studies

We identified relevant trial reports from a systematic review on modifying or reducing dietary fat intake for the prevention of cardiovascular disease (Hooper 2012) which included a search up to June 2010. We ran a search to update this full review to March 2014, and then split the review into a number of smaller, more manageable reviews, of which this is one.

### Electronic searches

The Cochrane Heart Group ran the update search for the full review (Hooper 2012) on 5 March 2014 on the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2014 on the Cochrane Library), MEDLINE (OVID, 1946 to February week 3, 2014) and EMBASE (OVID 1980 to 2014 Week 09). We used the same search terms as in Hooper 2012. Due to limited resources,

we applied filters to limit to core clinical journals (MEDLINE) and priority journals (EMBASE). We have saved the additional hits retrieved without these filters, and will incorporate them fully during the next update. We limited the CENTRAL and MEDLINE searches by publication date 2010 to 2014, and EMBASE to entry week 2010 to 2014, to only identify records newly added to the databases since the last search. The RCT filter for MEDLINE was the Cochrane sensitivity-maximising RCT filter, and for EMBASE we applied terms as recommended in the *Cochrane Handbook* (Lefebvre 2011). We applied no language restrictions to the searches, which are shown in Appendix 1.

### Searching other resources

We searched bibliographies of all identified systematic reviews, major non-systematic reviews and included trials for further studies. We contacted experts in the field for references to studies not yet identified by the search process. We attempted to obtain translations of relevant non-English articles, or we established contact with the author to enable assessment of eligibility.

## Data collection and analysis

### Selection of studies

Two authors (LH, NM) independently assessed studies from the latest search, to update Hooper 2012, and resolved differences by discussion. One author (LH) assessed studies from the Hooper 2012 review and update for inclusion in this review (which is a subset of the larger review).

We only rejected articles on initial screen if the author could determine from the title and abstract that the article was not a report of a randomised controlled trial; the trial did not address a low or modified fat diet; the trial was exclusively in children less than 18 years old, pregnant women or the critically ill; the trial was of less than 24 months duration; or the intervention was multifactorial. When we could not reject a title/abstract with certainty, we obtained the full text of the article for further evaluation.

### Data extraction and management

We used the data extraction form which was designed for the Hooper 2000, Hooper 2001 and Hooper 2012 reviews. We extracted data concerning participants, interventions and outcomes, trial quality characteristics (Chalmers 1990), data on potential effect modifiers including participants' baseline risk of cardiovascular disease, trial duration, intensity of intervention (dietary advice, diet provided, dietary advice plus supplementation, supplementation alone), medications used (particularly lipid-lowering medication) and smoking status, numbers of events and total participant years in trial. Where provided, we collected data on risk factors for cardiovascular disease including blood pressure, lipids and weight.

We defined baseline risk of cardiovascular disease as follows: high risk are participants with existing vascular disease including a history of myocardial infarction, stroke, peripheral vascular disease, angina, heart failure or previous coronary artery bypass grafting or angioplasty; moderate risk are participants with a familial risk, dyslipidaemia, diabetes mellitus, hypertension, chronic renal failure; low risk are other participants or mixed-population groups.

One author (LH) extracted additional data (dietary intakes of total fat, SFA, MUFA, PUFA, CHO, protein, data on ethnicity) from included studies in Hooper 2012 which are eligible for inclusion in this review. Two authors (LH, NM) independently extracted data from eligible studies from the search update.

### Assessment of risk of bias in included studies

We assessed trial quality characteristics using the Cochane 'Risk of bias' assessment tool (Higgins 2011). We assessed several new characteristics for this review, including studies being free of systematic differences in care, a study aiming to reduce SFA intake, achieving SFA reduction, and achieving total serum cholesterol reduction. A single author (LH) conducted these assessments for the studies which were eligible from Hooper 2012. Two authors (LH, NM) independently extracted validity data from studies identified by the new search, and resolved differences by discussion.

### Measures of treatment effect

The effect measures of choice were risk ratios (RR) for dichotomous data and Mean Difference (MD) for continuous data.

### Unit of analysis issues

We did not include any cluster-randomised trials in this review, as no relevant studies included at least six clusters.

Where there was more than one relevant intervention arm but only one control arm, we either pooled the relevant intervention arms to create a single pair-wise comparison (where the intervention arms were equivalently appropriate for this review) as described in the *Cochrane Handbook* (Higgins 2011), or we excluded intervention arms that were not appropriate for this review, or less appropriate than another arm. When two arms were appropriate for different subgroups (Rose corn oil 1965; Rose olive 1965), then we used the control group once with each intervention arm, and divided the number of events in the control group, and the number of participants in the control group, evenly between the two study comparisons.

When assessing event data, we aimed to avoid counting more than one outcome event for any one individual within any one comparison. Where we were unclear (for example, where a paper reported numbers of myocardial infarcts but not by arm) we asked authors for further information.

### Dealing with missing data

Where trials satisfied the inclusion criteria of our review but did not report mortality and morbidity, or not by study arm, we tried to contact study authors. This allowed inclusion of many studies that would otherwise have had to be excluded. We excluded studies which were otherwise relevant but where we could not establish the presence or absence of primary outcomes, despite multiple attempts at author contact.

It was often unclear whether data on primary or secondary outcome events may still have been missing, and so we did not impute data for this review.

### Assessment of heterogeneity

We examined heterogeneity using the $I^2$ test, and considered it important where greater than 50% (Higgins 2003; Higgins 2011).

### Assessment of reporting biases

We used funnel plots to examine the possibility of small study bias, including publication bias (Egger 1997), for the primary outcomes of total mortality and combined cardiovascular events.

### Data synthesis

We used numbers of events in each study arm, and total number of participants randomised, where extracted, and Mantel-Haenszel random-effects meta-analysis carried out in Review Manager 5 software, to assess risk ratios. We extracted event and continuous outcome data for the latest time point available within the trial, and always at least 24 months from inception.

We excluded trials where we knew that there were no events in either group. Where trials ran one control group and more than one included intervention group, we used data from the intervention group providing the comparison that best assessed the effect of altering dietary fat. Where the intervention groups appeared equal in this respect, we merged the intervention groups (simply added for dichotomous data, and using the techniques described in Higgins 2011 for continuous data). We had planned that if we identified trials randomised by cluster we would reduce the participant numbers to an "effective sample size" (as described by Hauck 1991); however, we found none that were both included and had cardiovascular events or deaths.

To assess the WHO NUGAG question on the effect of consuming < 10%E as SFA relative to > 10%E as SFA on the risk of non-communicable diseases (NCDs) in the population, we combined studies with a control group saturated fat intake of > 10%E and an intervention group saturated fat intake of < 10%E. To assess the effect of a reduction in %E from SFA from 10% in gradual increments relative to higher intake, we repeated this with saturated fat cut-offs between 7%E and 13%E.

### Subgroup analysis and investigation of heterogeneity

Prespecified analyses included:

Effects of SFA reduction compared with usual or standard diet on all (primary and secondary) outcomes and potential adverse effects. This main analysis addressed the main objective of the review and the first WHO specific question.

Prespecified subgroups for all outcomes included:

- energy substitution - we intended to subgroup studies according to the main energy replacement for SFA - PUFA, MUFA, CHO, a mixture of these, or unclear. However, when we presented these data to the WHO NUGAG group they suggested that this subgrouping be altered such that we used all studies where SFA was reduced and any of PUFA, MUFA, CHO or protein were statistically significantly increased ($P < 0.05$) in the intervention compared to the control group to assess the effects of replacement by each, regardless of whether or not it constituted the main replacement for SFA. This meant that some studies appeared in more than one subgroup. As there were almost no data in the studies on trans fats, we did not include a trans group. This subgrouping addresses the main objective of the review, and the third WHO specific question.

Further subgroups, run for primary and CVD health-related secondary outcomes only, included:

**Prespecified**:

- Baseline SFA intake, represented by control group SFA intake (up to 12%E from SFA, > 12 to 15%E, > 15 to 18%E, > 18%E from SFA, or unclear)
- Sex (men, women and mixed populations)
- Baseline CVD risk (low-risk or general populations, moderate-risk populations which were defined by risk factors for CVD such as hypertension or diabetes, high-risk populations with existing CVD at baseline)
- Duration in study (mean duration in trial up to 24 months, > 24 to 48 months, > 48 months, and unclear). Duration was a prespecified subgroup that we used in earlier versions of this review to separate studies with duration of less than two years from those of at least two years. As we have excluded shorter studies from this review, and have access to longer studies, we have explored duration over longer time spans. As some long studies had a high proportion of participants whose time in trial was censored, and we wanted to express mean experience of the trial, we used mean duration of participants in the study, rather than the formal study duration for this subgrouping, so that some two-year intervention trials, because they had some deaths or drop-outs, had a mean duration in trial of 21 or 22 months.

**WHO NUGAG added subgroups:**

- Degree of SFA reduction, represented by the difference between SFA intake in the intervention and control groups during the study (up to 4% E from SFA reduction achieved, > 4 to 8% reduction achieved, > 8% reduction achieved, unclear). We prespecified that we intended to explore the degree of SFA

reduction in meta-regression, but its addition as a subgroup was post hoc, and requested by the WHO NUGAG group.

- Serum total cholesterol reduction achieved (reduced by a mean of at least 0.2 mmol/L, reduced by less than 0.2 mmol/L or unclear). We prespecified that we intended to explore the degree of serum total cholesterol reduction in meta-regression.
- Ethnic group. Insufficient information was presented to make this feasible. Hence, we report ethnicity information in the Characteristics of included studies.

We explored the effects of different levels of SFA, PUFAs, MUFAs and total dietary fats, and CHO achieved in trials (all as difference between the intervention and control groups, as %E, and for SFA as a percentage of SFA in the intervention compared with control), baseline SFA intake (as %E), change in total cholesterol (difference between intervention and control groups, in mmol/L), sex, study duration in months, and baseline CVD risk using meta-regression on total cardiovascular events. We performed random-effects meta-regression (Berkley 1995) using the STATA command metareg (Sharp 1998; Sterne 2001; Sterne 2009).

To explore the WHO NUGAG specific question about the effect of the population consuming < 10%E as SFA relative to > 10%E SFA, we assessed effects of all studies where the intervention SFA was < 10%E and the control SFA was > 10%E. We explored the effect of reduction of %E from SFA in gradual increments by using cut-offs of 7%E (where all studies with an intervention SFA was < 7%E and control SFA was > 7%E were pooled), 8%, 9%, 10%, 11%, 12% and 13%. We omitted studies where SFA intakes were not reported from these analyses. For each primary outcome we plotted the pooled risk ratio of that outcome against the cut-off, %E from SFA.

**Referee-added subgroups:**

In response to the suggestion of a referee of this systematic review, and to better understand the effect of use of statins since the 1990s, we subgrouped studies by decade of publication.

### Sensitivity analysis

We carried out sensitivity analyses for primary outcomes assessing the effect of:

1. Excluding studies which did not state an aim to reduce SFA
2. Excluding studies which did not report SFA intake during the trial, or did not find a statistically significant reduction in SFA in the intervention compared to the control
3. Excluding studies where total cholesterol (TC) was not reduced (statistically significant reduction of TC, or of LDL where TC was not reported (considered reduced where $P < 0.05$), or where reduction was not at least 0.2 mmol/L in intervention compared to control where variance was not reported)
4. Excluding the largest study (WHI with CVD 2006; WHI without CVD 2006)
5. Analysis run with Mantel-Haenszel fixed-effect model
6. Analysis run with Peto fixed-effect model

### GRADE

The GRADE Working Group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations (www.gradeworkinggroup.org/). The evidence within this systematic review was first assessed using the GRADE system by the review authors and then discussed and modified by the WHO NUGAG group.

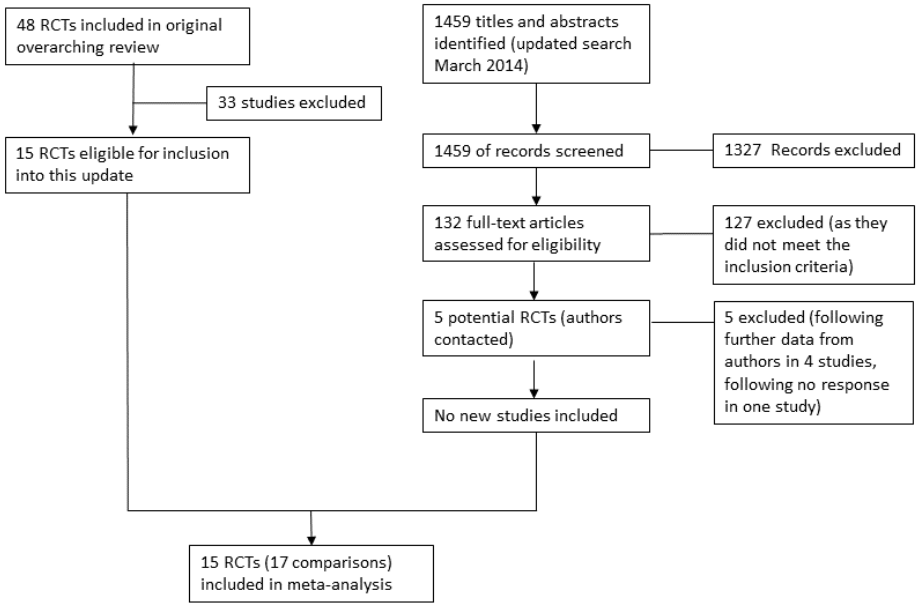
## RESULTS

### Description of studies

#### Results of the search

Figure 1 displays the flow diagram for inclusion of studies (based on Stovold 2014). We have assessed the 48 included studies from the Cochrane review on dietary fat overall (Hooper 2012) for eligibility for this review on saturated fat reduction. Fifteen of the 48 trials were eligible for inclusion in this review. We have now excluded the 15 trials which were allocated to studies awaiting classification in Hooper 2012 and the one study which was ongoing (PREDIMED 2008).

**Figure 1. Flow diagram for review**




The 2014 search update located 1459 studies, of which we retrieved 132 in full text for further assessment. Of these, five were potentially new studies, but we needed to contact the authors for further details. Four sets of authors replied, and further data resulted in the exclusion of four new studies (FIT Heart 2011; Haufe 2011; Troyer 2010; WINS UK 2011). We also excluded the study for which author contact could not be established (Lim 2010).
Of the full-text papers retrieved, three were further publications of included studies (WHI with CVD 2006; WHI without CVD 2006: Sydney Diet-Heart 1978) which we extracted for further study data. Twenty-six full-text papers were further publications of a previously ongoing and now excluded study (PREDIMED 2008).

### Included studies

We include 15 randomised controlled trials (RCTs) in the review ( Included studies), and describe them in Characteristics of included studies. The interventions are compared in Table 1. One included study has two comparison arms (Rose corn oil 1965; Rose olive 1965), where saturated fatty acids (SFAs) were replaced by a dose of either corn oil, replacing SFA with polyunsaturated fats (PUFAs), or olive oil, replacing SFA with monounsaturated fats (MUFAs)); and one study where data were reported in several sections (the Women's Health Initiative, reported by cardiovascular risk as WHI with CVD 2006; WHI without CVD 2006). As separated data were only occasionally provided, we report data for the study as WHI without CVD 2006 unless data were separated. We include 17 comparisons in total in the review.
The main study papers ranged in publication date from 1965 to 2006, but with supplementary publications included up to 2013. The comparisons were conducted in North America (7), Europe (8), and Australia/New Zealand (2) but no studies were carried out in industrialising or developing countries. Six of the comparisons included only people at high risk of cardiovascular disease, four at moderate risk, and five at low risk (three with raised cancer risk or cancer diagnosis, two with no specific health risks) (Table 1). Seven studies included only men, three only women, and five both men and women; however, as the largest trial, WHI with CVD 2006; WHI without CVD 2006, was in women only, women are the largest group represented. Trial duration ranged from two to

more than eight years, with a mean duration of 4.7 years.

The form of interventions varied (Table 1). Interventions were of advice to alter intake in 16 of the 17 intervention arms, and additional supplements such as oil or other foods were provided in four (MRC 1968; Oslo Diet-Heart 1966; Rose corn oil 1965; Rose olive 1965), while all food was provided in a residential facility in the 17th arm (Veterans Admin 1969). Of the 16 arms with an advice element, most interventions were delivered face-to-face, but this was unclear in three arms (Houtsmuller 1979; Rose corn oil 1965; Rose olive 1965). Advice was provided individually in nine intervention arms (followed by later group sessions in two arms), in groups only in three arms (Ley 2004; WHI with CVD 2006; WHI without CVD 2006), and unclear in four (Black 1994; Houtsmuller 1979; Rose corn oil 1965; Rose olive 1965). Advice was provided by a dietitian in nine arms, a nutritionist in two, a trained nurse in one and was unclear in four. Frequency of study visits for advice and follow-up varied between three times in the first year and twice annually thereafter up to 18 sessions in the first year and quarterly maintenance visits thereafter.

Of the 15 included studies (17 intervention arms) 11 RCTs (12 comparisons) provided data on all-cause mortality (including over 55,000 participants and 3276 deaths), 10 RCTs (12 comparisons) on CV mortality (> 53,000 participants and 1097 cardiovascular deaths), and 11 RCTs (13 comparisons) on combined cardiovascular CVD events (> 53,000 participants and 4377 events) (Table 2). In two included studies it was clear that events had occurred, but it was not clear in which arm(s) the events had occurred (Oxford Retinopathy 1978; Simon 1997), so that we could not include the data in the meta-analyses. Secondary health events and other secondary outcomes were reported in varying number of studies (between 1 to 15 studies reported on any single outcome) except for quality of life, where no data were reported in any of the studies (see Table 2; Table 3).

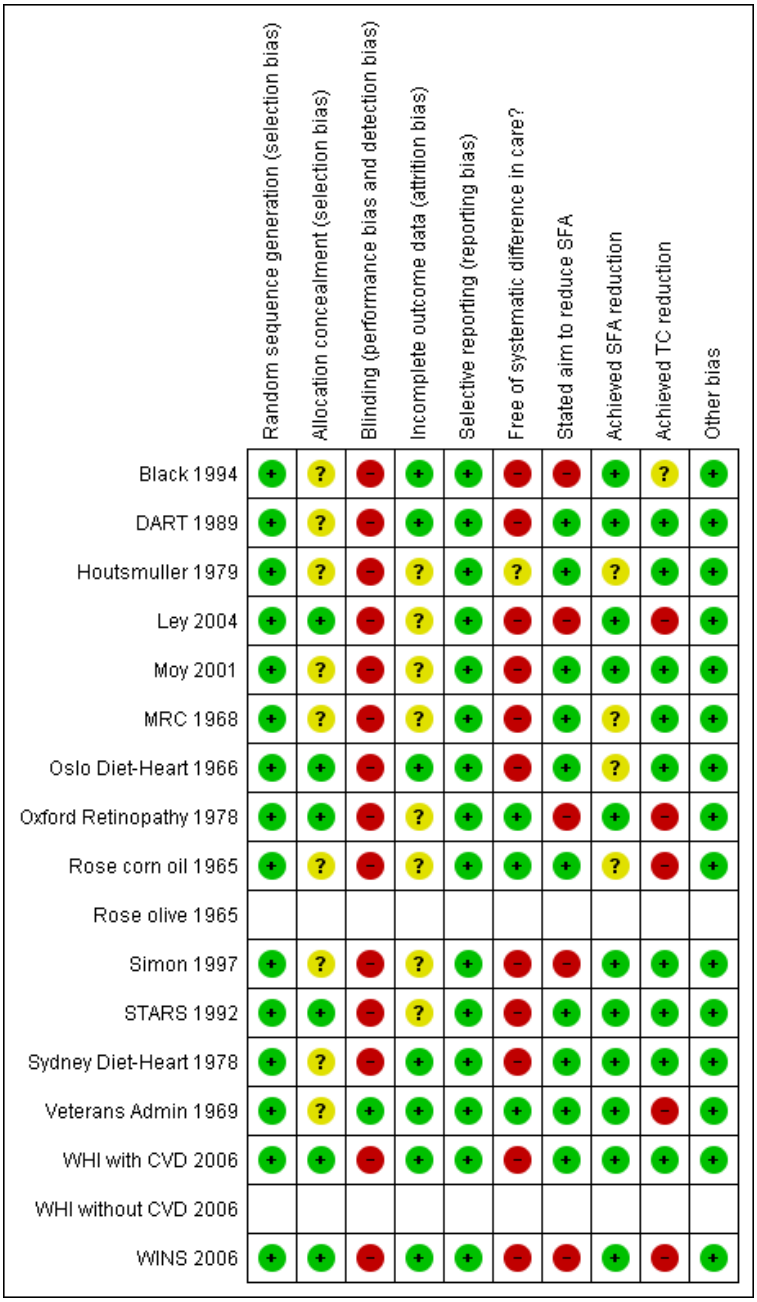
### Excluded studies

We excluded 314 trials (Excluded studies), having assessed the full texts in duplicate for inclusion. We describe the reasons for these exclusions in Characteristics of excluded studies tables. We excluded 29 studies where data on events were not reported in publications and contact with authors confirmed that there had been no deaths or cardiovascular events, where contact with authors confirmed that data were not available, or where we could not establish contact with authors.

## Risk of bias in included studies

We display 'Risk of bias' assessments in the individual included study arms in Figure 2.

**Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study. Please note that while Rose 1965 (Rose corn oil 1965; Rose olive 1965) and WHI 2006 (WHI with CVD 2006; WHI without CVD 2006) each appear twice in this summary, they are each a single trial. Rose 1965 was a 3-arm trial and we have used the two intervention arms separately in the review, while WHI 2006 provided some data separately for people with or without CVD at baseline.**



### Allocation

All the included trials were randomised controlled trials. We excluded those with detected pseudo-random allocation (for example where participants are randomised according to birth date or alphabetically from their name). We judged allocation concealment to be well done in six RCTs (seven comparisons, Ley 2004; Oslo Diet-Heart 1966; Oxford Retinopathy 1978; STARS 1992; WHI with CVD 2006; WHI without CVD 2006; WINS 2006), and unclear in the remainder.

### Blinding

Blinding of participants is not easy in dietary studies, as the participants usually have to follow instructions to attain the specific dietary goals. However, it is feasible in some circumstances, including when food is provided via an institutional setting, or meals provided at a central setting and remaining meals packed to take away, through use of a trial shop, where very specific food-based dietary advice is provided for all participants, or where the same dietary advice is provided to both groups but a different supplement (e.g. dietary advice to reduce fats, then provision of different oils or fats) is provided. Where participants are not blinded it is difficult to ensure that study staff, healthcare providers and outcome assessors are blinded. The single RCT that appears to have had adequate participant and study personnel blinding was Veterans Admin 1969, and we judged blinding to be inadequate in the remaining studies.

### Incomplete outcome data

Assessing whether incomplete outcome data have been addressed was difficult, as the primary outcomes for this review were often seen as drop-outs and exclusions from the original studies. When mortality or cardiovascular events or both were noted in any one study, it is still feasible that some participants left that study feeling unwell or because the diet was inconvenient, so were simply lost to follow-up from the perspective of the study, and later died or experienced a cardiovascular event. However, six of the studies checked medical records or death registers to ensure that such events were all collected (Black 1994, DART 1989; Oslo Diet-Heart 1966; Sydney Diet-Heart 1978; Veterans Admin 1969; WINS 2006). Within one study there was extensive medical records tracking and follow-up, with assessment of health status by blinded trained adjudicators (WHI with CVD 2006; WHI without CVD 2006), so few major events were likely to have been missed. In the other studies it is not possible to know whether additional deaths or cardiovascular events occurred, that were not counted or ascertained within this review.

### Selective reporting

Assessment of selective reporting is difficult when the outcome of interest was simply considered a cause of drop-outs in most included studies. We tried to contact all of the trialists to ask about deaths and outcome events, but it is possible that some trialists did not reply as they felt that their data did not reflect the expected or hoped-for pattern of events. All of the included studies have either reported that the participants did not experience any of our primary outcomes, have published their outcome data, or have provided the data they did possess. For this reason we have graded all the included studies as 'Free of selective reporting'.

### Other potential sources of bias

We assessed the studies for risk of bias in relation to 'systematic difference in care'. The three RCTs (four comparisons) free of systematic differences in care between the study arms included Rose corn oil 1965; Rose olive 1965; Oxford Retinopathy 1978; Veterans Admin 1969, while 11 RCTs (12 comparisons) clearly did have differences in care, such as differential time provided for those on the intervention to learn a new diet, and/or differential medical follow-up, and one was unclear (Houtsmuller 1979).

Some comparisons were partially confounded by dietary changes other than those directly related to dietary fat intakes; for example, some studies encouraged intervention participants to make changes to their fat intake as well as changes to fruit and vegetable or fibre or salt intakes. The 11 studies (12 comparisons) that appeared free of such differences included Black 1994; Ley 2004; DART 1989; Houtsmuller 1979; Rose corn oil 1965; Rose olive 1965; MRC 1968; Oxford Retinopathy 1978; Simon 1997; Sydney Diet-Heart 1978; Veterans Admin 1969; WINS 2006. However, we have omitted this factor from the formal validity assessment as we did not consider confounding changes in types of fat other than saturated fats.

As several studies did not provide clear aims for their interventions (other than to alter specific dietary components, for example), we assessed whether the study stated an aim to reduce saturated fat. Ten RCTs (12 comparisons) clearly aimed to reduce saturated fat in their intervention arms, either directly or indirectly, for example, by stating food goals (DART 1989; Houtsmuller 1979; Moy 2001; MRC 1968; Oslo Diet-Heart 1966; Rose corn oil 1965; Rose olive 1965; STARS 1992; Sydney Diet-Heart 1978; Veterans Admin 1969; WHI with CVD 2006; WHI without CVD 2006), while the remaining five did not (although they did achieve SFA reduction). Eleven RCTs (12 comparisons) assessed SFA intake during the study period and showed that SFA intake in the intervention arm was statistically significantly lower than that in the control arm (Black 1994; DART 1989; Ley 2004; Moy 2001; Oxford Retinopathy 1978; Simon 1997; STARS 1992; Sydney

Diet-Heart 1978; Veterans Admin 1969; WHI with CVD 2006; WHI without CVD 2006; WINS 2006). The remaining studies did not report SFA intake, so we rated them as unclear. Nine RCTs (10 comparisons) provided information on serum total cholesterol (or LDL cholesterol) levels in the intervention and control arms during the study, and found a reduction in the intervention arm compared to the control (P < 0.05 or where variances were not provided showed a reduction of at least 0.2 mmol/L in the mean intervention measure compared with control). The studies that successfully reduced serum total cholesterol compared with control were DART 1989; Houtsmuller 1979; Simon 1997; STARS 1992; Sydney Diet-Heart 1978; WHI with CVD 2006; WHI without CVD 2006, while Moy 2001 did not report total cholesterol (TC) but showed statistically significant reductions in LDL, and two studies (MRC 1968; Oslo Diet-Heart 1966) did not report variances but did reduce mean TC in the intervention arm compared with control. One study (Black 1994) did not report lipid levels during the study, while five others did report lipid levels but did not suggest clear changes (Ley 2004; Oxford Retinopathy 1978; Rose corn oil 1965; Rose olive 1965; Veterans Admin 1969; WINS 2006). We did not identify any further methodological issues.

## Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: What is the effect of reducing saturated fat compared to usual saturated fat on CVD risk in adults? (Note: for the full set of GRADE tables see additional tables 24 to 28)

### Primary outcomes

#### Total mortality

There was no clear effect of reducing saturated fat compared to usual or control diet on mortality (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.90 to 1.05, $I^2$ 3%, 55,858 participants, 3276 deaths, 11 RCTs $p_{effect}$ 0.47, Analysis 1.1; Figure 3). The funnel plot did not suggest any small study bias (Figure 4).

**Figure 3. Forest plot of comparison: 1 SFA reduction vs usual diet - health events, outcome: 1.1 All-cause mortality.**

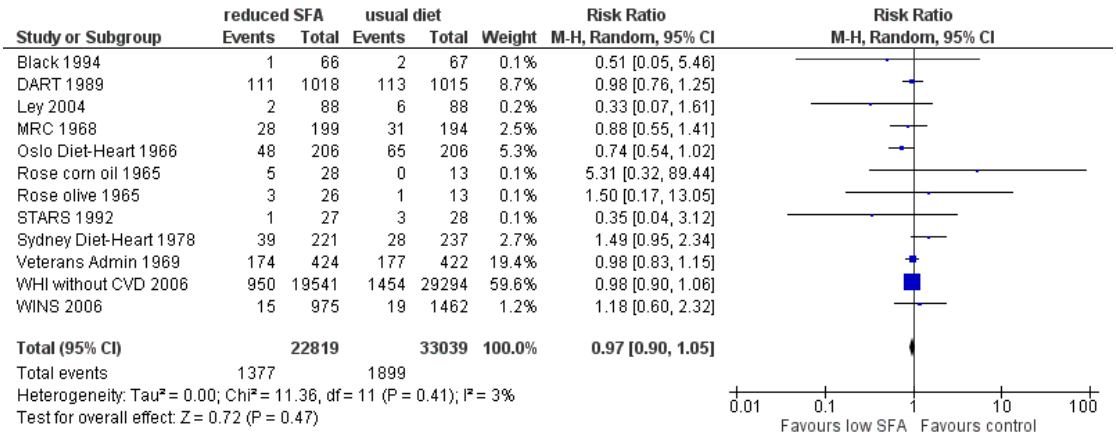
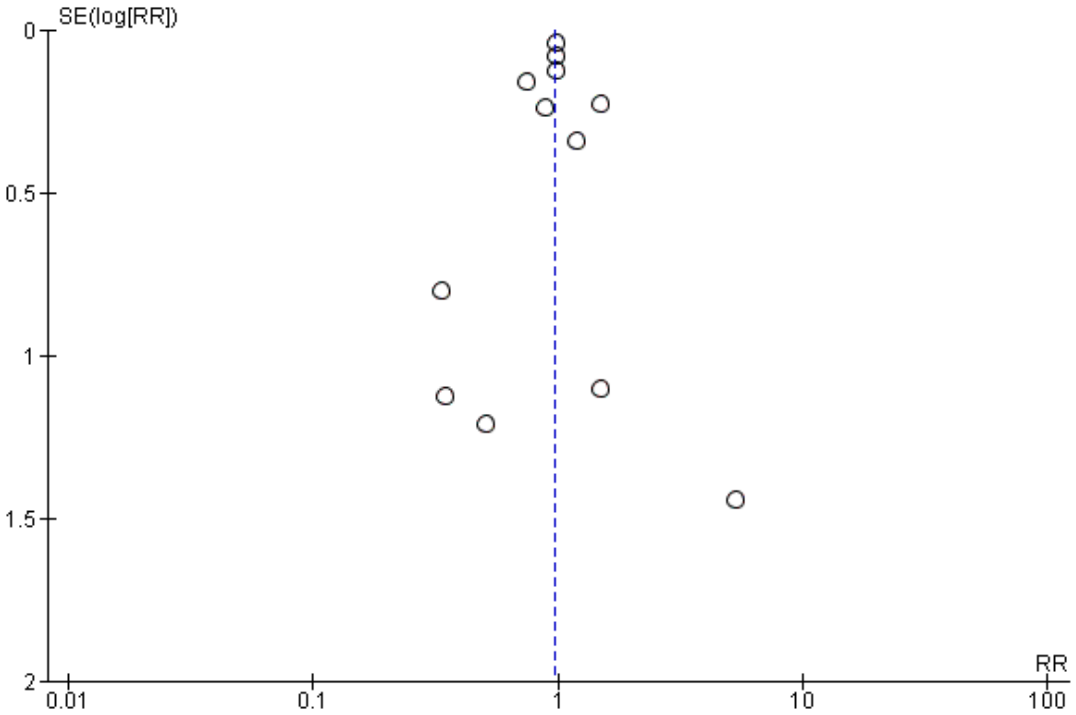


**Figure 4. Funnel plot of comparison: fat modification or reduction vs usual diet - total mortality.**



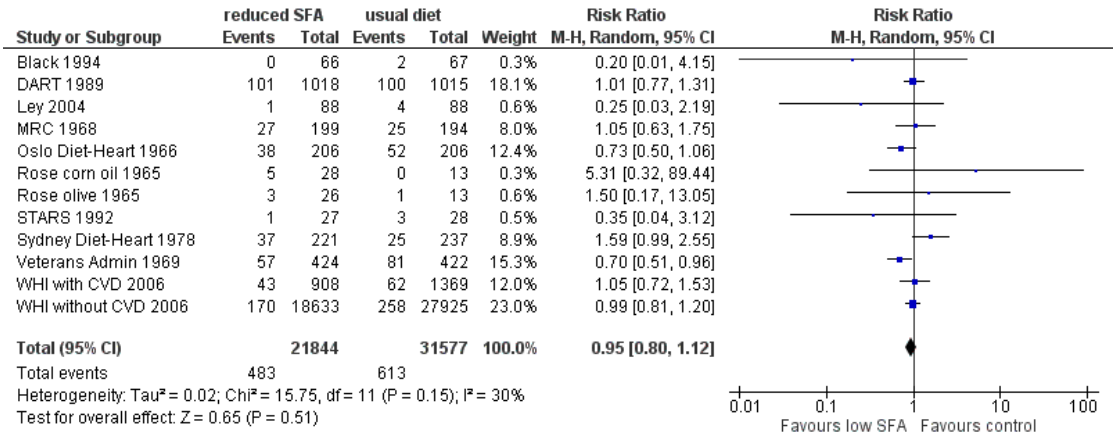

Sensitivity analyses (omitting studies that did not state an aim to reduce SFA intake, omitting studies that did not reduce SFA in the intervention compared to control during the study period, omitting studies where TC was not reduced in the intervention compared to control group, omitting studies without a reduction in serum total cholesterol, omitting both arms of the largest single study (WHI with CVD 2006; WHI without CVD 2006), running analyses with Mantel-Haenszel fixed-effect or Peto fixed-effect analyses consistently showed no evidence of any effect (Table 4).

We found no important effects of reducing SFA compared to usual or control diets on mortality when we subgrouped studies by SFA replacement (with PUFA, MUFA, CHO, or protein), mean duration, baseline SFA intake, or difference in SFA between intervention and control arms, decade of publication, or degree of reduction of serum total cholesterol. There was no suggestion of important differences between subgroups in any of these subgroupings (Chi² test for differences between subgroups all P > 0.05). Subgrouping did not suggest different effects in studies of men or women, or in people at different risk of cardiovascular disease (Table 5).

#### Cardiovascular mortality

There was no clear effect of SFA reduction compared to usual diet on cardiovascular mortality (RR 0.95, 95% CI 0.80 to 1.12, $I^2$ 30%, 10 RCTs, 53,421 participants, 1096 cardiovascular deaths), Analysis 1.2; Figure 5, and the funnel plot did not suggest small study bias (not shown). Sensitivity analyses did not alter the lack of clear effects of reduced SFA compared to usual or control diets on cardiovascular mortality (Table 6).

**Figure 5. Forest plot of comparison: 1 SFA reduction vs usual diet - Primary outcomes, outcome: 1.2 Cardiovascular mortality.**




Subgrouping did not suggest important effects of reduced SFA on cardiovascular mortality (Table 7), regardless of what was substituted for SFA, except that reductions in cardiovascular mortality were suggested in subgroups where baseline SFA was > 18%E and where the reduction in SFA from baseline was > 8%E. This would be consistent with a true effect of SFA reduction on cardiovascular mortality that we are not seeing in the full set of studies due to limited effect on SFA. Subgrouping by sex or baseline cardiovascular risk did not suggest different effects in any group. There was a suggestion that publication in different decades showed different effect sizes (P for subgroup differences 0.04) but this did not appear to relate to statin use, as there was a reduction in risk of CVD mortality in studies published in the 1960s and a marginal increase in risk in the one trial published during the 1970s (although the 95% confidence interval did include 1.0), both well before statins were in common use (the 4S trial which first showed that use of statins reduced mortality was published in 1994, 4S 1994).

### Cardiovascular events

There was a 17% reduction in cardiovascular events in people who had reduced SFA compared with those on usual diet (RR 0.83, 95% CI 0.72 to 0.96, $I^2$ 65%, 11 RCTs, 53,300 participants, 4377 people with cardiovascular events, $P_{effect}$ 0.01, Analysis 1.3; Figure 6). Sensitivity analyses all maintained this clear effect of the intervention, apart from the analysis removing studies without clear SFA reduction (Table 8). A funnel plot did not suggest severe small-study bias, but it is possible that a few small studies with more cardiovascular events in the intervention groups may be missing from the review (Figure 7).

**Figure 6. Forest plot of comparison: 1 SFA reduction vs usual diet - Primary outcomes, outcome: 1.3 Combined cardiovascular events.**

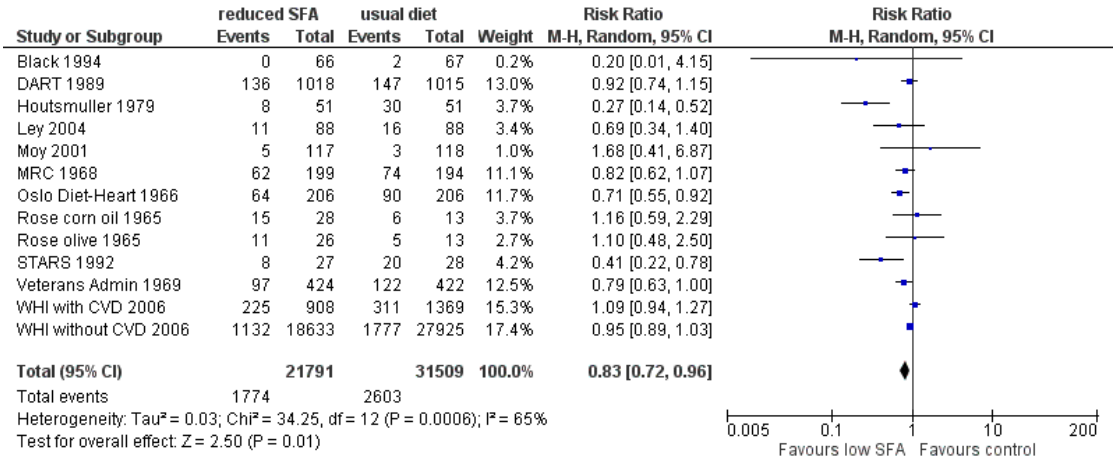
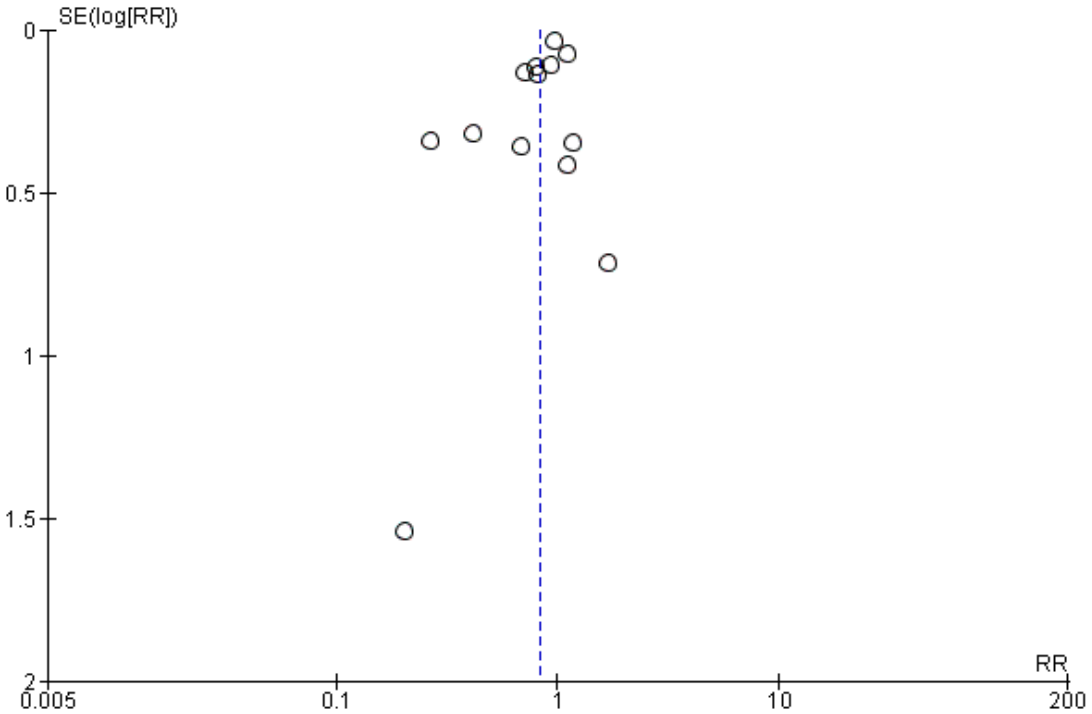



**Figure 7. Funnel plot of comparison: fat modification or reduction vs usual diet - combined cardiovascular events.**



When we subgrouped according to replacement for SFA, the PUFA replacement group suggested a 27% reduction in cardiovascular events, while there were no clear effects of other replacement groups (Table 9). Subgroups of participants with greater baseline SFA intake, and with greater reductions in SFA in the intervention group compared to control showed useful effects despite the reduction in power (Table 9). Similarly, the subgroup of studies which achieved a reduction in serum total cholesterol of at least 0.2 mmol/L reduced cardiovascular events by 26%, while studies that did not achieve this cholesterol reduction showed no clear effect. Although one study duration subgroup showed an effect, there was no clear progression with time (Table 9). When subgrouping by sex, effects in women (RR 1.00; 95% CI 0.88 to 1.14) appeared less dramatic than effects in men (RR 0.80; 95% CI 0.69 to 0.93, with the test for differences between subgroups marginal, P = 0.05), although this was confounded as the studies in women replaced SFA primarily by CHO. There was a suggestion that decade of publication may relate to effect size (P for subgroup differences < 0.0001), with studies published in the 1960s, 1970s and 1990s all suggesting reduction in risk with lower saturated fat intakes and studies published in the 1980s (one trial) and the 2000s (three trials, four comparisons) not suggesting important effects. Effect size did not appear to alter by baseline cardiovascular risk.

We explored the effects of dietary fats on cardiovascular events, by using meta-regression of the difference between the control and intervention of total fat intake, SFA intake, MUFA intake, PUFA intake, CHO intake (all by percentage of energy (%E)), serum total cholesterol (in mmol/L) achieved in trials, as well as baseline SFA intake, sex, study duration in months, and CVD risk of participants at baseline (Table 10). As we included only 13 studies for this outcome, we ran meta-regressions exploring single explanatory factors at once, and as data were limited, with many studies not reporting dietary intake data, these analyses were limited in power to assess outcomes. The data suggested that greater reductions in SFA intake and in total serum cholesterol levels reduced CVD events, greater baseline SFA intake was associated with greater improvement in CVD events with SFA reduction, and increases in PUFA and MUFA intakes were slightly protective of CVD events, but the relationship with serum total cholesterol was clearest (P = 0.04, accounting for 99% of between-study variation). Sex, study duration and baseline cardiovascular risk did not appear to influence effect size.

## Secondary outcomes - health events

### Myocardial Infarction (fatal and non-fatal)

There was a marginal effect of SFA reduction compared to usual diet on myocardial infarction (fatal and non-fatal, RR 0.90, 95% CI 0.80 to 1.01, $I^2$ 10%, 10 RCTs, 53,167 participants, 1714 people with MI, $P_{effect}$ 0.09), Analysis 2.1. One sensitivity analysis suggested reduction of MI with SFA reduction, but the remainder were not clear (Table 11). The funnel plot was difficult to interpret, but did not raise major concerns about small-study bias (not shown). Subgrouping did not suggest major modification of the effect by study duration, decade of publication, baseline SFA or degree of difference in SFA between intervention and control groups, or by replacement for SFA (PUFA, MUFA, CHO or protein) (Table 9). Subgrouping suggested reduction in myocardial infarction in studies of men only (but not women) and in studies that reduced serum total cholesterol by at least 0.2 mmol/L, but not in other subgroups (Table 12).

### Myocardial Infarction (non-fatal only)

There was no clear effect of SFA reduction compared to usual diet on non-fatal myocardial infarction (RR 0.95, 95% CI 0.80 to 1.13, $I^2$ 27%, 7 RCTs, 52,834 participants, 1348 people with non-fatal MI, $P_{effect}$ 0.57) Analysis 2.2. Sensitivity analyses did not suggest any clear reduction of non-fatal MI with SFA reduction (Table 13). The funnel plot did not raise major concerns about small-study bias (not shown). Subgrouping did not suggest major modification of the effect by study duration, baseline SFA or degree of difference in SFA between intervention and control groups, or by replacement for SFA (PUFA, MUFA, CHO or protein) (Table 14). Subgrouping did not suggest different effects in studies of men or women, by decade of publication, or by those at different baseline risk of cardiovascular disease.

### Stroke (any type, fatal or non-fatal)

As data on stroke were sparse it was not possible to tease out differential effects on ischaemic or haemorrhagic strokes, or whether a stroke was fatal. For this analysis we combined all stroke data from any study. There was no clear effect of SFA reduction compared to usual diet on stroke of any type with any outcome (RR 1.00, 95% CI 0.89 to 1.12, $I^2$ 0%, 7 RCTs, 50,952 participants, 1125 people with stroke, $P_{effect}$ 0.96, Analysis 2.3). Sensitivity analyses did not suggest any reduction of stroke with SFA reduction (Table 15). The funnel plot was difficult to interpret as it only included data from seven RCTs, but did not suggest major concerns (not shown). There was very little suggestion of heterogeneity between trials, and subgrouping did not suggest major modification of the effect by study duration, decade of publication, baseline SFA or degree of difference in SFA between intervention and control groups or by replacement for SFA (PUFA, MUFA, CHO or protein) (Table 16). Subgrouping by sex or cardiovascular risk did not suggest different effects in any subgroup.

### Coronary heart disease (CHD) mortality

Eight RCTs (10 comparisons) did not suggest that reducing saturated fat reduced CHD mortality (RR 0.98, 95% CI 0.84 to 1.15, $I^2$ 21%, 53,159 participants, 886 people died of coronary

heart disease, $P_{effect}$ 0.78) Analysis 2.4, and this was not altered in any sensitivity analyses (Table 17). Heterogeneity between studies was small, and we saw no clear effect when SFA was replaced by PUFA, MUFA, CHO or protein, and no clear effects in any other subgroups (Table 18).

#### Coronary heart disease events

There was the suggestion of a 13% reduction in CHD events as a result of saturated fat reduction (RR 0.87, 95% CI 0.74 to 1.03, $I^2$ 66%, 53,199 participants, 3307 people had at least one coronary heart disease event, $P_{effect}$ 0.07) Analysis 2.5. The effect was stronger in fixed-effect analyses (although heterogeneity between studies remained high, so fixed-effect analysis was probably not appropriate), but not in other sensitivity analyses (Table 19). Some of the heterogeneity between studies appeared to be explained by the degree of serum cholesterol lowering achieved, the degree of saturated fat reduction achieved, decade of publication and baseline saturated fat intake, with higher baseline SFA intake and greater reductions in SFA or TC associated with greater effect sizes (Table 20).

#### Type 2 diabetes, new diagnoses

Only one RCT reported on diagnosis of diabetes (WHI with CVD 2006; WHI without CVD 2006). There was no clear effect of reducing SFA intakes (compared to usual diet) on diagnosis of diabetes in this study (RR 0.96, 95% CI 0.90 to 1.02, 48,835 participants, $P_{effect}$ 0.21) Analysis 2.6. No subgrouping was possible.

### Secondary outcomes - blood levels

For details of blood and process outcomes see Table 21.

#### Serum blood lipids

**Total cholesterol (TC):** There was a reduction in TC in participants with reduced SFA compared to usual diet (mean difference (MD) -0.24 mmol/L, 95% CI -0.36 to -0.13, $I^2$ 60%, 13 RCTs, 7115 participants, $P_{effect}$ 0.0001) Analysis 3.1. We did not conduct sensitivity analyses and most subgroupings on secondary outcomes, but there was no clear differential effect on TC depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture). The funnel plot did not raise concerns about small-study bias (not shown).

**Low-density lipoprotein (LDL):** There was a reduction in LDL in participants with reduced SFA compared to usual diet (MD -0.19 mmol/L, 95% CI -0.33 to -0.05, $I^2$ 37%, 5 RCTs, 3291 participants, $P_{effect}$ 0.006) Analysis 3.2. There was no clear differential effect on LDL depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture). We could not interpret the funnel plot due to sparsity of studies (not shown).

**High-density lipoprotein (HDL):** There was no clear effect of reducing SFA intakes (compared to usual diet) on HDL (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, $I^2$ 0%, 7 RCTs, 5147 participants, $P_{effect}$ 0.21) Analysis 3.3. There was no clear differential effect on HDL depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture). We could not interpret the funnel plot due to sparsity of studies (not shown).

**Triglycerides (TG):** There was no clear effect of reducing SFA intakes (compared to usual diet) on TG (MD -0.08 mmol/L, 95% CI -0.21 to 0.04, $I^2$ 51%, 7 RCTs, 3845 participants) Analysis 3.4. There was no clear differential effect on TG depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture). We could not interpret the funnel plot due to sparsity of studies (not shown).

**TG/HDL ratio:** We did not find any studies that reported TG/HDL ratio.

**TC/HDL ratio:** Only three RCTs reported on TC/HDL ratio. There was no clear effect of reducing SFA intakes compared to usual diet on TC/HDL (MD -0.10, 95% CI -0.33 to 0.13, $I^2$ 24%, 2985 participants) Analysis 3.5. There were no clear differential effects of replacement on TC/HDL. We could not interpret the funnel plot due to sparsity of studies (not shown).

**LDL/HDL ratio:** Only one RCT reported on LDL/HDL ratio. There was no clear effect of reducing SFA intakes compared to usual diet on LDL/HDL in this study (MD -0.36, 95% CI -0.92 to 0.20, 50 participants) Analysis 3.6.

**Lipoprotein (a) (Lp(a)):** Only two RCTs reported on Lipoprotein (a), but these included 28,820 participants. There was no clear effect of reducing SFA intakes compared to usual diet on Lp(a) (MD 0.00, 95% CI -0.00 to 0.00, $I^2$ 0%, $P_{effect}$ 1.00) Analysis 3.7. There was no suggestion of differential effects of replacement on Lp(a). We could not interpret the funnel plot due to sparsity of studies (not shown).

**Homeostatic model assessment (HOMA):** Only one RCT reported on the effects of reducing SFA on insulin resistance using HOMA. There was no clear effect of reducing SFA intakes compared to usual diet on HOMA in this study (MD -0.00, 95% CI -0.04 to 0.04, 2832 participants, $P_{effect}$ 1.00) Analysis 3.8.

**Glucose at two hours post-glucose tolerance test (GTT):** Only three RCTs reported on glucose two hours post-GTT. There was a reduction in glucose after reducing SFA intakes compared to usual diet (MD -1.69 mmol/L, 95% CI -2.55 to -0.82, $I^2$ 45%, 249 participants, $P_{effect}$ 0.0001) Analysis 3.8. We could not interpret the funnel plot due to sparsity of studies (not shown).

**HbA1c (glycosylated haemoglobin):** HbA1c was not measured in any included RCTs.

### Secondary outcomes - other outcomes and potential harms

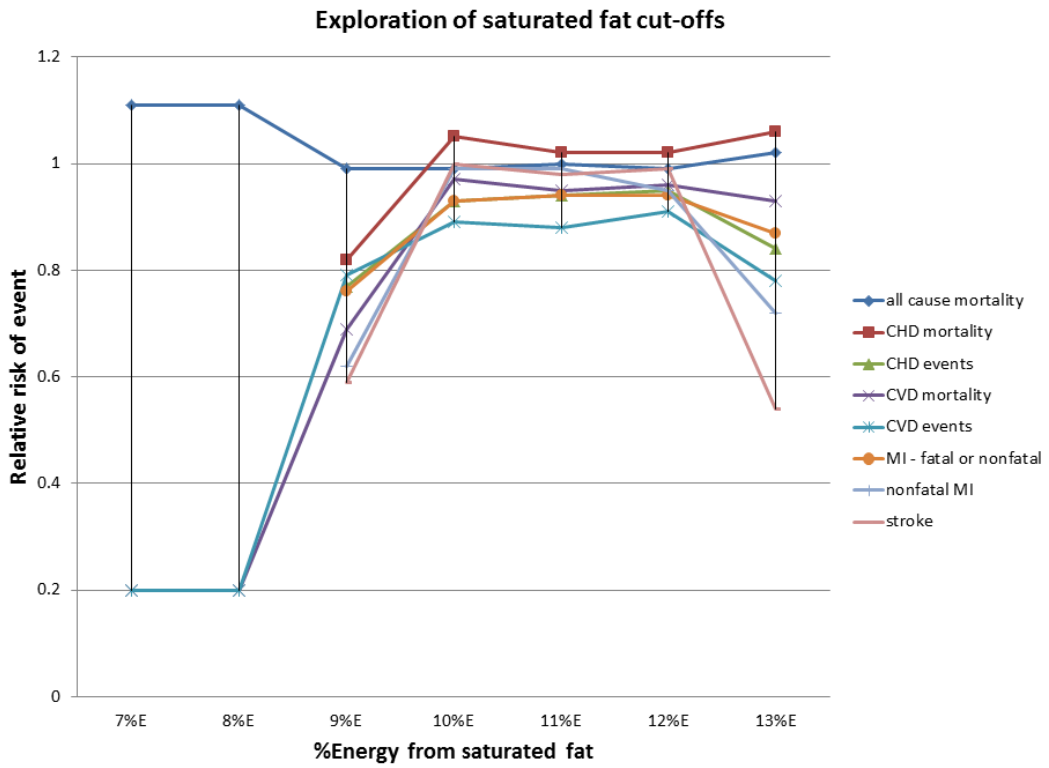
There was no effect of reducing SFA intakes on **cancer diagnoses**

of any type (RR 0.94, 95% CI 0.83 to 1.07, $I^2$ 33%, 4 RCTs, 52,294 participants, 5476 cancer diagnoses); **cancer deaths** (RR 1.00, 95% CI 0.61 to 1.64, $I^2$ 49%, 5 RCTs, 52,283 participants, 2472 cancer deaths); **systolic blood pressure** (MD -0.19 mmHg, 95% CI -1.36 to 0.97, $I^2$ 0%, 5 RCTs, 3812 participants); **diastolic blood pressure** (MD -0.36 mmHg, 95% CI -1.03 to 0.32, $I^2$ 0%, 5 RCTs, 3812 participants) (Table 22). Only one RCT reported assessing **quality of life**. The Women's Health Initiative (WHI with CVD 2006; WHI without CVD 2006) assessed quality of life at baseline using the SF-36 tool, but we were unable to establish whether quality of life was compared between dietary intervention and control groups during the study. There was evidence that reducing SFA intake resulted in small reductions in **body weight** (MD -1.97 kg, 95% CI -3.67 to -0.27, $I^2$ 72%, 6 RCTs, 4541 participants), and **body mass index** (MD -0.50, 95% CI -0.82 to -0.19, $I^2$ 55%, 6 RCTs, 5553 participants).

### Other results

To assess the effect in the population of consuming < 10%E as SFA relative to > 10%E as SFA for reduction in risk of non-communicable diseases (NCDs) we combined studies with a control group saturated fat intake of > 10%E and an intervention group saturated fat intake of < 10%E for all-cause mortality, cardiovascular and coronary heart disease mortality and events, myocardial infarctions, non-fatal myocardial infarctions, and stroke. To assess the effect in the population of a reduction in %E from SFA from 10% in gradual increments relative to higher intake we repeated this with saturated fat cut-offs between 7%E and 13%E. The data for these cut-offs are shown in Table 23, and were plotted for a visual overview (Figure 8). The figure suggests reductions in cardiovascular outcomes in studies where saturated fat intake was greater than 9%E in control groups, and less than 9%E in intervention groups.

**Figure 8. Exploring saturated fat cut-offs.**



### Additional WHO NUGAG specific questions, including GRADE assessments:

#### In adults what is the effect in the population of reduced percentage of energy (%E) intake from saturated fatty acids (SFA) relative to higher intake for reduction in risk of non-communicable diseases (NCDs)?

This question is addressed in the summary of main results, above. We found that reducing saturated fat for at least two years suggested no clear effects on all-cause or cardiovascular mortality, but a 17% reduction in combined cardiovascular events. Heterogeneity in this result was partially explained by greater (27%) reductions in cardiovascular events in studies that replaced saturated fats by PUFAs than in studies with replacement with MUFAs, CHO or protein, and greater reductions in cardiovascular events in studies with higher baseline saturated fat intakes, greater reduction in saturated fats in the intervention group, and greater serum total cholesterol reductions.

#### GRADE assessment

There is moderate-quality evidence that reducing saturated fat leads to reductions in cardiovascular events, and moderate-quality evidence that there is little effect on all-cause mortality, CVD mortality, myocardial infarction, stroke and CHD mortality. Low-quality evidence suggests a reduction in CHD events. The strengths and weaknesses are discussed in detail in the footnotes of Summary of findings for the main comparison (and in more detail in Table 24), but the main reason for downgrading from high-quality evidence was for a combination of imprecision (95% confidence intervals including both benefit and harm), and risk of bias from large long-term dietary change studies where allocation concealment was often unclear and blinding was not feasible. The WHO NUGAG group felt that a single downgrading from high- to moderate-quality evidence appropriately reflected these concerns.

#### What is the effect on coronary heart disease mortality and coronary heart disease events?

We found a marginal effect of SFA reduction on myocardial infarction and on CHD events, but saw no effects on CHD mortality, non-fatal myocardial infarctions, or stroke.

#### What is the effect in the population of replacing SFA with PUFAs, MUFAs, CHO (refined versus unrefined), protein or trans fatty acids (TFAs) relative to no replacement for reduction in risk of NCDs?

We found greater reductions (27%) in cardiovascular events in studies that replaced saturated fats by PUFAs than in studies with replacement with MUFAs, CHO or protein, where there was little evidence of any effect.

***What is the effect of replacing some saturated fat with PUFA on risk of CVD in adults?***

There is moderate-quality evidence that replacing saturated fat with PUFA reduces the risk of CVD events and myocardial infarction (Table 25), and that there is no effect on all-cause mortality or CHD mortality. Evidence for effects on CVD mortality and stroke was low or very low quality. Evidence was downgraded from high quality due to serious inconsistency or serious imprecision or both.

***What is the effect of replacing some saturated fat with MUFA on risk of CVD in adults?***

With only one included RCT there was very low-quality evidence of effects of replacing saturated fat with MUFA on any mortality or morbidity outcome (Table 26). We downgraded the quality of evidence due to serious risk of bias and serious imprecision.

***What is the effect of replacing some saturated fat with CHO on risk of CVD in adults?***

There was moderate-quality evidence that replacing saturated fat with CHO has no effect on all-cause mortality, CVD mortality, total and non-fatal MI, stroke or CHD mortality (Table 27). The evidence on CVD events, non-fatal MI, and CHD events was all low quality. We downgraded the quality of evidence due to imprecision of effect.

***What is the effect of replacing some saturated fat with protein on risk of CVD in adults?***

Moderate- or low-quality evidence suggested no clear effects of replacing saturated fat with protein on any health outcomes (Table 28). We downgraded the quality of evidence due to imprecision of effect.

#### What is the effect in the population of consuming < 10%E as SFA relative to > 10%E as SFA for reduction in risk of NCDs?

Cut-off data were difficult to interpret, and confidence intervals were wide, but they suggested greater reductions in cardiovascular events in studies where saturated fat intake was greater than 9%E in control groups, and less than 9%E in intervention groups (see Figure 8).

#### What is the effect in the population of a reduction in %E from SFA from 10% in gradual increments relative to higher intake for reduction in risk of NCDs?

The data from RCTs are too limited to be able to address this question.

## DISCUSSION

## Summary of main results

This systematic review of long-term randomised controlled trials of SFA reduction suggests that reducing saturated fat for at least two years had no clear effects on all-cause or cardiovascular mortality, but a 17% reduction in combined cardiovascular events with important heterogeneity. This clear effect on cardiovascular events was not lost on sensitivity analyses. Subgrouping suggested that there was a 27% reduction in cardiovascular events in studies that replaced saturated fats by PUFAs, but not in studies with replacement by MUFAs, CHO or protein. We could not explore data on trans fats. The reduction in cardiovascular events was clearer in subgroups with greater baseline saturated fat intakes, greater reduction in saturated fats in the intervention group, and studies with greater serum total cholesterol reductions. Meta-regression confirmed that degree of reduction in cardiovascular events was related to degree of reduction of serum total cholesterol, and there was a modest suggestion of greater protection with greater saturated fat reduction or greater increase in PUFAs and MUFAs.

There was modest evidence that SFA reduction reduced MI (fatal and non-fatal combined) and CHD events, but we saw no effects on CHD mortality, non-fatal myocardial infarctions, or stroke. Studies reducing saturated fat suggested reductions in serum total and LDL cholesterol, which did not differ according to type of replacement. We did not see effects of saturated fat reduction on serum HDL cholesterol, triglyceride, or any ratios (though these were assessed in only a few of the included studies). There were no clear effects on diabetes diagnoses or HOMA, but a suggestion of reduction in glucose two hours after a glucose load. While we found small reductions in body weight and body mass index with advice to reduce saturated fats, there were no effects on cancer diagnoses or deaths, or on systolic or diastolic blood pressure.

## Overall completeness and applicability of evidence

The review included adult participants at varying levels of risk of cardiovascular disease, men and women, in free-living and institutional settings, and across the past 50 years. All the studies were conducted in industrialised countries, and no data were available from developing or transitional countries. The effectiveness of SFA reduction has been well assessed, with trials of at least 24 months including more than 50,000 participants for most primary outcomes. Three thousand two hundred and seventy-six participants in the included trials died, 1096 died of a cardiovascular cause, and 4377 experienced at least one cardiovascular event.

Overall the external validity of the review in industrialised countries, men and women, people with low, moderate and high risk of cardiovascular disease was high, but it is not clear how this evidence relates to diets in developing and transitional countries.

## Quality of the evidence

See above for formal GRADE assessment. All 15 trials and 17 comparisons included were randomised controlled trials, allocation concealment was judged well done in six RCTs (seven comparisons), and blinding adequate in only one trial (difficult and expensive in dietary fat trials). We judged incomplete outcome data not to be a problem in seven RCTs, and selective reporting was not a problem in any trial. Three trials were free of differences in care between the intervention and control arms, 10 RCTs stated an aim to reduce saturated fat, 11 showed evidence they had reduced SFA intake (all studies did one or the other), and nine studies showed clear reductions in total cholesterol.

The lack of blinding in most dietary trials is unlikely to alter outcome assessment when outcomes include death and cardiovascular events, but lack of blinding in the participants may have led those in the control groups to alter their lifestyle and dietary practices (for example, feeling that they have not been helped to reduce their cardiovascular risk, they may act to reduce their own risk by altering other lifestyle behaviours such as smoking or exercise, leading to a potential lessening of the apparent effect of the dietary intervention). Systematic differences in care between arms may have led to intervention groups receiving additional support in areas like self efficacy and gaining support from new social circles, potentially beneficial to health regardless of dietary fat intake, or gaining additional healthcare professional time, possibly leading to earlier diagnosis and treatment of other risk factors such as raised blood pressure. Additional dietary messages such as those around fruit and vegetable intake, fibre, alcohol and sugars, present in many studies, may have been protective, or may have diluted the effect or attainability or both of the fat goals.

The quality of evidence balances the uncertainty over allocation concealment, lack of blinding and presence of systematic differences in care and additional dietary differences between arms (Figure 2) with the scale and consistency of the evidence across studies and across decades, despite very different designs and design flaws. For this reason, there is moderate-quality evidence that the interventions that reduce dietary saturated fat intake reduce cardiovascular risk.

### Complex interventions

With complex interventions, such as dietary ones, there are additional questions that need to be asked about included studies. Important issues to consider include defining the intervention, searching for and identifying all relevant studies, selecting studies for inclusion and data synthesis (Lenz 2007; Sheppherd 2009).

For this review we have worked to define the interventions clearly (see Characteristics of included studies), providing information on the type of intervention, stating the study aims and methods for each arm and the assessed total and saturated fat intakes attained within the study. However, while we have characterised the interventions, no two studies that reduced SFA had exactly the same dietary goals for the intervention groups. Methods of attaining the dietary goals varied from providing a whole diet over several years

(in studies based in institutions) to providing advice on diet alongside supplementary foods such as margarines or oils, to providing dietary advice with or without supplementary support in the way of group sessions, cooking classes, shopping tours, feedback, self-efficacy sessions and/or individual counselling. We aimed to use this variety in helping us to provide generalisability for the effects of the interventions.

We addressed identifying all the relevant studies through use of a wide search strategy, which was time-consuming. However, we believe that we have included most relevant trials. We also carefully defined acceptable interventions for each arm, so that decisions on inclusion were simpler, and the two independent assessors more often agreed. We augmented data synthesis by subgrouping and meta-regression, to help us understand the effects of individual elements of dietary fat changes.

A study that sets out to assess the effect of a 30% reduction in saturated fat intake may attain this level of reduction in some participants, exceed it in some and not achieve it at all in others. The actual mean change attained in the intervention group may be less dramatic than that aimed for, and the participants in the control group may also reduce their saturated fat intake by a small amount, narrowing the difference in saturated fat between the groups further and so reducing the scale of any outcome. This can be dealt with in the systematic review if we meta-regress the difference in saturated fat intake between the intervention and control group with the scale of the outcome (assuming a linear dose response), still allowing us to understand the effect of altering saturated fat intake. However, there is also a problem of measuring actual saturated fat intake achieved - some trials did not report this (whether because they did not assess it, or did assess it but didn't have space to report this relatively uninteresting outcome), and others did report the results of asking people what they were eating, using a food frequency questionnaire or several 24-hour food recalls. However, there is good evidence to believe that asking people how they are eating may produce somewhat biased information (Kristal 2005; Schatzkin 2003), and this may be a greater problem where the participant has been recently urged to eat in a particular way, as in a dietary trial.

The interventions used in the studies included in this review were varied, with some participants given all their food over a long period of time in an institutional setting, while most participants were given advice on how to achieve dietary changes, with or without the support of supplements such as oils and foods (Table 1). Advice was provided by a variety of health professionals, and with a variety of levels of intensity. The effect of this was that different degrees of saturated fat reduction were achieved in different studies. The level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null. Insofar as we were able to understand this issue, subgrouping and meta-regression suggested that greater reductions in saturated fats were associated with greater reductions in the risk of cardiovascular disease events. This suggestion of a dose response strengthens our belief that there is a true effect of reducing saturated fat on CVD events.

## Potential biases in the review process

In compiling the included studies we worked hard to locate randomised studies that altered dietary SFA intake for at least 24 months, even when cardiovascular events were not reported in study publications, or where such events were reported incidentally as reasons for participant drop-outs. We attempted to contact all authors of potentially includable studies to verify the presence or absence of our outcomes. In many studies no outcomes relevant to this review occurred or were recorded, and the numbers of events occurring within single studies varied from none to over 2000 deaths, over 500 cardiovascular deaths, and over 3000 cardiovascular events (all within the WHI trial, the largest single study with almost 50,000 participants for many years).

The number of cardiovascular deaths was relatively small (1096), so while we can be quite confident in reporting a reduction in cardiovascular events (4377 events) with SFA reduction, and a lack of effect on total mortality (3276 deaths) within the studies' time scales, the effect on cardiovascular mortality is less clear. The risk ratio of 0.95 (95% CI 0.80 to 1.12) may translate into a small protective effect, but this is unclear. The lack of effect on individual cardiovascular events is harder to explain; there were 1714 MIs, 1125 strokes and 1348 non-fatal MIs, 2472 cancer deaths, 3342 diabetes diagnoses and 5476 cancer diagnoses. Lack of clear effects on any of these outcomes is surprising, given the effects on total cardiovascular events, but may be due to the relatively short timescale of the included studies, compared to a usual lifespan during which risks of chronic illnesses develop over decades.

There is no suggestion from the funnel plots of small-study bias.

One surprising element of this review is the lack of ongoing trials. In all previous reviews we have been aware of ongoing trials, the results of which were likely to inform the review, but for this review we have not noted any new trials on the horizon and so perhaps the current evidence set is as definitive as we will achieve during the 'statin era'.

## Agreements and disagreements with other studies or reviews

In this review saturated fat reduction had no effect on all-cause or cardiovascular mortality but did appear to reduce cardiovascular events by 17%, although effects on MI and stroke individually were less clear. This result was rather different from those of Siri-Tarino 2010, who systematically reviewed cohort studies that assessed relationships between saturated fat and cardiovascular events. They included 21 studies and did not find associations between saturated fat intake and cardiovascular disease (RR 1.0,

95% CI 0.89 to 1.11). However, this meta-analysis has been criticised (Katan 2010; Scarborough 2010; Stamler 2010), as results of half of the studies included in their meta-analysis were adjusted for serum cholesterol concentrations, while there is an established relation between saturated fat intake and cholesterol level. The studies included in the meta-analysis also varied widely in the method used to assess intake, as half of the studies collected one-day intake data. However, as with our review they found no relationship between saturated fat intake and coronary heart disease (RR 1.07, 95% CI 0.96 to 1.19) or stroke (RR 0.81, 95%CI 0.62 to 1.05). In this review we found that replacing saturated fat with PUFAs (a modified-fat diet) appeared protective of cardiovascular events, while replacement with carbohydrates (a low-fat diet) was not beneficial. This was similar to results within our closely allied systematic review assessing health effects of total fat reduction, where modified-fat diets were protective and low-fat diets were not (Hooper 2012). Meta-regression did not suggest any relationship between either PUFAs or MUFAs and cardiovascular events in this review, although the analysis was underpowered. Alonso 2006 suggested a protective role for MUFA from olive oil, but not from meat sources (the main source of MUFA in the USA and Northern Europe). Our systematic review was not able to explore this issue as we included only one small study (underpowered to assess health outcomes on its own) that replaced SFA with MUFA, using an olive oil supplement (Rose olive 1965). A recent review by Mozaffarian 2010, which again included very similar studies to the last version of this review, with the Finnish Mental Hospital study and Women's Health Initiative data added, stated that their findings provided evidence that consuming PUFAs in place of saturated fat would reduce coronary heart disease. However, their evidence for this was limited and circumstantial, as they found that modifying fat reduced the risk of myocardial infarction or coronary heart disease death (combined) by 19% (similar to our result). As the mean increase in PUFAs in these studies was 9.9% of energy, they infer an effect of increasing PUFAs by 5% of energy of 10% reduction in risk of myocardial infarction or coronary heart disease death. They provided no suggestion or evidence of a relationship between degree of PUFAs increase and level of risk reduction. Another recently published review carried out during updating of the Nordic Nutritional Recommendations (Schwab 2014) included observational as well as intervention studies, and concluded that there was convincing evidence that partial replacement of SFA with PUFA decreases risk of CVD while replacement with CHO is associated with increased CVD risk. The review included studies performed solely in white participants or with a clear white majority.

Within the meta-regression we hoped to combine studies that effectively altered saturated fat by different degrees, so that studies that reduced saturated fat very little and studies that reduced it a great deal would all offer data points for the meta-regression against mortality and morbidity endpoints, and similarly for total fat, polyunsaturated, monounsaturated and trans fats. Unfortunately many of the included studies did not report data on assessed dietary intake during the trial, reducing the quantity of data available to understand the relationships. Another limitation in understanding effects of individual classes of fatty acids on mortality and morbidity (both in trials and in observational studies) was our ability to correctly assess participants' intake. We could overcome this by using biomarkers such as serum LDL cholesterol (differences between the LDL concentration in the intervention and control arms could be seen as a reasonable and independent approximation of saturated fat intake); however as many studies were carried out in the 1960s to 1990s few measured and reported LDL cholesterol. We used meta-regression with serum total cholesterol (although this is a composite marker and so less related to saturated fat intake), but although this was available for more studies than LDL it was still not available for all studies. Despite the limited data there was a clear suggestion from meta-regression that there was greater reduction of risk of cardiovascular events in studies with greater total serum cholesterol reduction, supporting the central role of serum lipids in the link between dietary saturated fats and cardiovascular events.

### Participants' level of risk

As the rate of events is higher in high-risk groups (by definition), it should require smaller sample sizes and shorter follow-up to observe an effect of an intervention in a high-risk group of participants (Davey Smith 1993). There have been suggestions that randomised controlled trials are unsuitable for assessing the effectiveness of interventions with very modest levels of effect in low-risk populations, because of the huge numbers of person-years of observation needed to gain sufficient statistical power to avoid Type II errors (Ebrahim 1997). However, with the publication of the Women's Health Initiative trial (WHI with CVD 2006; WHI without CVD 2006) we now have data on more cardiovascular events in people at low risk of cardiovascular disease than in people with moderate or high risk. The same is true for cardiovascular deaths and total mortality.

When endpoints such as total mortality are used, the situation becomes more difficult, as in low-risk groups the proportion of deaths which are unrelated to cardiovascular disease (and perhaps unlikely to be influenced by dietary fat changes) rises, again diluting any differences in the numbers of deaths between intervention and control groups. It is more likely that changes in cardiovascular deaths will be seen than in total mortality. The trend is certainly in this direction, with the pooled risk ratio for total mortality 0.97 (95% CI 0.90 to 1.05), and for cardiovascular mortality RR 0.95 (95% CI 0.80 to 1.12). Our best estimate is that SFA reduction results in a reduction of 5% in deaths due to cardiovascular disease, and a reduction of 3% in total deaths, but the confidence intervals are wide.

The high-risk participants in the dietary fat trials all show evidence of cardiovascular disease at baseline. Under current guidelines most high-risk participants with raised lipid levels should

be on lipid-lowering medication (ACC/AHA 2013; Fraker 2007; NICE 2014; O'Gara 2014). This raises the question of whether there is any additional advantage of adherence to a reduced SFA diet in addition to statin therapy. Little evidence exists at present to answer this question. However, in all parts of the world where drug budgets are restricted and use of lipid-lowering medication remains rationed even for those at high risk, the use of reduced SFA diets would appear to be a cost-effective option leading to considerable reductions in cardiovascular events for populations (and so in health budgets) in only a few years.

Low-risk participants are unlikely to be on lipid-lowering medication under current guidelines. The suggestion of protection of low-risk individuals from cardiovascular events, with a reduction of roughly 17% of events in just a few years of intervention, as there is no evidence that effects in the low-CVD-risk group are different from effects in the higher-risk groups, would appear to merit continued public health action.

A factor that may affect participant risk of cardiovascular disease, and also the effectiveness of reducing saturated fat intake, that has altered over time is the level of use of statins to control serum lipids in people at moderate and high risk of CVD. The 4S 1994 trial, which was the first trial to show that use of statins could reduce mortality in people with coronary heart disease, was published in 1994 and led to an explosion of the use of statins. For most health outcomes we saw no clear effect of a decade of publication on risk, but for combined CVD events and CHD events there were differences between subgroups. For combined CVD events there were reductions in risk with reduced saturated fat intakes in the 1960s, 1970s and 1990s (both trials published early in the decade), but no clear effect of reducing saturated fat in the 1980s (one trial with 283 events) or 2000s (three trials with more than 3400 events and over 49,000 participants). It is possible (but not clear) that participants in the trials published in the 2000s were protected by higher levels of statin use (statins were allowed in participants in the largest trial which we report as WHI with CVD 2006; WHI without CVD 2006).

# AUTHORS' CONCLUSIONS

## Implications for practice

Evidence supports the reduction of saturated fat to reduce cardiovascular events within the timescale of these dietary trials. Effects on total and cardiovascular mortality, at least on this timescale, are much less clear.

## Implications for research

To complement this review of long-term RCTs, we need reviews of metabolic studies to clarify the effects of specific replacements for saturated fat in the diet, and we need systematic reviews of cohort studies to clarify longer-term effects of saturated fat reductions.

The financial implications (costs and savings) of appropriate advice and legislation to modify fat intake in those at various levels of cardiovascular risk should be assessed and reflected in health policy. Whilst interventions to alter dietary fat intake in individuals at high cardiovascular risk have been fairly successful, such health promotion initiatives in the general population have been less successful. Further work is needed to help high- and low-risk individuals to make effective changes to reduce saturated fat and to maintain these changes over their lifetimes. Research into the effects of legislation to alter fat contents of foods, improved labelling, pricing initiatives and improved availability of healthier foods, linking food production and processing into the health agenda, may yield huge advances in this area.

It is not clear whether there is an additional benefit of reducing saturated fat in those at high risk of cardiovascular disease who are on lipid-lowering medication. Further research to examine the need for maintenance of reduced saturated fat whilst on lipid-lowering medication would be useful, but not as useful as understanding specific dietary fat replacements for saturated fat. However, we did not identify any relevant ongoing trials in our searches.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

**Black 1994**

| Methods | RCT |
|---|---|
| Participants | People with non-melanoma skin cancer (USA)<br>CVD risk: low<br>Control: randomised 67, analysed 58<br>Intervention: randomised 66, analysed 57<br>Mean years in trial: 1.9<br>% male: control 67%, intervention 54%<br>Age: mean control 52.3 (SD 13.2), intervention 50.6 (SD 9.7)<br>Ethnicity: white 100% (excluded from study if of Asian, Black, Hispanic or American Indian ancestry)<br>Statins use allowed: Unclear<br>% taking statins: Not reported |
| Interventions | Reduced fat vs usual diet<br>Control aims: no dietary advice<br>Intervention aims: total fat 20%E, protein 15%E, CHO 65%E<br>Control methods: no dietary change, 4-month intervals clinic examination by dermatologist<br>Intervention methods: 8 x weekly classes plus monthly follow-up sessions, with behavioural techniques being taught following individual approach (not clear if in a group or individual). 4-month intervals clinic examination by dermatologist<br>Intervention delivered face-to-face by a dietitian<br>Total fat intake, %E ("during study" months 4 - 24): cont 37.8 (SD 4.1), int 20.7 (SD 5.5) (mean difference -17.10, 95% CI -18.88 to -15.32) significant reduction<br>**Saturated fat intake, %E ("during study", months 4 - 24): cont 12.8 (SD 2.0), int 6.6 (SD 1.8), (mean difference -6.20, 95% CI -6.90 to -5.50) significant reduction**<br>PUFA intake, %E ("during study", months 4 - 24): cont 7.8 (SD 1.4), int 4.5 (SD 1.3) , (mean difference -3.30, 95% CI -3.79 to -2.81) significant reduction<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: Linoleic acid, Control 16.9 (SD 5.6) g, Int 8.5 (SD 3.3) g<br>MUFA intake, %E ("during study", months 4 - 24): cont 14.4 (SD 1.7), int 7.6 (SD 2. 2), (mean difference -6.80, 95% CI -7.52 to -6.08) significant reduction<br>CHO intake, %E ("during study", months 4 - 24): cont 44.6 (SD 6.9), int 60.3 (SD 6. 3), (mean difference 15.70, 95% CI 13.29 to 18.11) significant increase<br>Protein intake, %E ("during study", months 4 - 24): cont 15.7 (SD 2.4), int 17.7 (SD 2.2), (mean difference 2.00, 95% CI 1.16 to 2.84) significant increase<br>Trans fat intake: not reported<br>**Replacement for saturated fat: CHO and protein (by dietary aims and achievements)**<br>Style: diet advice<br>Setting: community |
| Outcomes | Stated trial outcomes: incidence of actinic keratosis and non-melanoma skin cancer<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes |

**Black 1994** (*Continued*)

| | |
|---|---|
| | Events available for combined cardiovascular events: cardiovascular deaths<br>Secondary outcomes: cancer deaths (none)<br>Tertiary outcomes: none (weight data provided, but no variance info) |
| Notes | **Study duration** 24 months.<br>**Study aim** was to achieve low-fat diet, but the study achieved a statistically significant reduction in saturated fat intake in the low-fat group compared to control<br>**SFA reduction achieved.**<br>**Total serum cholesterol: not reported**<br>At 2 years control -1.5 kg n = 50?, intervention -1 kg n = 51?<br>Trial dates: Study dates not reported (but still recruiting at first publication in 1994)<br>Funding: National Cancer Institute<br>Declarations of Interest of primary researchers: none stated, all authors work for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "list of randomly generated numbers" |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Physician blinding: adequate<br>Participant blinding: inadequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | For mortality. Unclear for other outcomes |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists asked for data |
| Free of systematic difference in care? | High risk | Minor, all have 4-monthly clinic visits, the intervention group had 8 behavioural technique classes that the control group did not have |
| Stated aim to reduce SFA | High risk | Aim to reduce SFA not stated |
| Achieved SFA reduction | Low risk | Statistically significant SFA reduction achieved |
| Achieved TC reduction | Unclear risk | Not reported |
| Other bias | Low risk | None noted |

**DART 1989**

| | |
|---|---|
| Methods | Factorial RCT |
| Participants | Men recovering from an MI (UK)<br>CVD risk: high<br>Control: randomised 1015, analysed unclear<br>Intervention: randomised 1018, analysed unclear<br>Mean years in trial: control 1.9, randomised 1.9<br>% male: 100%<br>Age: mean control 56.8, intervention 56.4 < 70)<br>Ethnicity: not stated<br>Statins use allowed? Unclear, but there do not appear to have been any medication-based exclusion criteria and included participants were taking anti-hypertensives, anti-anginals, anti-coagulants, anti-platelet, digoxin and "other cardiac drugs"<br>% taking statins: Not reported, but only 5.4% were taking "other cardiac drugs" which may have included statins |
| Interventions | Reduced and modified fat vs usual diet<br>Control aims: no dietary advice on fat, weight reducing advice if BMI > 30<br>Intervention aims: reduce fat intake to 30%E, increase P/S to 1.0, weight-reducing advice if BMI > 30<br>Note: This was a factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre<br>Control methods: dietitians provided 'sensible eating' advice without specific information on fats<br>Intervention methods: dietitians provided the participants and their wives with initial individual advice and a diet information sheet; participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months<br>Intervention delivered individually face-to-face by a dietitian<br>Total fat intake, %E (through study): cont 35 (SD 6), int 31 (SD 7) (mean difference -4.00, 95% CI -4.57 to -3.43) significant reduction<br>**Saturated fat intake, %E (through study): cont 15 (**SD**3), int 11 (**SD**3), (mean difference -4.00, 95% CI -4.26 to -3.74) significant reduction**<br>PUFA intake (through study): cont 7 (SD unclear), int 9 (SD unclear), (mean difference 2.00, 95% CI 1.57 to 2.43 assuming SDs of 5) significant increase<br>PUFA n-3 intake: EPA, Control 0.6 (SD 0.7) g/wk, Int 2.4 (SD 1.4) g/wk<br>PUFA n-6 intake: not reported<br>MUFA intake (through study): cont 13 (SD unclear), int 11 (SD unclear) (mean difference -2.00, 95% CI -2.43 to -1.57 assuming SDs of 5) significant reduction<br>CHO intake (through study): cont 44 (SD 6),int 46 (SD 7) (mean difference 2.00, 95% CI 1.43 to 2.57) significant increase<br>Protein intake (through study): cont 17 (SD 4), int 18 (SD 4) (mean difference 1.00, 95% CI 0.65 to 1.35) significant increase<br>Trans fat intake: not reported<br>**Replacement for saturated fat: PUFA and CHO (by dietary aims), PUFA, CHO and protein (by dietary achievements)**<br>Style: diet advice<br>Setting: community |

**DART 1989** (*Continued*)

| | |
|---|---|
| Outcomes | Stated trial outcomes: mortality, reinfarction<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: cardiovascular deaths (including stroke deaths) plus non-fatal MI<br>Secondary outcomes: cancer deaths, total MI, non-fatal MI, CHD mortality, CHD events (total MI)<br>Tertiary outcomes: total and HDL cholesterol |
| Notes | **Study duration** 24 months<br>**Study aim** was to achieve low fat diet with raised P/S ratio and saturated fat intake in the intervention group was significantly lower than in the control group<br>**SFA reduction aimed and achieved.**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0. 26 (95% CI -0.36 to -0.16), statistically significant reduction**<br>Estimated by subtraction (assuming total fat = SFA + PUFA + MUFA) or using the ratio (assuming P/S = PUFA/SFA)<br>Trial dates: Study dates not reported (published in 1989)<br>Funding: Welsh Scheme for the Development of Health and Social Research, Welsh Heart Research Foundation, Flora Project, Health Promotion Research Trust. (Seven Seas Health Care and Duncan Flockhart provided the MaxEPA capsules and Norgene provided 'Fybranta' tablets - but these were not used in the comparison discussed in this systematic review)<br>Declarations of Interest of primary researchers: none stated, all authors work for academic or health institutions |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | randomised using sealed envelopes |
| Allocation concealment (selection bias) | Unclear risk | Unclear if envelopes were opaque |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Physician blinding: yes<br>Participant blinding: unclear |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | GPs contacted for information on mortality and morbidity when participants did not attend |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as we asked all trialists for data |
| Free of systematic difference in care? | High risk | Different levels of advice appear to have been provided. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |

**DART 1989** (*Continued*)

| | | |
|---|---|---|
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | Low risk | Statistically significant TC fall |
| Other bias | Low risk | None noted |

**Houtsmuller 1979**

| | |
|---|---|
| Methods | RCT |
| Participants | Adults with newly-diagnosed diabetes (The Netherlands)<br>CVD risk: moderate<br>Control: 51 randomised, unclear how many analysed (all analysed re deaths)<br>Intervention: 51 randomised, unclear how many analysed (all re deaths)<br>Mean years in trial: unclear (max duration 6 years)<br>% male: 56% overall<br>Age: mean unclear<br>Baseline total fat intake: int cont<br>Baseline saturated fat intake: int cont<br>Ethnicity: not stated<br>Statins use allowed? Unclear<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Modified fat vs usual diet<br>Control aims: SFA 35%E, CHO 50%E, protein 15%E<br>Intervention aims: total fat 40%E, 1/3 linoleic acid, CHO 45%E, protein 15%E<br>Control methods: unclear, surveyed by dietitian<br>Intervention methods: unclear, surveyed by dietitian<br>Intervention appears to be delivered by dietitian but no clear details on format or frequency<br>Total fat intake: not reported<br>**Saturated fat intake: not reported (mean difference unclear)**<br>PUFA intake: not reported<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake: not reported<br>CHO intake: not reported<br>Protein intake: not reported<br>Trans fat intake: not reported<br>**Replacement for saturated fat: mainly PUFA (based on dietary aims)**<br>Style: diet advice?<br>Setting: community |
| Outcomes | Stated trial outcomes: progression of diabetic retinopathy<br>Data available on total mortality? no<br>Cardiovascular mortality? no |

**Houtsmuller 1979** (*Continued*)

| | |
|---|---|
| | Events available for combined cardiovascular events: total MI and angina<br>Secondary outcomes: total cholesterol, TGs (data read off graph), CHD mortality (fatal MI), CHD events (MI, angina) |
| Notes | Study duration 6 years. Study aim was for control group to take 35%E as saturated fat, and the intervention group 40%E from fat, of which 33% was from linoleic acid (so saturated fat < 27%E), but saturated fat intake during trial not reported<br>**SFA reduction aimed (unclear whether achieved).**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.47(95% CI -0.76 to -0.18), statistically significant reduction**<br>Trial dates: Study recruitment 1973 to (unclear)<br>Funding: Dutch Heart Foundation<br>Declarations of Interest of primary researchers: none stated, all authors work for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants matched in pairs then randomised |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Neither participants nor physicians appear blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as we asked all trialists for data |
| Free of systematic difference in care? | Unclear risk | Level and type of intervention unclear. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Unclear risk | SFA intake not reported |
| Achieved TC reduction | Low risk | Statistically significant TC fall |
| Other bias | Low risk | None noted |

**Ley 2004**

| | |
|---|---|
| Methods | RCT |
| Participants | People with impaired glucose intolerance or high normal blood glucose (New Zealand)<br>CVD risk: moderate<br>Control: unclear how many randomised (176 between both groups), unclear how many analysed (112 between both groups at 5 years)<br>Intervention: as above<br>Mean years in trial: 4.1 over whole trial<br>% male: control 80%, intervention 68%<br>Age: mean control 52.0 (SE 0.8), intervention 52.5 (SE 0.8)<br>Ethnicity: European 67% int, 77% control, Maori 11% int, 7% control, Pacific islander 20% int, 13% control, Other 3% int, 4% control (outcomes not provided by ethnicity)<br>Statins use allowed? Unclear<br>% taking statins: Not reported |
| Interventions | Reduced fat vs usual diet<br>Control aims: usual diet<br>Intervention aims: reduced fat diet (no specific goal stated)<br>Control methods: usual intake plus general advice on healthy eating consistent with the New Zealand guidelines and standard dietary information for people with nutrition-related problems upon entering the trial<br>Intervention methods: monthly small group meetings to follow a 1-year structured programme aimed at reducing fat in the diet, includes education, personal goal setting, self monitoring<br>Total fat intake, %E (at 1 year): int 26.1 (SD 7.7), cont 33.6 (SD 7.8) (mean difference -7.50, 95% CI -10.37 to -4.63) significant reduction<br>Intervention delivered in small face-to-face groups but unclear by whom<br>**Saturated fat intake, %E (at 1 year): cont 13.4 (SD 4.7), int 10.0 (SD 4.2) (mean difference -3.40, 95% CI -5.05 to -1.75) significant reduction**<br>PUFA intake, %E (at 1 year): cont 4.8 (SD 1.6), int 4.0 (SD 1.4) (mean difference -0.80, 95% CI -1.36 to -0.24) significant reduction<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E (at 1 year): cont 11.8 (SD 3.1), int 8.9 (SD 2.8) (mean difference -2.90, 95% CI -3.99 to -1.81) significant reduction<br>CHO intake, %E (at 1 year): cont 45.8 (SD 10.9), int 54.2 (SD 10.5) (mean difference 8.40, 95% CI 4.44 to 12.36) significant increase<br>Protein intake, %E (at 1 year): cont 16.6 (SD 3.9), int 18.4 (SD 3.5), (mean difference 1.80, 95% CI 0.43 to 3.17) significant increase<br>Trans fat intake: not reported<br>**Replacement for saturated fat: carbohydrate and protein (based on dietary achievements)**<br>Style: diet advice<br>Setting: community |
| Outcomes | Stated trial outcomes: lipids, glucose, blood pressure<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: MI, angina, stroke, heart failure<br>Secondary outcomes: total MI, stroke, cancer diagnoses, cancer deaths, CHD events (MI |

| | |
|---|---|
| | or angina)<br>Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs, BP |
| Notes | **Study duration** over 4 years<br>**Study aim** was to reduce total fat (not saturated fat), but saturated fat intake in the intervention group was significantly lower than in the control group<br>**SFA reduction achieved**.<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.05 (95% CI -0.46 to 0.36), NO statistically significant reduction and smaller than 0.20**<br>Trial dates: Recruitment 1988 to 1990<br>Funding: National Heart Foundation of New Zealand, Aukland Medical Research Foundation, Lotteries Medical Board and the Health Research Council of New Zealand<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Unmarked opaque envelopes were opened by the person recruiting, unable to alter allocation later |
| Allocation concealment (selection bias) | Low risk | Unmarked opaque envelopes were opened by the person recruiting, unable to alter allocation later |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants were not blinded, outcome assessors were |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear, deaths, cancer and CV events are drop-outs, trialists were asked for data - unclear if any data missing |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as we asked all trialists for data |
| Free of systematic difference in care? | High risk | See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | High risk | Aim to reduce SFA not stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | High risk | TC fall small (0.05 mmol/L only) and not statistically significant |
| Other bias | Low risk | None noted |

**Moy 2001**

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|---|---|
| Methods | RCT |
| Participants | Middle-aged siblings of people with early CHD, with at least 1 CVD risk factor (USA)<br>CVD risk: moderate<br>Control: randomised 132, analysed 118<br>Intervention: randomised 135, analysed 117<br>Mean years in trial: 1.9<br>% male: control 49%, intervention 55%<br>Age: control mean 45.7 (SD 7), intervention 46.2 (SD 7)<br>Ethnicity: African-American 18% int, 25% control (remainder of group ethnicity not described, and outcomes not presented by ethnicity)<br>Statins use allowed? Unclear (raised LDL cholesterol was a condition of entry, so use of statins probably minimal)<br>% taking statins: Not reported |
| Interventions | Reduced fat intake vs usual diet<br>Control aim: usual care<br>Intervention aim: total fat 40 g/d or less<br>Control methods: usual physician care with risk factor management at 0, 1 and 2 years<br>Intervention methods: Individualised counselling by trained nurse, appointments 6 - 8 weekly for 2 years<br>Intervention delivered individually, face-to-face by a trained nurse<br>Total fat intake, %E (at 2 years): int 34.1 (SD unclear), cont 38.0 (SD unclear) (mean difference -3.90, 95% CI -6.46 to -1.34 assuming SDs of 10) significant reduction<br>**Saturated fat intake, %E (at 2 years): int 11.5 (SD unclear), cont 14.4 (SD unclear) (mean difference -2.90, 95% CI -4.18 to -1.62 assuming SDs of 5) significant reduction**<br>PUFA intake: not reported<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake: not reported<br>CHO intake: not reported<br>Protein intake: not reported<br>Trans fat intake: not reported<br>**Replacement for saturated fat: unclear**<br>Style: diet advice<br>Setting: community |
| Outcomes | Stated trial outcomes: dietary intake<br>Data available on total mortality? yes, no deaths<br>Cardiovascular mortality? yes, no deaths<br>Events available for combined cardiovascular events: total MI, stroke, unstable angina, PVD and PTCA<br>Secondary outcomes: cancer diagnoses (no events), cancer deaths (none), stroke, total and non-fatal MI, CHD mortality (none), CHD events (MI or angina)<br>Tertiary outcomes: BMI, HDL and LDL cholesterol, TG |
| Notes | Study duration 2 years<br>**Study aim** was to reduce total fat based on ATPII dietary guidelines, and preliminary work established that this intervention reduced saturated fat and dietary cholesterol, and |

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|---|---|
| | saturated fat intake was significantly lower than in the control group<br>**SFA reduction aimed and achieved**<br>**Total serum cholesterol not reported, but LDL was, difference between intervention and control, mmol/L: -0.29 (95% CI -0.54 to -0.04), statistically significant reduction**<br>Trial dates: Study recruitment 1991 to 1994<br>Funding: National Institute of Nursing Research, General Clinical Research Center of the National Institutes of Health<br>Declarations of Interest of primary researchers: none stated, all authors work for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned via computerised schema after all eligible siblings from a family had been screened |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants and trialists clear about their allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear, deaths, cancer and CV events are drop-outs, trialists were asked for data - unclear if any data missing |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists asked for data |
| Free of systematic difference in care? | High risk | Differences in frequency of follow up, but unclear what differences in care occurred between the physician and nurse-led care. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | Low risk | Statistically significant LDL fall (though TC not reported) |
| Other bias | Low risk | None noted |

**MRC 1968**

| | |
|---|---|
| Methods | RCT |
| Participants | Free-living men who have survived a first MI (UK)<br>CVD risk: high<br>Control: randomised 194, analysed 181 at 2 years<br>Intervention: randomised 199, analysed 172 at 2 years<br>Mean years in trial: control 3.7, intervention 3.8<br>% male: 100<br>Age: unclear (all < 60)<br>Ethnicity: not stated<br>Statins use allowed? Unclear (anti-coagulants allowed, but few other medications appear to have been used)<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Modified fat vs usual diet<br>Control aims: usual diet<br>Intervention aims: reduce dietary fat to 35 g fat per day, add 84 g soya oil per day<br>Control methods: usual diet plus reducing diet (reduced CHO) for weight management for overweight men<br>Intervention methods: instructed to follow a dietary regimen removing saturated fat from the diet plus daily dose of 85 g soya oil; half of it had to be taken unheated. Reduced CHO diet for weight management in overweight men<br>Intervention appears to be delivered and supervised by trial dietitian but unclear how often<br>Total fat intake, %E (at 3.5 years): int 46 (SD unclear), cont 43 (SD unclear) (mean difference 3.00, 95% CI 0.91 to 5.09 assuming SDs of 10) significant increase<br>**Saturated fat intake: not reported (mean difference unclear)**<br>PUFA intake: not reported<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake: not reported<br>CHO intake: not reported<br>Protein intake: not reported<br>Trans fat intake: not reported<br>**Replacement for saturated fat: mainly PUFA (based on dietary goals)**<br>Style: diet advice & supplement (soy oil)<br>Setting: community |
| Outcomes | Stated trial outcomes: MI or sudden death<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: cardiovascular deaths and fatal or non-fatal MI<br>Secondary outcomes: total and non-fatal MI, stroke, cancer deaths, CHD mortality, CHD events (CHD mortality or non-fatal MI)<br>Tertiary outcomes: none (data for weight, total cholesterol and BP, but no variance info) |
| Notes | Study duration over 6 years<br>**Study aim** for intervention "saturated fats were replaced by polyunsaturated fats", but saturated fat intakes during trial were not reported |

**MRC 1968** (*Continued*)

| | |
|---|---|
| | **SFA reduction aimed**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0. 64 (95% CI unclear), reduction > 0.20**<br>For all, data at 4 years, control n = 89, intervention n = 88<br>Weight change: control -3 kg, intervention 0 kg<br>Total cholesterol change: control -0.47 mmol/L, intervention -1.11 mmol/L<br>Systolic BP change: control 0 mmHg, intervention +2 mmHg<br>Diastolic BP change: control +3 mmHg, intervention -1 mmHg<br>Trial dates: Study recruitment 1960 to 1965, analysed 1967<br>Funding: Medical Research Council<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "using random numbers, by blocks within hospitals" |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Physician blinding: adequate<br>Participant blinding: inadequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Data collection was thorough, but some participants dropped out and contact was lost, so some events may have been missed |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | High risk | Unlikely as control group continued diet as usual, intervention group were likely to have had additional contact. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Unclear risk | SFA intake not reported |
| Achieved TC reduction | Low risk | Although statistical significance was not reported or calculable, TC in the intervention group was 0.64 mmol/L lower than in the control group, a large fall (and almost certainly statistically significant) |
| Other bias | Low risk | None noted |

**Oslo Diet-Heart 1966**

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|---|---|
| Methods | RCT |
| Participants | Men with previous MI (Norway)<br>CVD risk: high<br>Control: randomised 206, analysed 148 (at 5 years)<br>Intervention: randomised 206, analysed 152 (at 5 years)<br>Mean years in trial: control 4.3, intervention 4.3<br>% male: 100<br>age: mean control 56.3, intervention 56.2 (all 30 - 67)<br>Ethnicity: ethnicity not mentioned<br>Statins use allowed? Unclear (medications not mentioned as exclusion criteria, most appeared to be on anti-coagulant medications, statins not mentioned)<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Modified fat diet vs control<br>Control aims: no dietary advice but direct questions answered, supplement = 1 vitamin tablet daily<br>Intervention aims: reduce meat and dairy fats, increase fish, vegetables, supplement - 1 vitamin tablet daily, 0.5 L soy bean oil per week (free to 25% of participants), sardines in cod liver oil (free at certain times to encourage compliance)<br>Control methods: usual diet<br>Intervention methods: continuous instruction and supervision by dietitian, including home visits, letters and phone calls<br>Total fat intake: unclear (note - intake of total fat, carbohydrate, protein and sugar was assessed in 17 "especially conscientious and positive" as well as intelligent dieters, but this is not reported here as unlikely to be representative, and lacking control group data)<br>**Saturated fat intake: unclear (mean difference unclear)**<br>PUFA intake: unclear<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake: unclear<br>CHO intake: unclear<br>Protein intake: unclear<br>Trans fat intake: unclear<br>**Replacement for saturated fat: PUFA (based on dietary goals)**<br>Style: diet advice and supplement (food)<br>Setting: community |
| Outcomes | Stated trial outcomes: coronary heart disease morbidity and mortality<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: total MI, sudden death, stroke, angina<br>Secondary outcomes: non-fatal and total MI, stroke, CHD mortality (fatal MI and sudden death), CHD events (MI, angina and sudden death)<br>Tertiary outcomes: weight, total cholesterol, systolic and diastolic BP (but no variance information is provided) |

| | |
|---|---|
| Notes | Study duration over 4 years<br>**Study aim** was to reduce serum cholesterol by a diet "low in saturated fats and in cholesterol, and rich in highly unsaturated fats", saturated fat intakes during study were not reported<br>**SFA reduction aimed (reduction unclear as not measured except in a highly compliant subgroup)**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -1.07 (95% CI unclear), reduction > 0.20**<br>Weight change from baseline was -0.5 kg in the control group (n ~ 155), -2.5 kg in the intervention group (n ~ 160) to 51 months<br>Total cholesterol change from baseline was -0.46 mmol/L in the control group and -1.53 mmol/L in the intervention group at 51 months<br>Systolic BP at baseline was 153.8 mmHg in control and 159.0 in intervention, and mean sBP through trial was 154.3 mmHg in control and 158.2 mmHg in the intervention group<br>Diastolic BP at baseline was 93.5 mmHg in control and 97.1 mmHg in intervention, through trial mean dBP was 95.5 mmHg in control and 98.6 mmHg in intervention participants<br>Trial dates: Recruitment 1956 to 1958<br>Funding: Det Norske Råd for Hjerte- og karsyk-dommer, A/S Freia Chokoladefabriks Arbeidsfond for Ernærings-forskning, JL Tiedemanns Tobaksfabrik Joh H Andresens medisinske fond, plus A/S Farmacöytisk Industri provided a multivitamin free of charge, DE-NO-FA and Lillleborg Fabriker provided soy bean oil at reduced prices, the Research Laboratory of the Norwegian Canning Industry, Stavanger Preserving Co and Kommendal Packing Comp provided Norwegian sardines in cod liver oil free to those in the intervention group<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "table of random numbers used", by Prof Knut Westlund |
| Allocation concealment (selection bias) | Low risk | Randomisation appears to have occurred before medical examination within the study |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants were aware of their allocation as was the main trialist. Outcomes were categorised by a diagnostic board, but their blinded status was unclear |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The participants who could not be directly followed up for the 5 years were followed until death or study end through personal interviews, or contact with their physicians or relatives |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |

**Oslo Diet-Heart 1966** (*Continued*)

| | | |
|---|---|---|
| Free of systematic difference in care? | High risk | Dietetic input level very different, although medical care appeared similar. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Unclear risk | SFA intake not reported |
| Achieved TC reduction | Low risk | Although statistical significance was not reported or calculable, TC in the intervention group was 1.07 mmol/L lower than in the control group, a large fall (and almost certainly statistically significant) |
| Other bias | Low risk | None noted |

**Oxford Retinopathy 1978**

| | |
|---|---|
| Methods | RCT |
| Participants | Newly-diagnosed non-insulin-dependent diabetics (UK)<br>CVD risk: moderate<br>Control: randomised unclear (249 split between the 2 groups, 125?), analysed for mortality unclear (all but 2 overall at 16 years)<br>Intervention: randomised unclear (249 split between the 2 groups, 125?), analysed as above<br>Mean years in trial: overall 9.3?<br>% male: overall 49<br>Age: mean overall 47.1 (all < 65)<br>Ethnicity: not stated<br>Statins use allowed? Unclear<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Reduced and modified dietary fat vs average diet<br>Control aims: total fat 40%E, PUFA 12%E, protein 20%E, CHO 40%E (reducing simple sugars), 1500 kcal/day<br>Intervention aims: total fat 26%E, PUFA 16%E, protein 20%E, CHO 54%E (reducing simple sugars), 1500 kcal/day<br>Control methods: dietary advice from diabetes dietitian<br>Intervention methods: dietary advice from diabetes dietitian<br>Total fat intake, %E (at 7 - 9 years)§: int 32 (SD unclear), cont 41 (SD unclear) (mean difference -9.00, 95% CI -11.48 to -6.52 assuming SDs of 10) significant reduction<br>**Saturated fat intake, %E (at 7 - 9 years)§: int 10.7 (SD unclear), cont 20.4 (SD unclear) (mean difference -9.70, 95% CI -10.94 to -8.46 assuming SD of 5) significant reduction**<br>PUFA intake, %E (at 7 - 9 years)§: int 11.8 (SD unclear), cont 2.1 (SD unclear) (mean difference 9.70, 95% CI 8.46 to 10.94 assuming SDs of 5) significant increase<br>PUFA n-3 intake: not reported |

**Oxford Retinopathy 1978** (*Continued*)

| | |
|---|---|
| | PUFA n-6 intake: not reported<br>MUFA intake, %E (at 7 - 9 years)§: int 9.5 (SD unclear), cont 18.6 (SD unclear) (mean difference -9.10, 95% CI -10.34 to 7.86 assuming SDs of 5) significant reduction<br>Carbohydrate intake: not reported<br>Protein intake: not reported<br>Trans fat intake: not reported<br>**Replacement for saturated fat: PUFA and CHO (based on dietary goals and achievements)**<br>Style: diet advice<br>Setting: community (outpatients clinic) |
| Outcomes | Stated trial outcomes: retinopathy<br>Data available on total mortality? yes, but unable to ascertain from which intervention groups (34 deaths at 10 years)<br>Cardiovascular mortality? no<br>Events available for combined cardiovascular events: none<br>Secondary outcomes: none<br>Tertiary outcomes: BMI, total cholesterol |
| Notes | Study duration over 9 years<br>**Study aim** was to reduce total fat and increase PUFAs (so reducing saturates), and saturated fat intake in the intervention group was significantly lower than in the control group<br>**SFA reduction achieved.**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: 0.07 (95% CI -0.34 to 0.48), NO statistically significant reduction and smaller than 0.20**<br>§validity of these data is questionable as it represents only 3 intervention and 3 control participants. Source: Lopez-Espinoza 1984<br>Trial dates: Recruitment 1973 to 1976<br>Funding: Oxford Diabetes Trust, British Diabetic Association, International Sugar Research Foundation Inc<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "random number sequence, provided and allotted by a separate agency" (Prof Richard Peto) |
| Allocation concealment (selection bias) | Low risk | "random number sequence, provided and allotted by a separate agency" (Prof Richard Peto) |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants not blinded, physicians unclear |

**Oxford Retinopathy 1978** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | Low risk | Dietetic advice for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | High risk | Aim to reduce SFA not stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | High risk | No statistically significant TC fall, and difference only 0.07 mmol/L |
| Other bias | Low risk | None noted |

**Rose corn oil 1965**

| | |
|---|---|
| Methods | RCT |
| Participants | Men (?) with angina or following MI (UK)<br>CVD risk: high<br>Control: randomised 26, analysed 18<br>Intervention - corn: randomised 26, analysed 13<br>Mean years in trial: control 1.7, corn 1.5<br>% male: unclear (100%?)<br>Age: mean control 58.8, corn 52.6 (all <70)<br>Ethnicity: not stated<br>Statins use allowed? Unclear (anti-coagulants not allowed, but all participants received conventional treatments at the discretion of their physicians)<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Modified fat vs usual diet<br>Control aims: usual diet<br>Intervention aims - corn: restrict dietary fat, plus 80 g/day corn oil provided<br>Control methods: usual physician care plus follow-up clinic monthly, then every 2 months, no dietary fat advice or oil provided<br>Intervention methods: usual physician care plus follow-up clinic monthly, then every 2 months, dietary fat advice plus oil provided<br>Unclear how the advice was delivered or by whom<br>Total fat intake, %E (at 18 months): corn 50.5 (SD unclear), cont 32.6 (SD unclear) (mean difference 17.90, 95% CI 10.77 to 25.03 assuming SDs of 10) significant increase<br>**Saturated fat intake: unclear (mean difference unclear)**<br>PUFA intake: unclear<br>PUFA n-3 intake: not reported |

| | |
|---|---|
| | PUFA n-6 intake: not reported<br>MUFA intake: unclear<br>CHO intake, %E (at 18 months): corn 36.5 (SD unclear), cont 51.5 (\|SD unclear) (mean difference -15.00, 95% CI -29.27 to -0.73 assuming SDs of 20) significant reduction<br>Protein intake, %E (at 18 months): corn 11.0 (SD unclear), cont 13.2 (SD unclear) (mean difference -2.20, 95% CI -5.77 to 1.37 assuming SDs of 5) no significant difference<br>Trans fat intake: unclear<br>**Replacement for saturated fat: mainly PUFA (based on aims and achievements)**<br>Style: diet advice and supplement (oil)<br>Setting: community |
| Outcomes | Stated trial outcomes: cardiac events<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke<br>Secondary outcomes: stroke (none), non-fatal and total MI, CHD mortality (fatal MI and sudden death), CHD events (all MI and sudden death)<br>Tertiary outcomes: total cholesterol |
| Notes | Study duration 2 years<br>**Study aim** was to reduce total fat (by restricting fatty meat, sausages, pastry, ice cream, cheese, cake, milk, eggs and butter) and prescribe vegetable oil (so reducing saturates), but saturated fat intakes during intervention were not reported<br>**SFA reduction aimed (but unclear whether achieved as SFA intake not reported)**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0. 58 (95% CI -1.42 to 0.26), NO statistically significant reduction but > 0.20**<br>Trial dates: unclear, published in 1965<br>Funding: probably unfunded (they thank the Paddington General Hospital for clinic facilities, and St Mary's and Paddington General Hospital physicians for referral of patients, but no funding acknowledged)<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "sealed envelopes" |
| Allocation concealment (selection bias) | Unclear risk | Unclear if envelopes were opaque |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Physician blinding: inadequate<br>Participant blinding: inadequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Some lost to follow-up by 2 years, so some events may have been missed |

**Rose corn oil 1965** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | Low risk | All received conventional treatments at the discretion of the physicians, all attended a special follow-up clinic. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Unclear risk | SFA intake not reported |
| Achieved TC reduction | High risk | Although the TC in the intervention group was 0.58 mmol/L lower than in the control group, this was not statistically significant in this small study |
| Other bias | Low risk | None noted |

**Rose olive 1965**

| | |
|---|---|
| Methods | RCT |
| Participants | Men (?) with angina or following MI (UK)<br>CVD risk: high<br>Control: randomised 26, analysed 18<br>Intervention - olive: randomised 28, analysed 12<br>Mean years in trial: control 1.7, olive 1.5<br>% male: unclear (100%?)<br>Age: mean control 58.8, olive 55.0 (all < 70)<br>Ethnicity: Not stated<br>Statins use allowed? Unclear (anti-coagulants not allowed, but all participants received conventional treatments at the discretion of their physicians)<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Modified fat vs usual diet<br>Control aims: usual diet<br>Intervention aims -olive: restrict dietary fat, plus 80 g/day olive oil provided<br>Control methods: usual physician care plus follow-up clinic monthly, then every 2 months, no dietary fat advice or oil provided<br>Intervention methods: usual physician care plus follow-up clinic monthly, then every 2 months, dietary fat advice plus oil provided<br>Unclear how the advice was delivered or by whom<br>Total fat intake, %E (at 18 months): olive 46.2 (SD unclear), cont 32.6 (SD unclear) (mean difference 13.60, 95% CI 6.30 to 20.90 assuming SDs of 10) significant increase<br>**Saturated fat intake: unclear (mean difference unclear)**<br>PUFA intake: unclear<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported |

**Rose olive 1965** (*Continued*)

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|---|---|
| | MUFA intake: unclear<br>CHO intake, %E (at 18 months): olive 42.2 (SD unclear), cont 51.5 (SD unclear) (mean difference -9.30, 95% CI -23.91 to 5.31 assuming SDs of 20) no significant difference<br>Protein intake, %E (at 18 months): olive 9.6 (SD unclear), cont 13.2 (SD unclear) (mean difference -3.60, 95% CI -7.25 to 0.05 assuming SDs of 5) no significant difference<br>Trans fat intake: unclear<br>**Replacement for saturated fat: mainly MUFA (based on dietary aims)**<br>Style: diet advice and supplement (oil)<br>Setting: community |
| Outcomes | Stated trial outcomes: cardiac events<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke<br>Secondary outcomes: stroke (none), non-fatal and total MI, CHD mortality (fatal MI and sudden death), CHD events (all MI and sudden death)<br>Tertiary outcomes: total cholesterol |
| Notes | Study duration 2 years<br>**Study aim** was to reduce total fat (by restricting fatty meat, sausages, pastry, ice cream, cheese, cake, milk, eggs and butter) and prescribe vegetable oil (so reducing saturates), but saturated fat intakes during intervention were not reported<br>**SFA reduction aimed (but unclear whether achieved as SFA intake not reported)**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: 0.30 (95% CI -0.93 to 1.53), NO statistically significant reduction, mean total cholesterol rose**<br>Trial dates: unclear, published in 1965<br>Funding: probably unfunded (they thank the Paddington General Hospital for clinic facilities, and St Mary's and Paddington General Hospital physicians for referral of patients, but no funding acknowledged)<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

**Simon 1997**

| Methods | RCT |
|---|---|
| Participants | Women with a high risk of breast cancer (USA)<br>CVD risk: low<br>Control: randomised 96, analysed 75<br>Intervention: randomised 98, analysed 72<br>Mean years in trial: control 1.8, intervention 1.7<br>% male: 0<br>Age: mean control 46, intervention 46<br>Ethnicity: White 89%, African-American 9%, Hispanic 2%<br>Statins use allowed? No (those on lipid-lowering medications were excluded)<br>% taking statins: 0% |
| Interventions | Reduced fat vs usual diet<br>Control aims: usual diet<br>Intervention aims: total fat 15%E<br>Control methods: continued usual diet |

| | |
|---|---|
| | Intervention methods: Bi-weekly individual dietetic appointments over 3 months followed by monthly individual or group appointments, including education, goal setting, evaluation, feedback and self monitoring<br>Intervention delivered face-to-face by a dietitian<br>Total fat intake, %E (at 12 months)§: int 17.6 (SD 5.8), cont 33.8 (SD 7.4) (mean difference -16.20, 95% CI -18.34 to -14.06) significant reduction<br>**Saturated fat intake, %E (at 12 months)§: int 6.0 (SD 3.0), cont 12.1 (SD 5.2) (mean difference -6.10, 95% CI -7.47 to -4.73) significant reduction**<br>PUFA intake, %E (at 12 months)§: int 3.8 (SD 1.7), cont 7.3 (SD 4.1) (mean difference -3.50, 95% CI -4.51 to -2.49) significant reduction<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E (at 12 months)§: int 6.1 (SD 3.0), cont 12.8 (SD 6.3) (mean difference -6.70, 95% CI -8.29 to -5.11) significant reduction<br>CHO intake: not reported<br>Protein intake: not reported<br>Trans fat intake: not reported<br>**Replacement for saturated fat: unclear, either carbohydrate or protein (based on aims and achievements)**<br>Style: diet advice<br>Setting: community |
| Outcomes | Stated trial outcomes: intervention feasibility<br>Data available on total mortality? yes (2 deaths, but not clear in which arms)<br>Cardiovascular mortality? no<br>Events available for combined cardiovascular events: none<br>Secondary outcomes: cancer diagnosis (8 diagnoses, but not clear in which arms)<br>Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs |
| Notes | Study duration 2 years<br>**Study aim** was to reduce total fat to 15%E (saturated fat not mentioned), but saturated fat intake in the intervention group was significantly lower than in the control group<br>**SFA reduction achieved**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.34 (95% CI -0.64 to -0.04), statistically significant reduction**<br>§Kasim 1993<br>Trial dates: Recruitment 1987 to 1989<br>Funding: Marilyn J Smith Fund, Harper-Grace Hospitals, the Wesley Foundation, National Cancer Institute, Karmanos Cancer Institute Core Grant, the United Foundation of Detroit<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions except PN Kim who was affiliated with Wesley Health Strategies (now Health Strategies, which offers a "full-service health and fitness centre with an educated fitness staff and spacious workout areas", see healthstrategiesfitness.com/) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Simon 1997** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Stratified by age and randomised (block size 2) |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants knew their allocation, unclear whether physicians did |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | High risk | Very different contact time with dietitian, but medical appointments same in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | High risk | Aim to reduce SFA not stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | Low risk | Statistically significant TC fall |
| Other bias | Low risk | None noted |

**STARS 1992**

| | |
|---|---|
| Methods | RCT |
| Participants | Men with angina referred for angiography (UK)<br>CVD risk: high<br>Control: unclear randomised (30?), analysed 24<br>Intervention: unclear how many randomised (30?), analysed 26<br>Mean years in trial: control 2.9, intervention 3.0<br>% male: 100<br>age: mean control 53.9, intervention 48.9 (all < 66)<br>Ethnicity: not stated<br>Statins use allowed? No (1 arm of the trial, not described here, prescribed cholestyramine)<br>% taking statins: 0% |
| Interventions | Reduced and modified fat diet vs usual diet<br>Control aims: no diet intervention but advised to lose weight if BMI > 25<br>Intervention aims: total fat 27%E, SFA 8 - 10%E, omega-3 and omega-6 PUFA 8%E, increase in plant-derived soluble fibre, dietary cholesterol 100 mg/1000 kcal, advised to lose weight if BMI > 25 |

| | |
|---|---|
| | Control methods: usual care but no formal dietetic counselling. They were counselled against smoking if appropriate and advised about daily exercise level<br>Intervention methods: Usual care plus dietetic individual assessment of diet and advice. Further dietetic counselling and food stuffs were given to participants who did not achieve or maintain certain levels of serum cholesterol reduction<br>Initial intervention was delivered individually face-to-face by a dietitian and follow-up by a clinician<br>Total fat intake, %E (through study): int 27 (SD 7), cont 37 (SD 5) (mean difference -10.00, 95% CI -13.35 to -6.65) significant reduction<br>**Saturated fat intake, %E (through study): int 9 (SD 3), cont 16 (SD 4) (mean difference -7.00, 95% CI -8.97 to -5.03) significant reduction**<br>PUFA intake, %E (through study)§: int 7 (SD 2), cont 5 (SD 2) (mean difference 2.00, 95% CI 0.89 to 3.11) significant increase<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E (through study)§: int 10 (SD 4), cont 17 (SD 5) (mean difference -7.00, 95% CI -9.52 to -4.48) significant reduction<br>CHO intake, %E (through study)§: int 49 (SD 7), cont 41 (SD 7) (mean difference 8.00, 95% CI 4.12 to 11.88) significant increase<br>Protein intake, %E (through study)§: int 19 (SD 4), cont 18 (SD 2) (mean difference 1.00, 95% CI -0.73 to 2.73) no significant effect<br>Trans fat intake: not reported<br>**Replacement for saturated fat: CHO and PUFA (based on aims and achievements)**<br>Style: diet advice<br>Setting: community |
| Outcomes | Stated trial outcomes: angiography<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke, CABG, angioplasty, stroke, total MI, , CHD events, plus cancer deaths (none)<br>Secondary outcomes: total, HDL, LDL cholesterol, TGs, total/HDL and LDL/HDL ratios, 2-hour post-load glucose (weight and BP "remained similar" but were not reported, Lp(a) reported but as geometric means) |
| Notes | Study duration 3 years<br>**Study aim** was to reduce saturated fats (to 8 - 10%E), and saturated fat intake in the intervention group was significantly reduced<br>**SFA reduction aimed and achieved**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.76 (95% CI -1.19 to -0.33), statistically significant reduction**<br>§Blann 1995<br>Trial dates: Study dates not reported (published in 1992)<br>Funding: Unilever plc, the Chemical Pathology Fund of St Thomas' Hospital, and Bristol-Meyers Ltd<br>Declarations of Interest of primary researchers: none stated, all authors work for academic or health institutions |

**STARS 1992** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "blinded random cards issued centrally by statistician advisor" |
| Allocation concealment (selection bias) | Low risk | "blinded random cards issued centrally by statistician advisor" |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Physician blinding: unclear<br>Participant blinding: inadequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | High risk | Usual care in both groups, dietetic counselling only in the intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | Low risk | Statistically significant TC fall |
| Other bias | Low risk | None noted |

**Sydney Diet-Heart 1978**

| | |
|---|---|
| Methods | RCT |
| Participants | Men with previous MI (Australia)<br>CVD risk: high<br>Control: randomised 237, analysed 221 at 2 years<br>Intervention: randomised 221, analysed 205 at 2 years<br>Mean years in trial: control 4.3, intervention 4.3<br>% male: 100<br>Age: mean control 49.1 (SD 6.5), intervention 48.7 (SD 6.8)<br>Ethnicity: not stated<br>Statins use allowed? Unclear (use of medication did not appear to be an exclusion criteria)<br>% taking statins: Not reported (probably none as too early, pre-1980) |

**Sydney Diet-Heart 1978** (*Continued*)

| | |
|---|---|
| Interventions | Modified fat diet vs usual diet<br>Control aims: reduction in energy if overweight, no other specific dietary advice, allowed to use PUFA margarine instead of butter<br>Intervention aims: SFA 10%E, PUFA 15%E, reduction in energy if overweight, dietary chol < 300 mg/day<br>Control methods: no specific dietary instruction (except re weight)<br>Intervention methods: advised and tutored individually, diet assessed 3 times in 1st year and twice annually thereafter<br>Intervention was delivered face-to-face individually but unclear by whom<br>Total fat intake, %E ("during follow up"): int 38.3 (SD 5.9), cont 38.1 (SD 5.4) (mean difference 0.20, 95% CI -0.88 to 1.28) no significant difference<br>**Saturated fat intake, %E ("during follow up"): int 9.8 (SD 2.6), cont 13.5 (SD 3. 2) (mean difference -3.70, 95% CI -4.25 to -3.15) significant reduction**<br>PUFA intake, %E ("during follow up"): int 15.1 (SD 4.3), cont 8.9 (SD 3.5) (mean difference 6.20, 95% CI 5.45 to 6.95) significant increase<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E ("during follow up"): int 11.5 (SD 2.1), cont 13.8 (SD 2.5) (mean difference -2.30, 95% CI -2.74 to -1.86) significant reduction<br>CHO intake, %E ("during follow up"): int 40.9 (SD 7.3), cont 40.3 (SD 7.3) (mean difference 0.60, 95% CI -0.79 to 1.99) no significant difference<br>Protein intake, %E ("during follow up"): int 15.2 (SD 2.8), cont 15.7 (SD 3.4) (mean difference -0.50, 95% CI -1.09 to 0.09) no significant difference<br>Trans fat intake: not reported<br>**Primary replacement for saturated fat: mainly PUFA (based on dietary aims and achievements)**<br>Style: diet advice<br>Setting: community |
| Outcomes | Stated trial outcomes: cardiovascular mortality and morbidity<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes (exact events included not stated)<br>Events available for combined cardiovascular events: none<br>Secondary outcomes: CHD deaths (exact events included not stated)<br>Tertiary outcomes: total cholesterol, TG, BMI, sBP, dBP |
| Notes | Study duration 7 years<br>**Study aim** was saturated fat 10%E, and saturated fat intake in the intervention group was less than 80% of that in the control (73%)<br>**SFA reduction aimed and achieved**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0. 30 (95% CI -0.51 to -0.09), statistically significant reduction**<br>Trial dates: Recruitment 1966 to [unclear] and followed for 2 to 7 years<br>Funding: Life Insurance Medical Research Fund of Australia and New Zealand<br>Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

**Sydney Diet-Heart 1978** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "random numbers" |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Physician blinding: adequate<br>participant blinding: inadequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Survival analysis used |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | High risk | Advice and follow-up in intervention group, not in control. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | Low risk | Statistically significant TC fall |
| Other bias | Low risk | None noted |

**Veterans Admin 1969**

| | |
|---|---|
| Methods | RCT |
| Participants | Men living at the Veterans Administration Center (USA)<br>CVD risk: low<br>Control: randomised 422, analysed 422<br>Intervention: randomised 424, analysed 424<br>Mean years in trial: control 3.7, intervention 3.7<br>% male: 100<br>Age: mean control 65.6, intervention 65.4 (all 54 - 88)<br>Ethnicity: White 90%, African-American 7%, Asian 1%, Mexican 1%, other 1%<br>Statins use allowed? Unclear (only 4 participants were taking nicotinic acid, 17 diuretics, 56 digitalis, none on heparin)<br>% taking statins: Not reported (probably none as too early, pre-1980) |
| Interventions | Modified fat vs usual diet<br>Control aims: provided, total fat 40%E<br>Intervention aims: total fat 40%E, % of SFA replaced by unsaturated fats, dietary chol reduced |

| | |
|---|---|
| | Control methods: whole diet provided<br>Intervention methods: whole diet provided<br>Total fat intake, %E (during trial): int 38.9 (SD unclear), cont 40 (SD unclear) (mean difference -1.10, 95% CI -2.45 to 0.25 assuming SDs of 10) no significant difference<br>**Saturated fat intake, %E (during trial): int 8.3 (SD unclear), cont 18.5 (SD unclear) (mean difference -10.20, 95% CI -10.87 to -9.53 assuming SDs of 5) significant reduction**<br>PUFA intake, %E (during trial)§: int 16.0 (SD ?), cont 4.9 (SD 0.10) (mean difference 11.10, 95% CI 10.62 to 11.58 assuming missing SD was 5) significant increase<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E (during trial): not reported, approx int 14.0, cont 17.2 (mean difference -3.20, 95% CI -3.87 to -2.53) significant reduction<br>CHO intake, %E (during trial): not reported, approx int 45.9, cont 44.8 (mean difference 1.10, 95% CI -1.60 to 3.80 assuming SDs of 20) no significant difference<br>Protein intake, %E (during trial)§: int 15.2 (SD ?), cont 15.2 (SD ?) (mean difference 0.00, 95% CI -0.67 to 0.67 assuming SDs of 5) no significant difference<br>Trans fat intake: not reported<br>**Replacement for saturated fat: mainly PUFA (based on dietary aims and achievements)**<br>Style: diet provided<br>Setting: residential institution |
| Outcomes | Stated trial outcomes: mortality, heart disease<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: sudden death, definite MI, definite stroke, angina, PV events<br>Secondary outcomes: cancer deaths, cancer diagnoses, stroke, non-fatal MI, total MI, CHD deaths (fatal MI and sudden death due to CHD), CHD events (any MI or sudden death due to CHD)<br>Tertiary outcomes: none (some data on total cholesterol, but no variance info) |
| Notes | Study duration over 8 years<br>**Study aim** was to replace 66% of saturated fat by unsaturated fats, and saturated fat intake in the intervention group was significantly lower than in control<br>**SFA reduction aimed and achieved**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.37 (95% CI -0.77 to 0.03), NO statistically significant reduction but reduction > 0.20**<br>§Dayton 1965<br>Estimated by subtraction (assuming total fat = SFA + PUFA + MUFA or energy intake = energy from fat + CHO + protein)<br>Trial dates: Recruitment 1959 to 1967<br>Funding: Veterans Administration, Aruthur Dodd Fuller Foundation, National Heart Institute, Los Angeles County Heart Association, plus gifts of foods from Mazola corn oil and Mazola margarine, the National Soybean Processors Association, Pitman-Moore Company (Emdee margarine) and Hi-Saff Imitation Ice-cream from Frozen Desserts Company. Edgmar Farms donated milk refrigeration equipment |

**Veterans Admin 1969** (*Continued*)

| | |
|---|---|
| | Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "table of random numbers used" |
| Allocation concealment (selection bias) | Unclear risk | Randomisation method not clearly described |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | physician blinding: adequate<br>participant blinding: adequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All followed up via Veterans Admin system |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | Low risk | All ate centre food as usual. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | High risk | No statistically significant TC fall, though fall was > 0.20 mmol/L |
| Other bias | Low risk | None noted |

**WHI with CVD 2006**

| | |
|---|---|
| Methods | RCT |
| Participants | Post-menopausal women aged 50 - 79 with CVD at baseline (USA)<br>CVD risk: high<br>Control: randomised 1369, analysed 1369<br>Intervention: randomised 908, analysed 908<br>Mean years in trial: control 8.1, intervention 8.1<br>% male: 0<br>Age: mean (women both with and without CVD at baseline) int 62.3 (SD 6.9), control 62.3 (SD 6.9)<br>Ethnicity (women both with and without CVD at baseline): white 82%, black 11%, Asian or pacific islander 2%, unknown 1%, American Indian or Alaskan native < 1%. |

| | |
|---|---|
| | No statistically significant effects of the intervention on CHD events was seen for any ethnic subgroup<br>Statins use allowed? Yes<br>% taking statins: 12% of women recruited were on lipid-lowering medication (these were a mixture of participants with and without CVD at baseline) |
| Interventions | Reduced fat vs usual diet<br>Control: diet-related education materials<br>Intervention: low-fat diet (20%E from fat), reducing saturated fat to 7%E, with increased fruit and vegetables<br>Control methods: given copy of 'Dietary Guidelines for Americans'<br>Intervention methods: 18 group sessions with trained and certified nutritionists in the 1st year, quarterly maintenance sessions thereafter, focusing on diet and behaviour modification<br>Intervention delivered face-to-face in a group by nutritionists<br>Intake data all relate to the full WHI cohort (not divided by whether participants have CVD at baseline or not):<br>Total fat intake, %E (at 6 years): int 28.8 (SD 8.4), cont 37.0 (SD 7.3) (mean difference -8.20, 95% CI -8.34 to -8.06) significant reduction<br>**Saturated fat intake, %E (at 6 years): int 9.5 (SD3.2), cont 12.4 (SD3.1) (mean difference -2.90, 95% CI -2.96 to -2.84 for full WHI population) significant reduction**<br>PUFA intake, %E (at 6 years)§: int 6.3 (SD?), cont 7.6 (SD?) (mean difference -1.30, 95% CI -1.72 to -0.88 assuming missing SDs were 5) significant reduction<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E (at 6 years)§: int 11.1 (SD?), cont 14.3 (SD?) (mean difference -3.20, 95% CI -3.62 to -2.78 assuming unclear SDs were 5) significant reduction<br>CHO intake, %E (at 6 years)§: int 53.9 (SD?), cont 46.3 (SD?) (mean difference 7.60, 95% CI 5.91 to 9.29 assuming SDs of 20) significant increase<br>Protein intake, %E (at 6 years)§: int 17.7 (SD?), cont 17.0 (SD?) (mean difference 0.70, 95% CI 0.28 to 1.12 assuming SDs of 5) significant increase<br>Trans fat intake, %E (at 6 years)§: int 1.8 (SD?), cont 2.4 (SD?) (mean difference unclear, no SDs assumed)<br>**Replacement for saturated fat: mainly CHO, some protein (based on dietary achievement)**<br>Style: dietary advice<br>Setting: community |
| Outcomes | Stated trial outcomes: breast cancer, mortality, other cancers, cardiovascular events, diabetes<br>Data available on total mortality? yes<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: CHD, stroke, heart failure, angina, peripheral vascular disease, revascularisation, pulmonary embolism, DVT<br>Secondary outcomes: cancer deaths*, cancer diagnoses*, stroke, non-fatal MI<br>Tertiary outcomes: weight, BMI, total, LDL and HDL cholesterol, TGs, systolic and diastolic BP<br>* these are only available for the whole cohort, not split between low and high CVD risk |

**WHI with CVD 2006** (*Continued*)

| | |
|---|---|
| | groups |
| Notes | Study duration over 8 years<br>**Study aim** was to reduce total fat to 20%E, reduce saturated fat to 7%E and increase fruit and vegetable intake (Patterson 2003), and saturated fat intake in the intervention group was significantly lower than in control<br>**SFA reduction aimed and achieved.**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.09 (95% CI -0.15 to -0.02), statistically significant reduction**<br>§Amongst the 881 intervention and 1373 control participants with blood samples at baseline, with or without CVD at baseline (Howard 2010).<br>Trial dates: Recruitment was between 1993 and 1998<br>Funding: National Heart, Lung and Blood Institute of the National Institutes of Health<br>Declarations of Interest of primary researchers: Declarations vary from paper to paper, but this is a typical one from Beresford 2006 "Dr Black has received research grants from Pfizer and AstraZeneca, was on the speakers bureaus for Pfizer, Novartis, Sanofi-Aventis, Bristol-Meyers Squibb, Searle, Pharmacia, and Boehringer and served as a consultant of on an advisory board for Myogen, Merck Sharp and Dohme, Novartis, Mylan-Bertek, Pfizer, Bristol-Meyers Squibb, and Sanofi-Aventis. Dr Howard has served on the advisory boards of Merck, Schering Plough, and the Egg Nutrition Council, has received research support from Merck and Pfizer, and has consulted for General Millls. Dr Assaf is an employee of Pfizer. No other disclosures were reported." |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer algorithm |
| Allocation concealment (selection bias) | Low risk | Computer algorithm |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants aware of allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | High risk | Intervention participants received 18 group sessions with behavioural modification plus quarterly maintenance sessions thereafter, control groups received a leaflet. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | Low risk | Aim to reduce SFA stated |

**WHI with CVD 2006** (*Continued*)

| | | |
|---|---|---|
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | Low risk | Statistically significant TC fall |
| Other bias | Low risk | None noted |

**WHI without CVD 2006**

| | |
|---|---|
| Methods | RCT |
| Participants | Post-menopausal women aged 50 - 79 without CVD at baseline (USA)<br>CVD risk: low<br>Control: randomised 29,294, analysed 29,294<br>Intervention: randomised 19,541, analysed 19,541<br>Mean years in trial: control 8.1, intervention 8.1<br>% male: 0<br>Age: mean (both with and without CVD at baseline) int 62.3 (SD 6.9), control 62.3 (SD 6.9)<br>Ethnicity (women both with and without CVD at baseline): white 82%, black 11%, Asian or pacific islander 2%, unknown 1%, American Indian or Alaskan native < 1%. No statistically significant effects of the intervention on CHD events was seen for any ethnic subgroup<br>Statins use allowed? Yes<br>% taking statins: 12% of women recruited were on lipid-lowering medication (these were a mixture of participants with and without CVD at baseline) |
| Interventions | Reduced fat vs usual diet<br>Control: diet-related education materials<br>Intervention: low-fat diet (20% E from fat), reduce saturated fat to 7%E with increased fruit and vegetables<br>Control methods: given copy of 'Dietary Guidelines for Americans'<br>Intervention methods: 18 group sessions with trained and certified nutritionists in the 1st year, quarterly maintenance sessions thereafter, focusing on diet and behaviour modification<br>Intervention delivered face-to-face in a group by nutritionists<br>Intake data all relate to the full WHI cohort (not divided by whether participants have CVD at baseline or not):<br>Total fat intake, %E (at 6 years): int 28.8 (SD 8.4), cont 37.0 (SD 7.3) (mean difference -8.20, 95% CI -8.34 to -8.06) significant reduction<br>**Saturated fat intake, %E (at 6 years): int 9.5 (**SD**3.2), cont 12.4 (**SD**3.1) (mean difference -2.90, 95% CI -2.96 to -2.84 for full WHI population) significant reduction**<br>PUFA intake, %E (at 6 years)§: int 6.3 (SD?), cont 7.6 (SD?) (mean difference -1.30, 95% CI -1.72 to -0.88 assuming missing SDs were 5) significant reduction<br>PUFA n-3 intake: not reported<br>PUFA n-6 intake: not reported<br>MUFA intake, %E (at 6 years)§: int 11.1 (SD?), cont 14.3 (SD?) (mean difference -3.20, 95% CI -3.62 to -2.78 assuming unclear SDs were 5) significant reduction<br>CHO intake, %E (at 6 years)§: int 53.9 (SD?), cont 46.3 (SD?) (mean difference 7.60, 95% CI 5.91 to 9.29 assuming SDs of 20) significant increase<br>Protein intake, %E (at 6 years)§: int 17.7 (SD?), cont 17.0 (SD?) (mean difference 0.70, 95% CI 0.28 to 1.12 assuming SDs of 5) significant increase<br>Trans fat intake, %E (at 6 years)§: int 1.8 (SD?), cont 2.4 (SD?) (mean difference unclear, no SDs assumed)<br>**Replacement for saturated fat: mainly carbohydrate, some protein (based on dietary achievement)** |

**WHI without CVD 2006** (*Continued*)

| | |
|---|---|
| | Style: dietary advice<br>Setting: community |
| Outcomes | Stated trial outcomes: breast cancer, mortality, other cancers, cardiovascular events, diabetes<br>Data available on total mortality? yes*<br>Cardiovascular mortality? yes<br>Events available for combined cardiovascular events: CHD, stroke, heart failure, angina, peripheral vascular disease, revascularisation, pulmonary embolism, DVT<br>Secondary outcomes: cancer deaths*, cancer diagnoses*, stroke, non-fatal MI, diabetes diagnosis*<br>Tertiary outcomes: weight, BMI, total, LDL and HDL cholesterol, TGs, systolic and diastolic BP (Lp(a) and HOMA reported as geometric means)<br>* these are only available for the whole cohort, not split between low and high CVD risk groups |
| Notes | Study duration over 8 years<br>**Study aim** was to reduce total fat to 20%E, reduce saturated fat to 7%E and increase fruit and vegetable intake (Patterson 2003), and saturated fat intake in the intervention group was significantly lower than in control<br>**SFA reduction aimed and achieved**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.09 (95% CI -0.15 to -0.02) , statistically significant reduction**<br>§Amongst the 881 intervention and 1373 control participants with blood samples at baseline, with or without CVD at baseline (Howard 2010).<br>Trial dates: Recruitment was between 1993 and 1998<br>Funding: National Heart, Lung and Blood Institute of the National Institutes of Health<br>Declarations of Interest of primary researchers: Declarations vary from paper to paper, but this is a typical one from Beresford 2006 "Dr Black has received research grants from Pfizer and AstraZeneca, was on the speakers bureaus for Pfizer, Novartis, Sanofi-Aventis, Bristol-Meyers Squibb, Searle, Pharmacia, and Boehringer and served as a consultant of on an advisory board for Myogen, Merck Sharp and Dohme, Novartis, Mylan-Bertek, Pfizer, Bristol-Meyers Squibb, and Sanofi-Aventis. Dr Howard has served on the advisory boards of Merck, Schering Plough, and the Egg Nutrition Council, has received research support from Merck and Pfizer, and has consulted for General Millls. Dr Assaf is an employee of Pfizer. No other disclosures were reported." |

**WINS 2006**

| Methods | RCT |
|---|---|
| Participants | Women with localised resected breast cancer (USA)<br>CVD risk: low<br>Control: 1462 randomised, 1462 analysed<br>Intervention: 975 randomised, 975 analysed<br>Mean years in trial: overall 5.0<br>% men: 0<br>Age: control mean 58.5 (95% CI 43.6 to 73.4), intervention mean 58.6 (95% CI 44.4 to 72.8) (all post-menopausal)<br>Ethnicity: 85% white, 5% black, 4% Hispanic, 5% Asian or pacific islander, <1% American Indian or unknown (no outcome data based on ethnicity)<br>Statins use allowed? Not stated (statins not mentioned in inclusion or exclusion criteria within trial protocol)<br>% taking statins: Not reported |

| | |
|---|---|
| Interventions | Reduced fat intake vs usual diet<br>Control aims: minimal nutritional counselling focused on nutritional adequacy<br>Intervention aims: total fat 15 - 20%E<br>Control methods: 1 baseline dietetic session plus 3-monthly sessions<br>Intervention methods: 8 bi-weekly individual dietetic sessions plus 3-monthly contact and optional monthly group sessions, incorporating individual fat gram goals, social cognitive theory, self monitoring, goal setting, modelling, social support and relapse prevention and management<br>Intervention was delivered face-to-face individually by trained dietitian<br>Total fat intake, %E (at 1 year): int 20.3 (SD 8.1), cont 29.2 (SD 7.4) (mean difference -8.90, 95% CI -9.53 to -8.27) Total fat %E (at 5 years): int 23.2 (SD 8.4) n = 380, cont 31.2 (SD 8.9) n = 648 (mean difference -8.00, 95% CI -9.09 to -6.91) significant reduction<br>**Saturated fat intake*, %E (at 1 year): int 6.4 (SD 0.14 [4.4]), cont 9.8 (SD 0.15 [5.7]) (mean difference -3.40, 95% CI -3.80 to -3.00 assuming reported SDs were actually SEs) significant reduction**<br>PUFA intake*, %E (at 1 year): int 4.5 (SD 0.09 (2.8)), cont 6.4 (SD 0.10 (3.8)) (mean difference -1.90, 95% CI -2.16 to -1.64) significant reduction<br>PUFA n-3 intake: not reported by study arm<br>PUFA n-6 intake: not reported by study arm<br>MUFA intake*, %E (at 1 year): int 7.6 (SD 0.14 (4.4)), cont 11.5 (SD 0.16 (6.1)) (mean difference -3.90, 95% CI -4.32 to -3.48) significant reduction<br>CHO intake, %E (at 6 months): int 60.8 (SD 19.6), cont 50.5 (SD 14.8) (mean difference 10.30, 95% CI 8.85 to 11.75) significant increase<br>Protein intake, %E (at 6 months): int 19.1 (SD 5.2), cont 17.6 (SD 4.1) (mean difference 1.50, 95% CI 1.11 to 1.89) significant increase<br>Trans fat intake: not reported<br>**Replacement for saturated fat: CHO and protein (based on dietary achievement)**<br>Style: dietary advice<br>Setting: community |
| Outcomes | Stated trial outcomes: dietary fat intake, total cholesterol, weight and waist<br>Data available on total mortality? yes<br>Cardiovascular mortality? no<br>Events available for combined cardiovascular events: none<br>Secondary outcomes: cancer diagnoses<br>Tertiary outcomes: weight, BMI, total cholesterol |
| Notes | Study duration 5 years<br>**Study aim** was to reduce total fat to 15 - 20%E, but saturated fat intake in the intervention group was significantly lower than in control<br>**SFA reduction achieved**<br>**Total serum cholesterol, difference between intervention and control, mmol/L: -0.14 (95% CI -0.34 to 0.05), NO statistically significant reduction and reduction < 0.20**<br>*SDs appear incorrect, probably SEs?<br>Trial dates: Recruitment 1994 to 2001<br>Funding: National Cancer Institute, Breast Cancer Research Foundation, American Institute for Cancer Research |

| | |
|---|---|
| | Declarations of Interest of primary researchers: none stated, all authors worked for academic or health institutions except that Njeri Karanja worked for Kaiser Permanente Center for Health Research, Bette Caan for Kaiser Permanente Medical Group, and Barbara L Winters for Campbell's Soup Company |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS |
| Allocation concealment (selection bias) | Low risk | Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Participants not blinded, not relevant for assessment of mortality by researchers |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All assessed. |
| Selective reporting (reporting bias) | Low risk | Not relevant for primary and secondary outcomes as all trialists were asked for data |
| Free of systematic difference in care? | High risk | Differences in attention - more time for those in intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Stated aim to reduce SFA | High risk | Aim to reduce SFA not stated |
| Achieved SFA reduction | Low risk | SFA reduction achieved |
| Achieved TC reduction | High risk | No statistically significant TC fall |
| Other bias | Low risk | None noted |

%E = percent of total energy intake
ATPII - Adult treatment panel II
CABG = coronary artery bypass graft
CHD = coronary heart disease
CHO = carbohydrates
chol = cholesterol
CI = confidence interval
CVD = cardiovascular disease
dBP = diastolic blood pressure
DVT = deep vein thrombosis
HOMA = homeostatic model assessment

Lp(a) = lipoprotein
MI = myocardial infarction
MUFA = monounsaturated fats
P/S = polyunsaturated/saturated fat ratio
PCTA = percutaneous transluminal coronary angioplasty
PUFA = polyunsaturated fats
PVD = peripheral vascular disease
RCT = randomised controlled trial
sBP = systolic blood pressure
SD = standard deviation
SE = standard error
SFA = saturated fats
TC = total cholesterol
TG = triglyceride

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

| Study | Reason for exclusion |
|---|---|
| Agewall 2001 | Multifactorial intervention |
| Ammerman 2003 | No appropriate control group (and not low fat vs modified fat) |
| Anderson 1990 | Follow-up less than 24 months |
| Aquilani 2000 | No appropriate control group (and not low fat vs modified fat) |
| Arntzenius 1985 | No appropriate control group (and not low fat vs modified fat) |
| Aro 1990 | Intervention and randomised follow-up less than 6 months |
| ASSIST 2001 | Intervention is not dietary fat modification or low fat diet |
| Australian Polyp Prev 95 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Azadbakht 2007 | Follow-up less than 24 months |
| Bakx 1997 | Multifactorial intervention |
| Ball 1965 | Study aim was to assess effects of a low-fat diet and methods state that the "nature of the fat consumed was not altered". Saturated fat content of diet was not reported |
| Barnard 2009 | Weight reduction encouraged in the conventional diet, but not in the vegan diet arm |
| Barndt 1977 | No appropriate control group (and not low fat vs modified fat) |
| Baron 1990 | Multifactorial intervention |

(*Continued*)

| | |
|---|---|
| Barr 1990 | Intervention and randomised follow-up less than 6 months |
| Barsotti 1991 | Complex paper in Italian, unclear whether cardiovascular events occurred, contact with authors not established |
| Baumann 1982 | Intervention and randomised follow-up less than 6 months |
| BDIT Pilot Studies 1996 | Study aim was to reduce total fat intake to 15%E with no specific intervention on saturated fat. Saturated fat in intervention group was more than 80% of that in the control group |
| Beckmann 1995 | Intervention is not dietary fat modification or low-fat diet |
| beFIT 1997 | Follow-up less than 24 months |
| Beresford 1992 | Intervention and randomised follow-up less than 6 months |
| Bergstrom 1967 | Intervention and randomised follow-up less than 6 months |
| Bierenbaum 1963 | No appropriate control group (and not low fat vs modified fat) |
| Bloemberg 1991 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Bloomgarden 1987 | Multifactorial intervention |
| Bonk 1975 | Trial, unclear if randomised, contact could not be established with trialists |
| Bonnema 1995 | No appropriate control group (and not low fat vs modified fat) |
| Bosaeus 1992 | Intervention and randomised follow-up less than 6 months |
| Boyd 1988 | Follow-up less than 24 months |
| Brehm 2009 | Unclear whether any relevant events occurred, not able to contact trialists |
| Brensike 1982 | No appropriate control group (and not low fat vs modified fat) |
| BRIDGES 2001 | Follow-up less than 24 months |
| Broekmans 2003 | Intervention is not dietary fat modification or low fat diet |
| Brown 1984 | No appropriate control group (and not low fat vs modified fat) |
| Bruce 1994 | No appropriate control group (and not low fat vs modified fat) |
| Bruno 1983 | Multifactorial intervention |

(*Continued*)

| | |
|---|---|
| Butcher 1990 | Intervention and randomised follow-up less than 6 months |
| Byers 1995 | No appropriate control group (and not low fat vs modified fat) |
| Caggiula 1996 | No appropriate control group (and not low fat vs modified fat) |
| Canadian DBCP 1997 | Unable to establish contact with authors to provide data on numbers of deaths and CV events |
| CARMEN 2000 | Follow-up less than 24 months |
| CARMEN sub-study 2002 | Follow-up less than 24 months |
| Cerin 1993 | Intervention and randomised follow-up less than 6 months |
| Chan 1993 | Intervention and randomised follow-up less than 6 months |
| Chapman 1950 | Intervention and randomised follow-up less than 6 months |
| Charbonnier 1975 | Intervention and randomised follow-up less than 6 months |
| Cheng 2004 | Intervention and randomised follow-up less than 6 months |
| Chiostri 1988 | Intervention and randomised follow-up less than 6 months |
| Choudhury 1984 | Intervention and randomised follow-up less than 6 months |
| Clark 1997 | Multifactorial intervention |
| Clifton 1992 | Intervention and randomised follow-up less than 6 months |
| Cobb 1991 | Intervention and randomised follow-up less than 6 months |
| Cohen 1991 | Intervention is not dietary fat modification or low fat diet |
| Cole 1988 | Intervention and randomised follow-up less than 6 months |
| Colquhoun 1990 | Intervention and randomised follow-up less than 6 months |
| Consolazio 1946 | Intervention and randomised follow-up less than 6 months |
| Cox 1996 | Multifactorial intervention |
| Croft 1986 | Intervention is not dietary fat modification or low fat diet |
| Curzio 1989 | Follow-up less than 24 months |
| Da Qing IGT 1997 | Intervention is not dietary fat modification or low-fat diet |

(*Continued*)

| | |
|---|---|
| Dalgard 2001 | No appropriate control group (and not low fat vs modified fat) |
| DAS 2000 | No appropriate control group (and not low fat vs modified fat) |
| DASH 1997 | Intervention and randomised follow-up less than 6 months |
| Davey Smith 2005 | Multifactorial intervention |
| De Boer 1983 | Intervention and randomised follow-up less than 6 months |
| De Bont 1981 | Neither mortality nor cardiovascular morbidity data available as study data have been lost |
| DeBusk 1994 | Multifactorial intervention |
| DEER 1998 | Duration 1 year only |
| Delahanty 2001 | No appropriate control group (and not low fat vs modified fat) |
| Delius 1969 | Intervention is not dietary fat modification or low fat diet |
| Demark 1990 | Intervention and randomised follow-up less than 6 months |
| Dengel 1995 | No appropriate control group (and not low fat vs modified fat) |
| Denke 1994 | Intervention and randomised follow-up less than 6 months |
| Diabetes CCT 1995 | Intervention is not dietary fat modification or low fat diet |
| Diet & Hormone Study 2003 | Duration 1 year only |
| DIET 1998 | Multifactorial intervention |
| Ding 1992 | Intervention and randomised follow-up less than 6 months |
| DIRECT 2009 | Unable to establish contact with authors to establish whether relevant events occurred |
| DO IT 2006 | Intervention aim was for a "mediterranean diet" with total fat 27 - 30%E, protein 15 - 18%E, CHO 50 - 55%E, no specific aim to reduce saturated fat (though polyunsaturated margarine given to intervention group), and intervention group saturated fat was more than 80% of that in the control |
| Dobs 1991 | No appropriate control group (and not low fat vs modified fat) |
| Due 2008 | Follow-up less than 24 months |
| Duffield 1982 | Multifactorial intervention |
| Dullaart 1992 | Study authors confirmed that no deaths or cardiovascular events occurred during the study |

(*Continued*)

| | |
|---|---|
| Eating Patterns 1997 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Ehnholm 1982 | Intervention and randomised follow-up less than 6 months |
| Ehnholm 1984 | Intervention and randomised follow-up less than 6 months |
| Eisenberg 1990 | Intervention and randomised follow-up less than 6 months |
| Elder 2000 | No appropriate control group (and not low fat vs modified fat) |
| Ellegard 1991 | Intervention and randomised follow-up less than 6 months |
| Esposito 2003 | No appropriate control group (and not low fat vs modified fat) |
| Esposito 2004 | Unable to establish contact with authors to assess whether any relevant events occurred |
| EUROACTION 2008 | Multifactorial intervention |
| FARIS 1997 | Multifactorial intervention |
| Fasting HGS 1997 | No appropriate control group (and not low fat vs modified fat) |
| Ferrara 2000 | No appropriate control group (and not low fat vs modified fat) |
| Fielding 1995 | Intervention and randomised follow-up less than 6 months |
| Finnish Diabet Prev 2000 | Multifactorial intervention |
| Finnish Mental Hosp 1972 | Not randomised (cluster-randomised, but < 6 clusters) |
| Fisher 1981 | Intervention and randomised follow-up less than 6 months |
| FIT Heart 2011 | Authors confirmed that differences between intervention and control groups included smoking and physical activity, as well as dietary changes |
| Fleming 2002 | No appropriate control group (and not low fat vs modified fat) |
| Fortmann 1988 | Intervention is not dietary fat modification or low fat diet |
| Foster 2003 | Weight reduction in 1 arm but not the other |
| Frenkiel 1986 | Follow-up less than 24 months |
| FRESH START 2007 | Participants were newly diagnosed with cancer |
| Gambera 1995 | Intervention and randomised follow-up less than 6 months |

(*Continued*)

| | |
|---|---|
| Gaullier 2007 | No appropriate control group (and not low fat vs modified fat) |
| Ginsberg 1988 | Intervention and randomised follow-up less than 6 months |
| Gjone 1972 | Intervention and randomised follow-up less than 6 months |
| Glatzel 1966 | No appropriate control group (and not low fat vs modified fat) |
| Goodpaster 1999 | No appropriate control group (and not low fat vs modified fat) |
| Grundy 1986 | Intervention and randomised follow-up less than 6 months |
| Hardcastle 2008 | Multifactorial intervention |
| Harris 1990 | Intervention and randomised follow-up less than 6 months |
| Hartman 1993 | No appropriate control group (and not low fat vs modified fat) |
| Hartwell 1986 | No appropriate control group (and not low fat vs modified fat) |
| Hashim 1960 | Intervention and randomised follow-up less than 6 months |
| Haufe 2011 | Aim was to reduce total fat or reduce carbohydrate, but no saturated fat aims were stated, and effects of the diets on saturated fat intakes were unclear |
| Haynes 1984 | Intervention is not dietary fat modification or low fat diet |
| Heber 1991 | Intervention and randomised follow-up less than 6 months |
| Heine 1989 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Hellenius 1995 | The study aimed for weight loss in 1 arm and not in the comparison arm |
| Heller 1993 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Hildreth 1951 | No appropriate control group (and not low fat vs modified fat) |
| Holm 1990 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Horlick 1957 | Intervention and randomised follow-up less than 6 months |
| Horlick 1960 | Intervention and randomised follow-up less than 6 months |
| Howard 1977 | Intervention and randomised follow-up less than 6 months |

(*Continued*)

| | |
|---|---|
| Hunninghake 1990 | Intervention and randomised follow-up less than 6 months |
| Hutchison 1983 | No appropriate control group (and not low fat vs modified fat) |
| Hyman 1998 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Iacono 1981 | Not randomised, Intervention and randomised follow-up less than 6 months |
| IMPACT 1995 | Multifactorial intervention |
| Iso 1991 | No appropriate control group (and not low fat vs modified fat) |
| Ives 1993 | Multifactorial intervention |
| Jalkanen 1991 | Multifactorial intervention |
| Jerusalem Nut 1992 | Intervention and randomised follow-up less than 6 months |
| Jula 1990 | Multifactorial intervention |
| Junker 2001 | Intervention and randomised follow-up less than 6 months |
| Karmally 1990 | Intervention and randomised follow-up less than 6 months |
| Karvetti 1992 | Multifactorial intervention |
| Kastarinen 2002 | Multifactorial intervention |
| Kather 1985 | Intervention and randomised follow-up less than 6 months |
| Katzel 1995 | Intervention is not dietary fat modification or low fat diet |
| Kawamura 1993 | Intervention and randomised follow-up less than 6 months |
| Keidar 1988 | Intervention and randomised follow-up less than 6 months |
| Kempner 1948 | No appropriate control group (and not low fat vs modified fat) |
| Keys 1957a | Intervention and randomised follow-up less than 6 months |
| Keys 1957b | Intervention and randomised follow-up less than 6 months |
| Keys 1957c | Intervention and randomised follow-up less than 6 months |
| Khan 2003 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |

(*Continued*)

| | |
|---|---|
| King 2000 | Intervention and randomised follow-up less than 6 months |
| Kingsbury 1961 | Intervention and randomised follow-up less than 6 months |
| Koopman 1990 | Intervention and randomised follow-up less than 6 months |
| Koranyi 1963 | Unclear whether randomised, unable to contact authors to discuss |
| Korhonen 2003 | Multifactorial intervention |
| Kriketos 2001 | Intervention and randomised follow-up less than 6 months |
| Kris 1994 | Intervention and randomised follow-up less than 6 months |
| Kristal 1997 | Multifactorial intervention |
| Kromhout 1987 | No appropriate control group (and not low fat vs modified fat) |
| Kummel 2008 | Intervention is not dietary fat modification or low-fat diet |
| Laitinen 1993 | Multifactorial intervention |
| Laitinen 1994 | Multifactorial intervention |
| Lean 1997 | Follow-up less than 24 months |
| Leduc 1994 | Multifactorial intervention |
| Lewis 1958 | Intervention and randomised follow-up less than 6 months |
| Lewis 1981 | Intervention and randomised follow-up less than 6 months |
| Lewis 1985 | Multifactorial intervention |
| Lichtenstein 2002 | Intervention and randomised follow-up less than 6 months |
| Lim 2010 | Unable to establish contact with authors to gain access to data on health outcomes (none reported in paper) |
| Linko 1957 | Intervention and randomised follow-up less than 6 months |
| Lipid Res Clinic 1984 | No appropriate control group (and not low fat vs modified fat) |
| Little 1990 | Intervention and randomised follow-up less than 6 months |
| Little 2004 | Intervention is not dietary fat modification or low-fat diet |

(*Continued*)

| | |
|---|---|
| Lottenberg 1996 | Intervention and randomised follow-up less than 6 months |
| Luszczynska 2007 | No appropriate control group (and not low fat vs modified fat) |
| Lyon Diet Heart 1994 | Intervention is not dietary fat modification or low-fat diet |
| Lysikova 2003 | Intervention and randomised follow-up less than 6 months |
| Macdonald 1972 | Intervention and randomised follow-up less than 6 months |
| Mansel 1990 | Intervention is not dietary fat modification or low-fat diet |
| MARGARIN 2002 | No appropriate control group (and not low fat vs modified fat) |
| Marniemi 1990 | Both intervention groups aimed to lose weight, while the control group did not |
| Mattson 1985 | Intervention and randomised follow-up less than 6 months |
| McAuley 2005 | Follow-up less than 24 months |
| McCarron 1997 | Intervention and randomised follow-up less than 6 months |
| McCarron 2001 | Intervention is not dietary fat modification or low-fat diet |
| McKeown-Eyssen 1994 | Intervention aim was to reduce total fat and increase dietary fibre (saturated fat not mentioned), and no saturated fat intakes during trial reported |
| McManus 2001 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| McNamara 1981 | Intervention and randomised follow-up less than 6 months |
| Medi-RIVAGE 2004 | Weight reduction for some low-fat diet participants (those with BMI > 25) but not in Mediterranean group |
| MeDiet 2002 | Follow-up less than 24 months |
| Mensink 1987 | Intervention and randomised follow-up less than 6 months |
| Mensink 1989 | Intervention and randomised follow-up less than 6 months |
| Mensink 1990a | Intervention and randomised follow-up less than 6 months |
| Mensink 1990b | Intervention and randomised follow-up less than 6 months |
| Metroville Health 2003 | Unable to establish contact with authors to assess whether any relevant events occurred |

(*Continued*)

| | |
|---|---|
| Michalsen 2006 | Diet plus stress management vs no intervention |
| Miettinen 1994 | Intervention and randomised follow-up less than 6 months |
| Millar 1973 | No appropriate control group (and not low fat vs modified fat) |
| Miller 1998 | Intervention and randomised follow-up less than 6 months |
| Miller 2001 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Milne 1994 | No appropriate control group (and not low fat vs modified fat) - the high CHO diet is neither 'usual' or 'low fat' to compare with the modified fat diet |
| Minnesota Coronary 1989 | Although the study proceeded for over 4 years participants (patients) came and went and mean follow-up was only 1 year |
| Minnesota HHP 1990 | No appropriate control group (and not low fat vs modified fat) |
| Mojonnier 1980 | Unable to establish contact with authors to assess whether any relevant events occurred |
| Mokuno 1988 | Intervention and randomised follow-up less than 6 months |
| Mortensen 1983 | Intervention and randomised follow-up less than 6 months |
| MRFIT substudy 1986 | Intervention and randomised follow-up less than 6 months |
| MSDELTA 1995 | Intervention and randomised follow-up less than 6 months |
| MSFAT 1997 | Follow-up less than 24 months |
| Mujeres Felices 2003 | Diet and breast self examination vs no intervention |
| Mutanen 1997 | Intervention and randomised follow-up less than 6 months |
| Muzio 2007 | Intervention and randomised follow-up less than 6 months |
| Naglak 2000 | Unable to establish contact with authors to assess whether any relevant events occurred |
| NAS 1987 | Intervention and randomised follow-up less than 6 months |
| National Diet Heart 1968 | Follow-up less than 24 months |
| NCEP weight 1991 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Neil 1995 | No appropriate control group (and not low fat vs modified fat) |

(*Continued*)

| | |
|---|---|
| Neverov 1997 | Multifactorial intervention |
| Next Step 1995 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Nordoy 1971 | Intervention and randomised follow-up less than 6 months |
| Norway Veg Oil 1968 | No appropriate control group (and not low fat vs modified fat) |
| Nutrition Breast Health | Follow-up less than 24 months |
| O'Brien 1976 | Intervention and randomised follow-up less than 6 months |
| ODES 2006 | The study aimed for weight loss in 1 arm and not in the other arm |
| Oldroyd 2001 | Multifactorial intervention |
| Ole Study 2002 | Follow-up less than 24 months |
| OLIVE 1997 | Unable to establish contact with authors to assess whether any relevant events occurred |
| ORIGIN 2008 | Intervention is not dietary fat modification or low-fat diet |
| Oslo Study 2004 | Multifactorial intervention |
| Pascale 1995 | Multifactorial intervention |
| PEP 2001 | Multifactorial intervention |
| PHYLLIS 1993 | No appropriate control group (and not low fat vs modified fat) |
| Pilkington 1960 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Polyp Prevention 1996 | Intervention aim was to reduce total fat and increase dietary fibre, fruit and vegetables (saturated fat not mentioned), and no saturated fat intakes during trial reported |
| POUNDS LOST 2009 | All study arms (low or high total fat) prescribed low saturated fat intake (8%E), no usual fat comparator |
| PREDIMED 2008 | Total fat goals in the low-fat arm were unclear and authors confirmed that aims were non-specific (if aims < 30%E this study would be included) |
| PREMIER 2003 | Follow-up less than 24 months |
| Pritchard 2002 | The study aimed for weight loss in 1 arm and not in the comparison arm |

(*Continued*)

| | |
|---|---|
| Puget Sound EP 2000 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Rabast 1979 | Intervention and randomised follow-up less than 6 months |
| Rabkin 1981 | Intervention and randomised follow-up less than 6 months |
| Radack 1990 | Intervention and randomised follow-up less than 6 months |
| Rasmussen 1995 | Intervention and randomised follow-up less than 6 months |
| Reaven 2001 | Intervention and randomised follow-up less than 6 months |
| Reid 2002 | No appropriate control group (and not low fat vs modified fat) |
| Renaud 1986 | Not randomised |
| Rivellese 1994 | Follow-up less than 24 months |
| Rivellese 2003 | Intervention and randomised follow-up less than 6 months |
| Roderick 1997 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Roman CHD prev 1986 | Multifactorial intervention |
| Rose 1987 | No appropriate control group (and not low fat vs modified fat) |
| Sarkkinen 1995 | Follow-up less than 24 months |
| Schaefer 1995a | Intervention and randomised follow-up less than 6 months |
| Schaefer 1995b | Intervention and randomised follow-up less than 6 months |
| Schectman 1996 | Multifactorial intervention |
| Schlierf 1995 | Multifactorial intervention |
| Seppanen-Laakso 1992 | Intervention and randomised follow-up less than 6 months |
| Seppelt 1996 | Follow-up less than 24 months |
| Singh 1991 | Multifactorial intervention |
| Singh 1992 | No appropriate control group (and not low fat vs modified fat) |
| Sirtori 1992 | Intervention and randomised follow-up less than 6 months |

(*Continued*)

| | |
|---|---|
| SLIM 2008 | Multifactorial intervention |
| Sopotsinskaia 1992 | The study aimed for weight loss in 1 arm and not in the comparison arm |
| Stanford NAP 1997 | Intervention and randomised follow-up less than 6 months |
| Stanford Weight 1994 | The study aimed for weight loss in 1 arm and not in the comparison arm |
| Starmans 1995 | Intervention and randomised follow-up less than 6 months |
| Steinbach 1996 | Multifactorial intervention |
| Steptoe 2001 | No appropriate control group (and not low fat vs modified fat) |
| Stevens 2002 | Diet plus breast self examination vs no intervention |
| Stevenson 1988 | No appropriate control group (and not low fat vs modified fat) |
| Strychar 2009 | Follow-up less than 24 months |
| Sweeney 2004 | Intervention is not dietary fat modification or low fat diet |
| Søndergaard 2003 | Follow-up less than 24 months |
| TAIM 1992 | Intervention is not dietary fat modification or low fat diet |
| Tapsell 2004 | Unable to establish contact with authors to assess whether any relevant events occurred |
| THIS DIET 2008 | All study arms prescribed low saturated fat intake, no usual fat comparator |
| TOHP I 1992 | Multifactorial intervention |
| TONE 1997 | Intervention is not dietary fat modification or low-fat diet |
| Toobert 2003 | Multifactorial intervention |
| Towle 1994 | Intervention and randomised follow-up less than 6 months |
| TRANSFACT 2006 | Intervention and randomised follow-up less than 6 months |
| Treatwell 1992 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Tromsø Heart 1989 | Multifactorial intervention |
| Troyer 2010 | Longest duration only 12 months |

(*Continued*)

| | |
|---|---|
| UK PDS 1996 | No appropriate control group (and not low fat vs modified fat) |
| Urbach 1952 | No appropriate control group (and not low fat vs modified fat) |
| Uusitupa 1993 | Multifactorial intervention |
| Vavrikova 1958 | Intervention and randomised follow-up less than 6 months |
| Verheiden 2003 | Unable to establish contact with authors to assess whether any relevant events occurred |
| Wass 1981 | Intervention and randomised follow-up less than 6 months |
| Wassertheil 1985 | Intervention is not dietary fat modification or low fat diet |
| WATCH 1999 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Watts 1988 | Intervention and randomised follow-up less than 6 months |
| Weintraub 1992 | No appropriate control group (and not low fat vs modified fat) |
| Westman 2006 | Intervention is not dietary fat modification or low fat diet |
| Weststrate 1998 | Intervention and randomised follow-up less than 6 months |
| WHEL 2007 | Study aimed to reduce total fat, but saturated fat goals were not mentioned, and saturated fat intake in the intervention group was more than 80% of that in the control (81%) |
| WHO primary prev 1979 | Multifactorial intervention |
| WHT 1990 | Neither mortality nor cardiovascular morbidity data available as such data were not collected in the study |
| WHT Feasibility 2003 | Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least 1 author) |
| Wilke 1974 | Intervention and randomised follow-up less than 6 months |
| Williams 1990 | Intervention is not dietary fat modification or low-fat diet |
| Williams 1992 | Intervention is not dietary fat modification or low-fat diet |
| Williams 1994 | Intervention is not dietary fat modification or low-fat diet |
| Wilmot 1952 | No appropriate control group (and not low fat vs modified fat) |
| Wing 1998 | No appropriate control group (and not low fat vs modified fat) |

(*Continued*)

| | |
|---|---|
| WINS UK 2011 | Stated aim was to reduce total fat by 50%, no saturated fat aims |
| WOMAN 2007 | Lifestyle intervention includes exercise and weight as well as diet |
| Wood 1988 | Intervention is not dietary fat modification or low-fat diet |
| Woollard 2003 | Multifactorial intervention including smoking, weight, exercise and alcohol components |
| Working Well 1996 | Multifactorial intervention |
| Zock 1995 | Intervention and randomised follow-up less than 6 months |

## DATA AND ANALYSES

### Comparison 1. SFA reduction vs usual diet - Primary outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 All-cause mortality | 12 | 55858 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.90, 1.05] |
| 2 Cardiovascular mortality | 12 | 53421 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.80, 1.12] |
| 3 Combined cardiovascular events | 13 | 53300 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.72, 0.96] |

### Comparison 2. SFA reduction vs usual diet - secondary health events

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Myocardial infarctions | 11 | 53167 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.80, 1.01] |
| 2 Non-fatal MI | 9 | 52834 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.80, 1.13] |
| 3 Stroke | 8 | 50952 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.89, 1.12] |
| 4 CHD mortality | 10 | 53159 | Risk Ratio (M-H, Random, 95% CI) | 0.98 [0.84, 1.15] |
| 5 CHD events | 12 | 53199 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.74, 1.03] |
| 6 Diabetes diagnoses | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |

### Comparison 3. SFA reduction vs usual diet - other secondary outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Total cholesterol, mmol/L | 14 | 7115 | Mean Difference (IV, Random, 95% CI) | -0.24 [-0.36, -0.13] |
| 2 LDL cholesterol, mmol/L | 5 | 3291 | Mean Difference (IV, Random, 95% CI) | -0.19 [-0.33, -0.05] |
| 3 HDL cholesterol, mmol/L | 6 | 5147 | Mean Difference (IV, Random, 95% CI) | -0.01 [-0.02, 0.01] |
| 4 Triglycerides, mmol/L | 7 | 3845 | Mean Difference (IV, Random, 95% CI) | -0.08 [-0.21, 0.04] |
| 5 total cholesterol /HDL ratio | 3 | 2985 | Mean Difference (IV, Random, 95% CI) | -0.10 [-0.33, 0.13] |
| 6 LDL /HDL ratio | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7 Lp(a), mmol/L | 2 | 2882 | Mean Difference (IV, Random, 95% CI) | 0.0 [-0.00, 0.00] |
| 8 Insulin sensitivity | 4 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 8.1 HbA1c (glycosylated haemoglobin), % | 0 | 0 | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.2 GTT (glucose tolerance test), glucose at 2 hours, mmol/L | 3 | 249 | Mean Difference (IV, Random, 95% CI) | -1.69 [-2.55, -0.82] |
| 8.3 HOMA | 1 | 2832 | Mean Difference (IV, Random, 95% CI) | 0.0 [-0.04, 0.04] |

## Analysis 1.1. Comparison 1 SFA reduction vs usual diet - Primary outcomes, Outcome 1 All-cause mortality.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 1 SFA reduction vs usual diet - Primary outcomes

Outcome: 1 All-cause mortality

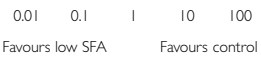
| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Black 1994 | 1/66 | 2/67 | | 0.1 % | 0.51 [ 0.05, 5.46 ] |
| DART 1989 | 111/1018 | 113/1015 | | 8.7 % | 0.98 [ 0.76, 1.25 ] |
| Ley 2004 | 2/88 | 6/88 | | 0.2 % | 0.33 [ 0.07, 1.61 ] |
| MRC 1968 | 28/199 | 31/194 | | 2.5 % | 0.88 [ 0.55, 1.41 ] |
| Oslo Diet-Heart 1966 | 48/206 | 65/206 | | 5.3 % | 0.74 [ 0.54, 1.02 ] |
| Rose corn oil 1965 | 5/28 | 0/13 | | 0.1 % | 5.31 [ 0.32, 89.44 ] |
| Rose olive 1965 | 3/26 | 1/13 | | 0.1 % | 1.50 [ 0.17, 13.05 ] |
| STARS 1992 | 1/27 | 3/28 | | 0.1 % | 0.35 [ 0.04, 3.12 ] |
| Sydney Diet-Heart 1978 | 39/221 | 28/237 | | 2.7 % | 1.49 [ 0.95, 2.34 ] |
| Veterans Admin 1969 | 174/424 | 177/422 | | 19.4 % | 0.98 [ 0.83, 1.15 ] |
| WHI without CVD 2006 | 950/19541 | 1454/29294 | | 59.6 % | 0.98 [ 0.90, 1.06 ] |
| WINS 2006 | 15/975 | 19/1462 | | 1.2 % | 1.18 [ 0.60, 2.32 ] |
| **Total (95% CI)** | **22819** | **33039** | | **100.0 %** | **0.97 [ 0.90, 1.05 ]** |

Total events: 1377 (reduced SFA), 1899 (usual diet)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.36$, df = 11 (P = 0.41); $I^2 = 3\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable



## Analysis 1.2. Comparison 1 SFA reduction vs usual diet - Primary outcomes, Outcome 2 Cardiovascular mortality.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 1 SFA reduction vs usual diet - Primary outcomes

Outcome: 2 Cardiovascular mortality

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Black 1994 | 0/66 | 2/67 | | 0.3 % | 0.20 [ 0.01, 4.15 ] |
| DART 1989 | 101/1018 | 100/1015 | | 18.1 % | 1.01 [ 0.77, 1.31 ] |
| Ley 2004 | 1/88 | 4/88 | | 0.6 % | 0.25 [ 0.03, 2.19 ] |
| MRC 1968 | 27/199 | 25/194 | | 8.0 % | 1.05 [ 0.63, 1.75 ] |
| Oslo Diet-Heart 1966 | 38/206 | 52/206 | | 12.4 % | 0.73 [ 0.50, 1.06 ] |
| Rose corn oil 1965 | 5/28 | 0/13 | | 0.3 % | 5.31 [ 0.32, 89.44 ] |
| Rose olive 1965 | 3/26 | 1/13 | | 0.6 % | 1.50 [ 0.17, 13.05 ] |
| STARS 1992 | 1/27 | 3/28 | | 0.5 % | 0.35 [ 0.04, 3.12 ] |
| Sydney Diet-Heart 1978 | 37/221 | 25/237 | | 8.9 % | 1.59 [ 0.99, 2.55 ] |
| Veterans Admin 1969 | 57/424 | 81/422 | | 15.3 % | 0.70 [ 0.51, 0.96 ] |
| WHI with CVD 2006 | 43/908 | 62/1369 | | 12.0 % | 1.05 [ 0.72, 1.53 ] |
| WHI without CVD 2006 | 170/18633 | 258/27925 | | 23.0 % | 0.99 [ 0.81, 1.20 ] |
| **Total (95% CI)** | **21844** | **31577** | | **100.0 %** | **0.95 [ 0.80, 1.12 ]** |

Total events: 483 (reduced SFA), 613 (usual diet)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 15.75$, df = 11 (P = 0.15); $I^2 = 30\%$

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

Test for subgroup differences: Not applicable

## Analysis 1.3. Comparison 1 SFA reduction vs usual diet - Primary outcomes, Outcome 3 Combined cardiovascular events.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 1 SFA reduction vs usual diet - Primary outcomes

Outcome: 3 Combined cardiovascular events

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Black 1994 | 0/66 | 2/67 | | 0.2 % | 0.20 [ 0.01, 4.15 ] |
| DART 1989 | 136/1018 | 147/1015 | | 13.0 % | 0.92 [ 0.74, 1.15 ] |
| Houtsmuller 1979 | 8/51 | 30/51 | | 3.7 % | 0.27 [ 0.14, 0.52 ] |
| Ley 2004 | 11/88 | 16/88 | | 3.4 % | 0.69 [ 0.34, 1.40 ] |
| Moy 2001 | 5/117 | 3/118 | | 1.0 % | 1.68 [ 0.41, 6.87 ] |
| MRC 1968 | 62/199 | 74/194 | | 11.1 % | 0.82 [ 0.62, 1.07 ] |
| Oslo Diet-Heart 1966 | 64/206 | 90/206 | | 11.7 % | 0.71 [ 0.55, 0.92 ] |
| Rose corn oil 1965 | 15/28 | 6/13 | | 3.7 % | 1.16 [ 0.59, 2.29 ] |
| Rose olive 1965 | 11/26 | 5/13 | | 2.7 % | 1.10 [ 0.48, 2.50 ] |
| STARS 1992 | 8/27 | 20/28 | | 4.2 % | 0.41 [ 0.22, 0.78 ] |
| Veterans Admin 1969 | 97/424 | 122/422 | | 12.5 % | 0.79 [ 0.63, 1.00 ] |
| WHI with CVD 2006 | 225/908 | 311/1369 | | 15.3 % | 1.09 [ 0.94, 1.27 ] |
| WHI without CVD 2006 | 1132/18633 | 1777/27925 | | 17.4 % | 0.95 [ 0.89, 1.03 ] |
| **Total (95% CI)** | **21791** | **31509** | | **100.0 %** | **0.83 [ 0.72, 0.96 ]** |

Total events: 1774 (reduced SFA), 2603 (usual diet)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 34.25$, df = 12 (P = 0.00062); $I^2 = 65\%$

Test for overall effect: Z = 2.50 (P = 0.013)

Test for subgroup differences: Not applicable

## Analysis 2.1. Comparison 2 SFA reduction vs usual diet - secondary health events, Outcome 1 Myocardial infarctions.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 2 SFA reduction vs usual diet - secondary health events

Outcome: 1 Myocardial infarctions

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| DART 1989 | 132/1018 | 144/1015 | | 21.9 % | 0.91 [ 0.73, 1.14 ] |
| Houtsmuller 1979 | 0/51 | 6/51 | | 0.2 % | 0.08 [ 0.00, 1.33 ] |
| Ley 2004 | 4/88 | 3/88 | | 0.6 % | 1.33 [ 0.31, 5.78 ] |
| Moy 2001 | 2/117 | 1/118 | | 0.2 % | 2.02 [ 0.19, 21.94 ] |
| MRC 1968 | 39/199 | 40/194 | | 8.2 % | 0.95 [ 0.64, 1.41 ] |
| Oslo Diet-Heart 1966 | 34/206 | 54/206 | | 8.6 % | 0.63 [ 0.43, 0.92 ] |
| Rose corn oil 1965 | 9/28 | 3/13 | | 1.1 % | 1.39 [ 0.45, 4.31 ] |
| Rose olive 1965 | 7/26 | 2/13 | | 0.7 % | 1.75 [ 0.42, 7.27 ] |
| STARS 1992 | 1/27 | 2/28 | | 0.3 % | 0.52 [ 0.05, 5.39 ] |
| Veterans Admin 1969 | 54/424 | 71/422 | | 11.4 % | 0.76 [ 0.55, 1.05 ] |
| WHI without CVD 2006 | 435/19541 | 671/29294 | | 46.7 % | 0.97 [ 0.86, 1.09 ] |
| **Total (95% CI)** | **21725** | **31442** | | **100.0 %** | **0.90 [ 0.80, 1.01 ]** |

Total events: 717 (reduced SFA), 997 (usual diet)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.07$, df = 10 (P = 0.35); $I^2 = 10\%$

Test for overall effect: Z = 1.72 (P = 0.085)

Test for subgroup differences: Not applicable

## Analysis 2.2. Comparison 2 SFA reduction vs usual diet - secondary health events, Outcome 2 Non-fatal MI.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 2 SFA reduction vs usual diet - secondary health events

Outcome: 2 Non-fatal MI

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| DART 1989 | 35/1018 | 47/1015 | | 12.4 % | 0.74 [ 0.48, 1.14 ] |
| Moy 2001 | 2/117 | 1/118 | | 0.5 % | 2.02 [ 0.19, 21.94 ] |
| MRC 1968 | 25/199 | 25/194 | | 9.3 % | 0.97 [ 0.58, 1.64 ] |
| Oslo Diet-Heart 1966 | 24/206 | 31/206 | | 10.0 % | 0.77 [ 0.47, 1.27 ] |
| Rose corn oil 1965 | 7/28 | 3/13 | | 2.1 % | 1.08 [ 0.33, 3.53 ] |
| Rose olive 1965 | 6/26 | 2/13 | | 1.4 % | 1.50 [ 0.35, 6.43 ] |
| Veterans Admin 1969 | 13/424 | 21/422 | | 5.9 % | 0.62 [ 0.31, 1.21 ] |
| WHI with CVD 2006 | 82/908 | 90/1369 | | 20.9 % | 1.37 [ 1.03, 1.83 ] |
| WHI without CVD 2006 | 353/18633 | 581/27925 | | 37.3 % | 0.91 [ 0.80, 1.04 ] |
| **Total (95% CI)** | **21559** | **31275** | | **100.0 %** | **0.95 [ 0.80, 1.13 ]** |

Total events: 547 (reduced SFA), 801 (usual diet)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.03$, df = 8 (P = 0.20); $I^2 = 27\%$

Test for overall effect: Z = 0.56 (P = 0.57)

Test for subgroup differences: Not applicable

### Analysis 2.3. Comparison 2 SFA reduction vs usual diet - secondary health events, Outcome 3 Stroke.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 2 SFA reduction vs usual diet - secondary health events

Outcome: 3 Stroke

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Ley 2004 | 1/88 | 5/88 | | 0.3 % | 0.20 [ 0.02, 1.68 ] |
| Moy 2001 | 1/117 | 1/118 | | 0.2 % | 1.01 [ 0.06, 15.93 ] |
| MRC 1968 | 2/199 | 0/194 | | 0.1 % | 4.88 [ 0.24, 100.89 ] |
| Oslo Diet-Heart 1966 | 2/206 | 1/206 | | 0.2 % | 2.00 [ 0.18, 21.89 ] |
| STARS 1992 | 0/27 | 1/28 | | 0.1 % | 0.35 [ 0.01, 8.12 ] |
| Veterans Admin 1969 | 13/424 | 22/422 | | 2.8 % | 0.59 [ 0.30, 1.15 ] |
| WHI with CVD 2006 | 206/908 | 308/1369 | | 51.8 % | 1.01 [ 0.86, 1.18 ] |
| WHI without CVD 2006 | 228/18633 | 334/27925 | | 44.5 % | 1.02 [ 0.87, 1.21 ] |
| **Total (95% CI)** | **20602** | **30350** | | **100.0 %** | **1.00 [ 0.89, 1.12 ]** |

Total events: 453 (reduced SFA), 672 (usual diet)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.49$, df = 7 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

## Analysis 2.4. Comparison 2 SFA reduction vs usual diet - secondary health events, Outcome 4 CHD mortality.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 2 SFA reduction vs usual diet - secondary health events

Outcome: 4 CHD mortality

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| DART 1989 | 97/1018 | 97/1015 | | 20.9 % | 1.00 [ 0.76, 1.30 ] |
| Houtsmuller 1979 | 0/51 | 5/51 | | 0.3 % | 0.09 [ 0.01, 1.60 ] |
| MRC 1968 | 25/199 | 25/194 | | 7.9 % | 0.97 [ 0.58, 1.64 ] |
| Oslo Diet-Heart 1966 | 37/206 | 50/206 | | 13.1 % | 0.74 [ 0.51, 1.08 ] |
| Rose corn oil 1965 | 5/28 | 1/13 | | 0.6 % | 2.32 [ 0.30, 17.92 ] |
| Rose olive 1965 | 3/26 | 0/13 | | 0.3 % | 3.63 [ 0.20, 65.44 ] |
| Sydney Diet-Heart 1978 | 35/221 | 23/237 | | 8.6 % | 1.63 [ 1.00, 2.67 ] |
| Veterans Admin 1969 | 41/424 | 50/422 | | 12.5 % | 0.82 [ 0.55, 1.21 ] |
| WHI with CVD 2006 | 34/908 | 49/1369 | | 10.7 % | 1.05 [ 0.68, 1.61 ] |
| WHI without CVD 2006 | 124/18633 | 185/27925 | | 25.2 % | 1.00 [ 0.80, 1.26 ] |
| **Total (95% CI)** | **21714** | **31445** | | **100.0 %** | **0.98 [ 0.84, 1.15 ]** |

Total events: 401 (reduced SFA), 485 (usual diet)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.33$, df = 9 (P = 0.25); $I^2 = 21\%$

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

### Analysis 2.5. Comparison 2 SFA reduction vs usual diet - secondary health events, Outcome 5 CHD events.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 2 SFA reduction vs usual diet - secondary health events

Outcome: 5 CHD events

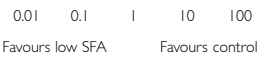
| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| DART 1989 | 132/1018 | 144/1015 | | 14.9 % | 0.91 [ 0.73, 1.14 ] |
| Houtsmuller 1979 | 8/51 | 30/51 | | 4.8 % | 0.27 [ 0.14, 0.52 ] |
| Ley 2004 | 5/88 | 3/88 | | 1.4 % | 1.67 [ 0.41, 6.76 ] |
| Moy 2001 | 3/135 | 1/132 | | 0.6 % | 2.93 [ 0.31, 27.84 ] |
| MRC 1968 | 50/199 | 50/194 | | 11.1 % | 0.97 [ 0.69, 1.37 ] |
| Oslo Diet-Heart 1966 | 64/206 | 90/206 | | 13.7 % | 0.71 [ 0.55, 0.92 ] |
| Rose corn oil 1965 | 12/28 | 3/13 | | 2.2 % | 1.86 [ 0.63, 5.47 ] |
| Rose olive 1965 | 9/26 | 3/13 | | 2.0 % | 1.50 [ 0.49, 4.62 ] |
| STARS 1992 | 3/27 | 10/28 | | 1.9 % | 0.31 [ 0.10, 1.01 ] |
| Veterans Admin 1969 | 60/424 | 78/422 | | 12.0 % | 0.77 [ 0.56, 1.04 ] |
| WHI with CVD 2006 | 194/908 | 257/1369 | | 16.7 % | 1.14 [ 0.96, 1.34 ] |
| WHI without CVD 2006 | 806/18633 | 1292/27925 | | 18.9 % | 0.93 [ 0.86, 1.02 ] |
| **Total (95% CI)** | **21743** | **31456** | | **100.0 %** | **0.87 [ 0.74, 1.03 ]** |

Total events: 1346 (reduced SFA), 1961 (usual diet)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 31.88$, df = 11 (P = 0.00080); $I^2 = 66\%$

Test for overall effect: Z = 1.57 (P = 0.12)

Test for subgroup differences: Not applicable



## Analysis 2.6. Comparison 2 SFA reduction vs usual diet - secondary health events, Outcome 6 Diabetes diagnoses.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 2 SFA reduction vs usual diet - secondary health events

Outcome: 6 Diabetes diagnoses

| Study or subgroup | reduced SFA n/N | usual diet n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| WHI without CVD 2006 | 1303/19541 | 2039/29294 | | | 0.96 [ 0.90, 1.02 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 1303 (reduced SFA), 2039 (usual diet) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

## Analysis 3.1. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 1 Total cholesterol, mmol/L.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

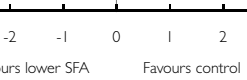
Outcome: 1 Total cholesterol, mmol/L

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| DART 1989 | 924 | 6.31 (1.14) | 931 | 6.57 (1.16) | | 17.0 % | -0.26 [ -0.36, -0.16 ] |
| Houtsmuller 1979 | 48 | 6.43 (0.65) | 48 | 6.9 (0.81) | | 8.3 % | -0.47 [ -0.76, -0.18 ] |
| Ley 2004 | 51 | -0.2 (0.79) | 52 | -0.15 (1.3) | | 5.3 % | -0.05 [ -0.46, 0.36 ] |
| MRC 1968 | 88 | -1.11 (0) | 89 | -0.47 (0) | | | Not estimable |
| Oslo Diet-Heart 1966 | 168 | 6.12 (0) | 161 | 7.19 (0) | | | Not estimable |
| Oxford Retinopathy 1978 | 29 | 4.94 (0.82) | 29 | 4.87 (0.79) | | 5.3 % | 0.07 [ -0.34, 0.48 ] |
| Rose corn oil 1965 | 13 | -0.78 (0.923) | 9 | -0.2 (1.031) | | 1.6 % | -0.58 [ -1.42, 0.26 ] |
| Rose olive 1965 | 15 | 0.1 (2.023) | 9 | -0.2 (1.031) | | 0.8 % | 0.30 [ -0.93, 1.53 ] |
| Simon 1997 | 34 | 4.87 (0.87) | 38 | 5.21 (0.18) | | 8.2 % | -0.34 [ -0.64, -0.04 ] |
| STARS 1992 | 26 | 6.17 (0.459) | 24 | 6.93 (0.98) | | 5.0 % | -0.76 [ -1.19, -0.33 ] |
| Sydney Diet-Heart 1978 | 221 | 6.5 (1.2) | 237 | 6.8 (1.1) | | 11.6 % | -0.30 [ -0.51, -0.09 ] |
| Veterans Admin 1969 | 423 | 4.93 (3.72) | 420 | 5.3 (1.87) | | 5.6 % | -0.37 [ -0.77, 0.03 ] |
| WHI without CVD 2006 | 1133 | -0.264 (0.828) | 1699 | -0.18 (0.825) | | 18.9 % | -0.09 [ -0.15, -0.02 ] |
| WINS 2006 | 96 | -0.0005 (0.728) | 100 | 0.14 (0.675) | | 12.3 % | -0.14 [ -0.34, 0.05 ] |
| **Total (95% CI)** | **3269** | | **3846** | | | **100.0 %** | **-0.24 [ -0.36, -0.13 ]** |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 27.85$, df = 11 (P = 0.003); $I^2 = 60\%$

Test for overall effect: Z = 4.32 (P = 0.000015)

Test for subgroup differences: Not applicable



## Analysis 3.2. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 2 LDL cholesterol, mmol/L.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

Outcome: 2 LDL cholesterol, mmol/L

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Ley 2004 | 51 | -0.32 (0.64) | 52 | -0.16 (1.15) | | 11.7 % | -0.16 [ -0.52, 0.20 ] |
| Moy 2001 | 117 | -0.69 (1.1) | 118 | -0.4 (0.8) | | 20.0 % | -0.29 [ -0.54, -0.04 ] |
| Simon 1997 | 34 | 2.79 (0.82) | 37 | 3.09 (0.99) | | 9.0 % | -0.30 [ -0.72, 0.12 ] |
| STARS 1992 | 26 | 4.19 (0.51) | 24 | 4.67 (0.931) | | 9.0 % | -0.48 [ -0.90, -0.06 ] |
| WHI without CVD 2006 | 1133 | -0.251 (0.758) | 1699 | -0.16 (0.753) | | 50.3 % | -0.09 [ -0.15, -0.03 ] |
| **Total (95% CI)** | **1361** | | **1930** | | | **100.0 %** | **-0.19 [ -0.33, -0.05 ]** |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.30$, df = 4 (P = 0.18); $I^2 = 37\%$

Test for overall effect: Z = 2.73 (P = 0.0063)

Test for subgroup differences: Not applicable

## Analysis 3.3. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 3 HDL cholesterol, mmol/L.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

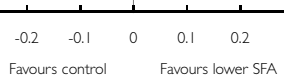
Outcome: 3 HDL cholesterol, mmol/L

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| DART 1989 | 924 | 1.04 (0.31) | 931 | 1.05 (0.3) | | 28.9 % | -0.01 [ -0.04, 0.02 ] |
| Ley 2004 | 51 | 0.01 (0.14) | 52 | 0.06 (0.36) | | 2.0 % | -0.05 [ -0.16, 0.06 ] |
| Moy 2001 | 117 | 0.044 (0.3) | 118 | 0.01 (0.2) | | 5.2 % | 0.04 [ -0.03, 0.10 ] |
| Simon 1997 | 34 | 1.44 (0.58) | 38 | 1.56 (0.55) | | 0.3 % | -0.12 [ -0.38, 0.14 ] |
| STARS 1992 | 26 | 1.14 (0.153) | 24 | 1.21 (0.294) | | 1.3 % | -0.07 [ -0.20, 0.06 ] |
| WHI without CVD 2006 | 1133 | -0.018 (0.243) | 1699 | -0.01 (0.264) | | 62.2 % | -0.01 [ -0.03, 0.01 ] |
| **Total (95% CI)** | **2285** | | **2862** | | | **100.0 %** | **-0.01 [ -0.02, 0.01 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.94$, df = 5 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 1.25 (P = 0.21)

Test for subgroup differences: Not applicable



## Analysis 3.4. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 4 Triglycerides, mmol/L.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

Outcome: 4 Triglycerides, mmol/L

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Houtsmuller 1979 | 48 | 0.79 (0.6) | 48 | 1.05 (0.6) | | 15.9 % | -0.26 [ -0.50, -0.02 ] |
| Ley 2004 | 51 | 0.37 (0.71) | 52 | 0.12 (1.59) | | 6.0 % | 0.25 [ -0.22, 0.72 ] |
| Moy 2001 | 117 | -0.4 (2) | 118 | -0.06 (1.9) | | 5.5 % | -0.34 [ -0.84, 0.16 ] |
| Simon 1997 | 34 | 1.35 (1.05) | 37 | 1.25 (0.61) | | 7.8 % | 0.10 [ -0.30, 0.50 ] |
| STARS 1992 | 26 | 1.85 (1.02) | 24 | 2.35 (0.98) | | 4.6 % | -0.50 [ -1.05, 0.05 ] |
| Sydney Diet-Heart 1978 | 221 | 1.6 (0.9) | 237 | 1.7 (0.9) | | 22.9 % | -0.10 [ -0.26, 0.06 ] |
| WHI without CVD 2006 | 1133 | 0.011 (0.005) | 1699 | 0.01 (0.003) | | 37.5 % | 0.0 [ 0.00, 0.00 ] |
| **Total (95% CI)** | **1630** | | **2215** | | | **100.0 %** | **-0.08 [ -0.21, 0.04 ]** |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.13$, df = 6 (P = 0.06); $I^2 = 51\%$

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable

### Analysis 3.5. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 5 total cholesterol /HDL ratio.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

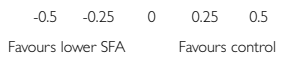
Outcome: 5 total cholesterol /HDL ratio

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Ley 2004 | 51 | -0.34 (1) | 52 | -0.53 (1.73) | | 14.6 % | 0.19 [ -0.35, 0.73 ] |
| STARS 1992 | 26 | 5.5 (0.918) | 24 | 6.08 (1.666) | | 8.3 % | -0.58 [ -1.33, 0.17 ] |
| WHI without CVD 2006 | 1133 | -0.2 (0.8) | 1699 | -0.1 (1) | | 77.0 % | -0.10 [ -0.17, -0.03 ] |
| **Total (95% CI)** | **1210** | | **1775** | | | **100.0 %** | **-0.10 [ -0.33, 0.13 ]** |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.65$, df = 2 (P = 0.27); $I^2$ =24%

Test for overall effect: Z = 0.83 (P = 0.40)

Test for subgroup differences: Not applicable




### Analysis 3.6. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 6 LDL /HDL ratio.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

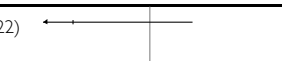
Outcome: 6 LDL /HDL ratio

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| STARS 1992 | 26 | 3.74 (0.71) | 24 | 4.1 (1.22) | | | -0.36 [ -0.92, 0.20 ] |
| **Subtotal (95% CI)** | **0** | | **0** | | | | **0.0 [ 0.0, 0.0 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 3.7. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 7 Lp(a), mmol/L.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

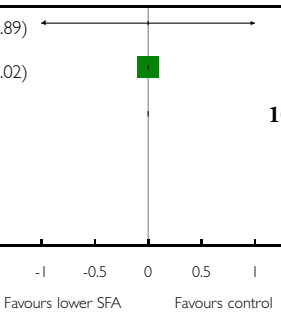
Outcome: 7 Lp(a), mmol/L

| Study or subgroup | Reduced SFA N | Mean(SD) | Control or usual diet N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| STARS 1992 | 26 | 0.96 (1.89) | 24 | 0.96 (2.89) | | 0.0 % | 0.0 [ -1.37, 1.37 ] |
| WHI without CVD 2006 | 1133 | 0.03 (0.02) | 1699 | 0.03 (0.02) | | 100.0 % | 0.0 [ 0.00, 0.00 ] |
| **Total (95% CI)** | **1159** | | **1723** | | | **100.0 %** | **0.0 [ 0.00, 0.00 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

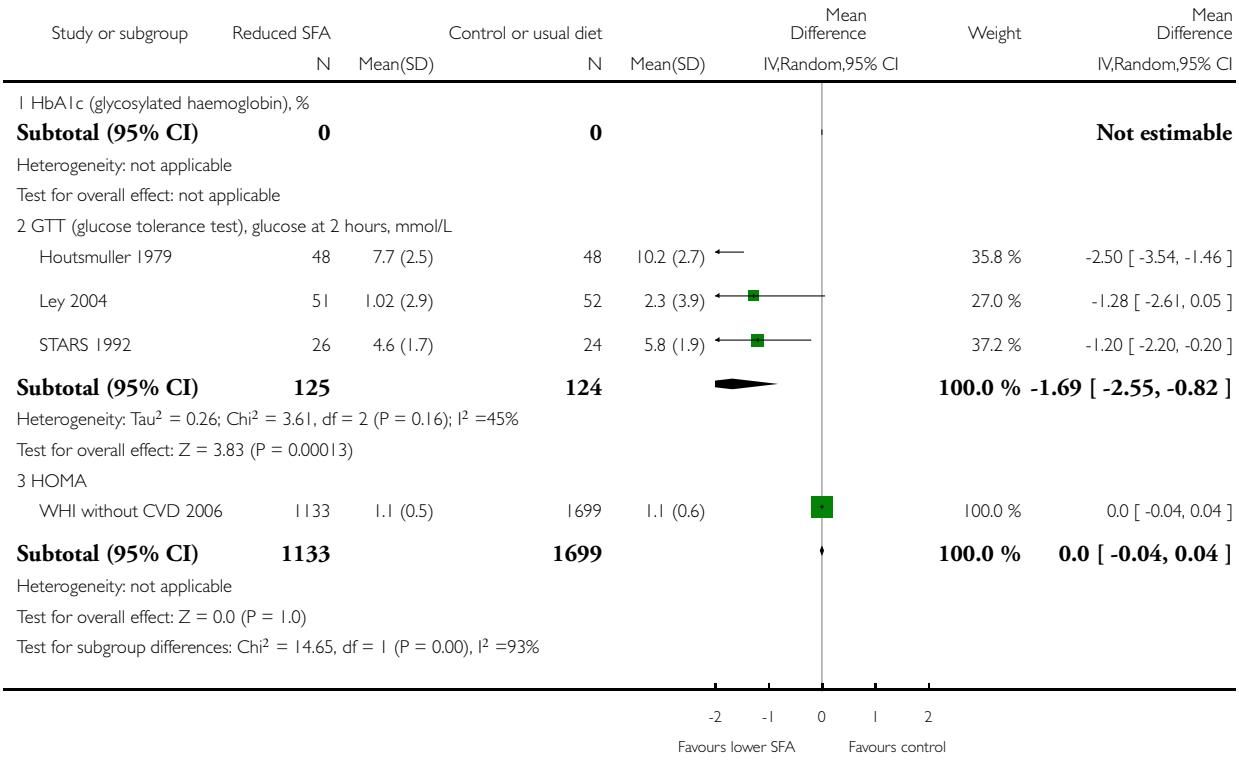


### Analysis 3.8. Comparison 3 SFA reduction vs usual diet - other secondary outcomes, Outcome 8 Insulin sensitivity.

Review: Reduction in saturated fat intake for cardiovascular disease

Comparison: 3 SFA reduction vs usual diet - other secondary outcomes

Outcome: 8 Insulin sensitivity




## ADDITIONAL TABLES

**Table 1. Comparison of study interventions for included RCTs**

| Reference | Population | CVD risk category | Is intervention delivered to Individual or group? | intervention given by? | Face-to-face or other? | Number of visits | Is intervention advice only or other intervention? |
|---|---|---|---|---|---|---|---|
| Black 1994 | People with non-melanoma skin cancer | Low | Unclear | Dietitian | Face-to-face | 8 x weekly classes then monthly follow-up ses- | Advice (behaviour techniques learning) |

**Table 1. Comparison of study interventions for included RCTs** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | sions | |
| **DART 1989** | Men recovering from a MI | High | Individual | Dietitian | Face-to-face | 9 | Advice (diet advice, recipes and encouragement) |
| **Houtsmuller 1979** | Adults with newly-diagnosed diabetes | Moderate | Unclear | Dietitian | Unclear | Unclear | Advice? |
| **Ley 2004** | People with impaired glucose intolerance or high normal blood glucose | Moderate | Small group | Unclear | Face-to-face | Monthly meetings | Advice (education, personal goal setting, self-monitoring) |
| **Moy 2001** | Middle-aged siblings of people with early CHD, with at least 1 CVD risk factor | Moderate | Individual | Trained nurse | Face-to-face | 6 - 8 weekly for 2 years | Advice (individualised counselling sessions) |
| **MRC 1968** | Free-living men who have survived a 1st MI | High | Individual | Dietitian | Face-to-face | Unclear | Advice and supplement (soy oil) |
| **Oslo Diet-Heart 1966** | Men with previous MI | High | Individual | Dietitian | Face-to-face and other | Unclear | Advice and supplement (food) |
| **Oxford Retinopathy 1978** | Newly-diagnosed non-insulin-dependent diabetics | Moderate | Individual | Diabetes dietitian | Face-to-face | After 1 month then at 3-month intervals | Advice |
| **Rose corn oil 1965** | Men (?) with angina or following MI | High | Unclear | Unclear | Unclear | Follow-up clinic monthly, then every 2 months | Advice and supplement (oil) |
| **Rose olive 1965** | Men (?) with angina or following MI | High | Unclear | Unclear | Unclear | Follow-up clinic monthly, then | Advice and supplement (oil) |

**Table 1. Comparison of study interventions for included RCTs** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | every 2 months | |
| **Simon 1997** | Women with a high risk of breast cancer | Low | Individual followed by individual or group | Dietitian | Face-to-face | Bi-weekly over 3 months followed by monthly | Advice (individualised eating plan and counselling sessions) |
| **STARS 1992** | Men with angina referred for angiography | High | individual | Dietitian | Face-to-face | Clinic visits at 3-months intervals | Advice |
| **Sydney Diet-Heart 1978** | Men with angina referred for angiography | High | Individual | Unclear | Face-to-face | 3 times in 1st year and twice annually thereafter | Advice |
| **Veterans Admin 1969** | Men living at the Veterans Administration Center | Low | Individual | Unclear (whole diet provided) | N/A | N/A | Diet provided |
| **WHI with CVD 2006** | Post-menopausal women aged 50 - 79 with CVD at baseline | High | Group | Nutritionists | Face-to-face | 18 sessions/ 1st yr and quarterly maintenance sessions after | Advice |
| **WHI without CVD 2006** | Post-menopausal women aged 50 - 79 without CVD at baseline | Low | Group | Nutritionists | Face-to-face | 18 sessions/ 1st yr and quarterly maintenance sessions after | Advice |
| **WINS 2006** | Women with localised resected breast cancer | Low | Individual followed by group | Dietitian | Face-to-face | 8 bi-weekly sessions, then 3-monthly contact and optional monthly sessions | Advice |

N/A: not applicable

**Table 2. Number of participants and number of outcomes for dichotomous variables (by intervention arm)**

| | Participants | All-cause mortality | CV mortality | CVD events | MI | Non-fatal MI | Stroke | CHD mortality | CHD events | Diabetes Diagnoses |
|---|---|---|---|---|---|---|---|---|---|---|
| Black 1994 | 133 | 133 | 133 | 133 | 0 | 0 | 0 | 0 | 0 | 0 |
| DART 1989 | 2033 | 2033 | 2033 | 2033 | 2033 | 2033 | 0 | 2033 | 2033 | 0 |
| Houtsmull 1979 | 102 | 0 | 0 | 102 | 102 | 0 | 0 | 102 | 102 | 0 |
| Ley 2004 | 176 | 176 | 176 | 176 | 176 | 0 | 176 | 0 | 176 | 0 |
| Moy 2001 | 267 | 0 | 0 | 235 | 235 | 235 | 235 | 0 | 267 | 0 |
| MRC 1968 | 393 | 393 | 393 | 393 | 393 | 393 | 393 | 393 | 393 | 0 |
| Oslo Diet-Heart 1966 | 412 | 412 | 412 | 412 | 412 | 412 | 412 | 412 | 412 | 0 |
| Oxford Retinopathy 1978 | 249 (data not provided by arm) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rose corn oil 1965 | 41 | 41 | 41 | 41 | 41 | 41 | 0 | 41 | 41 | 0 |
| Rose olive 1965 | 39 | 39 | 39 | 39 | 39 | 39 | 0 | 39 | 39 | 0 |
| Simon 1997 | 194 (data not provided by arm) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| STARS 1992 | 60 | 55 | 55 | 55 | 55 | 0 | 55 | 0 | 55 | 0 |

**Table 2. Number of participants and number of outcomes for dichotomous variables (by intervention arm)** (*Continued*)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Sydney Diet-Heart 1978** | 458 | 458 | 458 | 0 | 0 | 0 | 0 | 458 | 0 | 0 |
| **Veterans Admin 1969** | 846 | 846 | 846 | 846 | 846 | 846 | 846 | 846 | 846 | 0 |
| **WHI with CVD 2006** | 2277 | 0 | 2277 | 2277 | 0 | 2277 | 2277 | 2277 | 2277 | 0 |
| **WHI without CVD 2006** | 48835 | 48835 | 46558 | 46558 | 48835 | 46558 | 46558 | 46558 | 46558 | 48835 |
| **WINS 2006** | 2437 | 2437 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total Participants** | 58509 | 55858 | 53421 | 53300 | 53167 | 52834 | 50952 | 53159 | 53204 | 48835 |
| **Percent of participants for this outcome** | 100% | 95% | 91% | 91% | 91% | 90% | 87% | 91% | 91% | 83% |

These numbers are the numbers of participants in each study who were available for assessment of outcomes within meta-analysis (not necessarily the number of participants randomised within the trial).

**Table 3. Number of participants and number of participants with data for continuous outcomes (by intervention arm)**

| | Participants | Total cholesterol | LDL cholesterol | HDL cholesterol | Triglycerides | TG/ HDL ratio | Total cholesterol/ HDL ratio | LDL/ HDL ratio | LP (a) | Insulin sensitivity |
|---|---|---|---|---|---|---|---|---|---|---|
| **Black 1994** | 133 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 3. Number of participants and number of participants with data for continuous outcomes (by intervention arm)** (*Continued*)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **DART 1989** | 2033 | 1855 | 0 | 1855 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Houtsmull 1979** | 102 | 96 | 0 | 0 | 96 | 0 | 0 | 0 | 0 | 96 |
| **Ley 2004** | 176 | 103 | 103 | 103 | 103 | 0 | 103 | 0 | 0 | 103 |
| **Moy 2001** | 267 | 0 | 235 | 235 | 235 | 0 | 0 | 0 | 0 | 0 |
| **MRC 1968** | 393 | 177 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Oslo Diet-Heart 1966** | 412 | 329 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Oxford Retinopathy 1978** | 249 | 58 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Rose corn oil 1965** | 41 | 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Rose olive 1965** | 39 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Simon 1997** | 194 | 72 | 71 | 72 | 71 | 0 | 0 | 0 | 0 | 0 |
| **STARS 1992** | 55 | 50 | 50 | 50 | 50 | 0 | 50 | 50 | 50 | 50 |
| **Sydney Diet-Heart 1978** | 458 | 458 | 0 | 0 | 458 | 0 | 0 | 0 | 0 | 0 |
| **Veterans Admin 1969** | 846 | 843 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 3. Number of participants and number of participants with data for continuous outcomes (by intervention arm)** (*Continued*)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **WHI with CVD 2006** | 2277 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **WHI without CVD 2006** | 48835 | 2832 | 2832 | 2832 | 2832 | 0 | 2832 | 0 | 2832 | 2832 |
| **WINS 2006** | 2437 | 196 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total Participants** | 58952 | 7115 | 3291 | 5147 | 3845 | 0 | 2985 | 50 | 2882 | 3081 |
| **Percent of participants for this outcome** | 100% | 12% | 6% | 9% | 7% | 0% | 5% | 0.1% | 5% | 5% |

These numbers are the numbers of participants in each study who were available for assessment of outcomes within meta-analysis (not necessarily the number of participants randomised within the trial).

**Table 4. All-cause mortality, sensitivity analyses**

| **Analysis** | | **RR (95% CI) of all-cause mortality** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.97 (0.90 to 1.05) | 3% | 3276 | > 55,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.97 (0.89 to 1.06) | 11% | 3231 | > 53,000 |
| | SFA significantly reduced | 0.99 (0.92 to 1.06) | 0% | 3095 | > 54,000 |
| | TC significantly reduced | 0.96 (0.83 to 1.11) | 33% | 2871 | > 52,000 |
| | Minus WHI | 0.96 (0.84 to 1.11) | 12% | 872 | > 7000 |
| | Mantel-Haenszel fixed-effect | 0.98 (0.91 to 1.04) | 3% | 3276 | > 55,000 |

**Table 4. All-cause mortality, sensitivity analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | Peto fixed-effect | 0.97 (0.90 to 1.05) | 16% | 3276 | > 55,000 |

SFA: saturated fatty acids
TC: total cholesterol

**Table 5. All-cause mortality, subgroup data**

| **Analysis, P value for subgroup differences** | | **RR (95% CI) of all-cause mortality** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.79** | PUFA replacement | 0.96 (0.82 to 1.13) | 26% | 824 | > 4000 |
| | MUFA replacement | 3.00 (0.33 to 26.99) | N/A | 4 | 52 |
| | CHO replacement | 0.98 (0.91 to 1.05) | 0% | 2677 | > 53,000 |
| | Protein replacement | 0.98 (0.91 to 1.06) | 0% | 2673 | > 53,000 |
| **Subgroup by duration, P = 0.60** | Up to 24 months | 0.99 (0.78 to 1.26) | 0% | 236 | > 2000 |
| | > 24 to 48 months | 0.96 (0.83 to 1.12) | 0% | 414 | > 1000 |
| | > 48 months | 1.00 (0.79 to 1.27) | 55% | 2618 | > 52,000 |
| | Unclear duration | 0.33 (0.07 to 1.61) | N/A | 8 | > 100 |
| **Subgroup by baseline SFA, P = 0.48** | Up to 12%E SFA | 1.18 (0.60 to 2.32) | N/A | 34 | > 2400 |
| | > 12 to 15%E SFA | 1.01 (0.86 to 1.19) | 26% | 2706 | > 51,000 |
| | > 15 to 18%E SFA | 0.35 (0.04 to 3.12) | N/A | 4 | 55 |
| | > 18%E SFA | 0.98 (0.83 to 1.15) | N/A | 351 | 846 |
| **Subgroup by SFA change, P = 0.31** | Up to 4%E SFA difference | 1.02 (0.88 to 1.19) | 26% | 2737 | > 53,000 |
| | > 4 to 8%E SFA difference | 0.41 (0.08 to 2.07) | 0% | 7 | > 100 |
| | > 8%E SFA difference | 0.98 (0.83 to 1.15) | N/A | 351 | > 800 |
| **Subgroup by sex, P = 0.40** | Men | 0.96 (0.83 to 1.11) | 13% | 830 | > 4000 |

**Table 5. All-cause mortality, subgroup data** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | Women | 0.98 (0.91 to 1.06) | 0% | 2438 | > 51,000 |
| | Mixed, men and women | 0.33 (0.07 to 1.61) | N/A | 8 | 176 |
| **Subgroup by CVD risk, P = 0.40** | Low CVD risk | 0.98 (0.91 to 1.05) | 0% | 2792 | > 52,000 |
| | Moderate CVD risk | 0.33 (0.07 to 1.61) | N/A | 8 | 176 |
| | Existing CVD | 0.97 (0.90 to 1.05) | 33% | 476 | > 3000 |
| **Subgroup by serum TC reduction, P = 0.85** | TC reduced by ≥ 0.2 mmol/L | 0.96 (0.81 to 1.14) | 32% | 823 | > 4000 |
| | TC reduced by < 0.2 mmol/L | 0.98 (0.91 to 1.06) | 0% | 2450 | > 51,000 |
| | Unclear TC change | 0.51 (0.05 to 5.46) | N/A | 3 | > 100 |
| **Subgroup by decade of publication, P = 0.28** | 1960s | 0.92 (0.80 to 1.07) | 2% | 532 | > 1700 |
| | 1970s | 1.49 (0.95 to 2.34) | N/A | 67 | 458 |
| | 1980s | 0.98 (0.76 to 1.25) | N/A | 224 | 2033 |
| | 1990s | 0.41 (0.08 to 2.07) | 0% | 7 | 188 |
| | 2000s | 0.98 (0.83 to 1.15) | 5% | 2446 | > 51,000 |

CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 6. CVD mortality, sensitivity analyses**

| **Analysis** | | **RR (95% CI) of CVD mortality** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.95 (0.80 to 1.12) | 30% | 1096 | >53000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.96 (0.81 to 1.13) | 32% | 1089 | > 53,000 |

**Table 6. CVD mortality, sensitivity analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | SFA significantly reduced | 0.96 (0.79 to 1.18) | 42% | 945 | > 52,000 |
| | TC significantly reduced | 1.00 (0.86 to 1.16) | 19% | 942 | > 52,000 |
| | Minus WHI | 0.92 (0.72 to 1.18) | 40% | 563 | > 4000 |
| | Mantel-Haenszel fixed-effect | 0.95 (0.85 to 1.07) | 30% | 1096 | > 53,000 |
| | Peto fixed-effect | 0.95 (0.84 to 1.08) | 41% | 1096 | > 53,000 |

SFA: saturated fatty acid
TC: total cholesterol

**Table 7. CVD mortality, subgroup data**

| **Analysis, P value for subgroup differences** | | **RR (95% CI) of CVD mortality** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.79** | PUFA replacement | 0.95 (0.73 to 1.25) | 55% | 553 | > 4000 |
| | MUFA replacement | 3.00 (0.33 to 26.99) | N/A | 4 | 52 |
| | CHO replacement | 0.99 (0.86 to 1.14) | 0% | 745 | > 51,000 |
| | Protein replacement | 0.99 (0.86 to 1.14) | 0% | 741 | > 51,000 |
| **Subgroup by duration, P = 0.33** | Up to 24 months | 1.26 (0.54 to 2.94) | 26% | 213 | > 2000 |
| | > 24 to 48 months | 0.79 (0.57 to 1.08) | 14% | 194 | > 1000 |
| | > 48 months | 1.01 (0.79 to 1.30) | 54% | 685 | > 49,000 |
| | Unclear duration | 0.25 (0.03 to 2.19) | N/A | 5 | > 100 |
| **Subgroup by baseline SFA, P = 0.13** | Up to 12%E SFA | | N/A | | |
| | > 12 to 15%E SFA | 1.04 (0.88 to 1.24) | 19% | 803 | > 51,000 |
| | > 15 to 18%E SFA | 0.35 (0.04 to 3.12) | N/A | 4 | 55 |
| | > 18%E SFA | 0.70 (0.51 to 0.96) | N/A | 138 | 846 |

**Table 7. CVD mortality, subgroup data** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **Subgroup by SFA change, P = 0.08** | Up to 4%E SFA difference | 1.05 (0.89 to 1.24) | 21% | 801 | >51000 |
| | > 4 to 8%E SFA difference | 0.29 (0.05 to 1.70) | 0% | 6 | > 100 |
| | > 8%E SFA difference | 0.70 (0.51 to 0.96) | N/A | 152 | > 900 |
| **Subgroup by sex, P = 0.45** | Men | 0.96 (0.73 to 1.25) | 48% | 559 | > 4000 |
| | Women | 1.00 (0.84 to 1.19) | 0% | 533 | > 48,000 |
| | Mixed, men and women | 0.25 (0.03 to 2.19) | NA | 5 | 176 |
| **Subgroup by CVD risk, p=0.26** | Low CVD risk | 0.84 (0.60 to 1.16) | 54% | 568 | > 47,000 |
| | Moderate CVD risk | 0.25 (0.03 to 2.19) | NA | 5 | 176 |
| | Existing CVD | 1.04 (0.83 to 1.31) | 33% | 524 | > 5000 |
| **Subgroup by serum TC reduction, P = 0.57** | TC reduced by ≥ 0.2 mmol/L | 0.95 (0.73 to 1.25) | 55% | 553 | > 4000 |
| | TC reduced by < 0.2 mmol/L | 1.00 (0.84 to 1.18) | 0% | 542 | > 49,000 |
| | Unclear TC change | 0.20 (0.01 to 4.15) | N/A | 2 | > 100 |
| **Subgroup by decade of publication, P = 0.04** | 1960s | 0.78 (0.63 to 0.97) | 2% | 289 | > 1700 |
| | 1970s | 1.59 (0.99 to 2.55) | N/A | 62 | 458 |
| | 1980s | 1.01 (0.77 to 1.31) | N/A | 201 | > 2000 |
| | 1990s | 0.29 (0.05 to 1.70) | 0% | 6 | 188 |
| | 2000s | 0.99 (0.83 to 1.18) | 0% | 538 | > 49,000 |

CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 8. CVD events, sensitivity analyses**

| Analysis | | RR (95% CI) of CVD events | $I^2$ | No. of events | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.83 (0.72 to 0.96) | 65% | 4377 | > 53,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.84 (0.72 to 0.97) | 69% | 4354 | > 52,000 |
| | SFA significantly reduced | 0.91 (0.79 to 1.04) | 53% | 4012 | > 52,000 |
| | TC significantly reduced | 0.81 (0.68 to 0.98) | 77% | 4092 | > 52,000 |
| | Minus WHI | 0.75 (0.61 to 0.91) | 51% | 932 | > 4000 |
| | Mantel-Haenszel fixed-effect | 0.93 (0.88 to 0.98) | 65% | 4377 | > 53,000 |
| | Peto fixed-effect | 0.92 (0.86 to 0.98) | 72% | 4377 | > 53,000 |

SFA: saturated fatty ac5d
TC: total cholesterol

**Table 9. CVD events, subgroup data**

| Analysis, P value for subgroup differences | | RR (95% CI) of CVD events | $I^2$ | No. of events | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.14** | PUFA replacement | 0.73 (0.58 to 0.92) | 69% | 884 | > 3000 |
| | MUFA replacement | 1.00 (0.53 to 1.89) | NA | 22 | 52 |
| | CHO replacement | 0.93 (0.79 to 1.08) | 57% | 3785 | > 51,000 |
| | Protein replacement | 0.98 (0.90 to 1.06) | 15% | 3757 | > 51,000 |
| **Subgroup by duration, P = 0.15** | Up to 24 months | 0.96 (0.78 to 1.16) | 0% | 330 | > 2000 |
| | > 24 to 48 months | 0.73 (0.56 to 0.95) | 50% | 383 | > 1000 |
| | > 48 months | 0.93 (0.79 to 1.11) | 75% | 3599 | > 49,000 |
| | Unclear duration | 0.43 (0.17 to 1.08) | NA | 65 | > 200 |

**Table 9. CVD events, subgroup data** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **Subgroup by baseline SFA, P = 0.13** | Up to 12%E SFA | | NA | | |
| | > 12 to 15%E SFA | 0.98 (0.91 to 1.05) | 6% | 3765 | > 51,000 |
| | > 15 to 18%E SFA | 0.41 (0.22 to 0.78) | NA | 28 | 55 |
| | > 18%E SFA | 0.79 (0.63 to 1.00) | NA | 219 | 846 |
| **Subgroup by SFA change, P = 0.005** | Up to 4%E SFA difference | 0.98 (0.91 to 1.05) | 6% | 3763 | > 51,000 |
| | > 4 to 8%E SFA difference | 0.40 (0.22 to 0.74) | 0% | 30 | > 100 |
| | > 8%E SFA difference | 0.79 (0.63 to 1.00) | NA | 219 | > 800 |
| **Subgroup by sex, P = 0.05** | Men | 0.80 (0.69 to 0.93) | 24% | 859 | > 3000 |
| | Women | 1.00 (0.88 to 1.14) | 60% | 3445 | > 48,000 |
| | Mixed, men and women | 0.59 (0.23 to 1.49) | 71% | 73 | > 500 |
| **Subgroup by CVD risk, P = 0.67** | Low CVD risk | 0.89 (0.75 to 1.06) | 40% | 3130 | > 47,000 |
| | Moderate CVD risk | 0.59 (0.23 to 1.49) | 71% | 73 | > 500 |
| | Existing CVD | 0.86 (0.71 to 1.05) | 63% | 1174 | > 5000 |
| **Subgroup by serum TC reduction, P = 0.03** | TC reduced by ≥ 0.2 mmol/L | 0.74 (0.59 to 0.92) | 63% | 887 | > 4000 |
| | TC reduced by < 0.2 mmol/L | 0.99 (0.90 to 1.08) | 15% | 3488 | > 49,00 |
| | Unclear TC change | 0.20 (0.01 to 4.15) | NA | 2 | > 100 |
| **Subgroup by decade of publication, P , 0.0001** | 1960s | 0.79 (0.69 to 0.91) | 0% | 546 | > 1700 |
| | 1970s | 0.27 (0.14 to 0.52) | NA | 38 | 102 |
| | 1980s | 0.92 (0.74 to 1.15) | NA | 283 | > 2000 |
| | 1990s | 0.40 (0.22 to 0.74) | 0% | 30 | 188 |
| | 2000s | 0.99 (0.89 to 1.11) | 25% | 3480 | > 49,000 |

CHO: carbohydrate
CVD: cardiovascular disease

MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 10. Metaregression of effects of SFA reduction on cardiovascular events**

| Regression factor | No. of studies | Constant | Coefficient (95% CI) | P value | Proportion of between study variation explained |
|---|---|---|---|---|---|
| **Change in SFA as %E** | 8 | 0.01 | 0.05 (-0.03 to 0.13) | 0.16 | 89% |
| **Change in SFA as % of control** | 8 | 0.26 | 0.01 (-0.01 to 0.03) | 0.14 | 89% |
| **Baseline SFA as %E** | 8 | 0.68 | -0.06 (-0.15 to 0.04) | 0.19 | 81% |
| **Change in TC, mmol/L** | 12 | 0.03 | 0.69 (0.05 to 1.33) | 0.04 | 99% |
| **Change in PUFA as %E** | 5 | -0.01 | -0.02 (-0.08 to 0.03) | 0.25 | 100% |
| **Change in MUFA as %E** | 5 | -0.26 | -0.03 (-0.14 to 0.09) | 0.50 | -87% |
| **Change in CHO as %E** | 7 | -0.11 | -0.00 (-0.05 to 0.05) | 0.92 | -273% |
| **Change in total fat intake as %E** | 9 | -0.17 | -0.01 (-0.03 to 0.01) | 0.28 | 100% |
| **Gender*** | 13 | -0.17 | -0.14 (-0.63 to 0.35) | 0.55 | -13% |
| **Study duration** | 13 | -0.47 | 0.00 (-0.01 to 0.02) | 0.76 | -24.8 |
| **CVD risk at baseline**** | 13 | -0.44 | 0.03 (-0.48 to 0.55) | 0.89 | -39% |

*0 = women, 1 = mixed, 2 = men
** 1 = Low CVD risk, 2 = Moderate CVD risk, 3 = existing CVD
CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid

**Table 11. Myocardial infarction (fatal and non-fatal), sensitivity analyses**

| Analysis | | RR (95% CI) of any MI | $I^2$ | No. of events | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.90 (0.80 to 1.01) | 10% | 1714 | > 53,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.89 (0.78 to 1.02) | 17% | 1707 | > 53,000 |
| | SFA significantly reduced | 0.94 (0.85 to 1.04) | 0% | 1520 | > 52,000 |
| | TC significantly reduced | 0.89 (0.76 to 1.05) | 26% | 1561 | > 52,000 |
| | Minus WHI | 0.85 (0.73 to 0.98) | 1% | 608 | > 4000 |
| | Mantel-Haenszel fixed-effect | 0.92 (0.84 to 1.01) | 10% | 1714 | > 53,000 |
| | Peto fixed-effect | 0.92 (0.83 to 1.01) | 31% | 1714 | > 53,000 |

SFA: saturated fatty acid
TC: total cholesterol

**Table 12. Myocardial infarction (fatal and non-fatal), subgroup data**

| Analysis, P value for subgroup differences | | RR (95% CI) of any MI | $I^2$ | No. of events | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.48** | PUFA replacement | 0.83 (0.67 to 1.02) | 29% | 591 | > 3000 |
| | MUFA replacement | 1.40 (0.51 to 3.85) | N/A | 12 | 52 |
| | CHO replacement | 0.96 (0.86 to 1.06) | 0% | 1392 | > 51,000 |
| | Protein replacement | 0.96 (0.86 to 1.07) | 0% | 1389 | > 51,000 |
| **Subgroup by duration, P = 0.78** | Up to 24 months | 0.95 (0.77 to 1.17) | 0% | 300 | > 2000 |
| | > 24 to 48 months | 0.83 (0.64 to 1.06) | 0% | 207 | > 1000 |
| | > 48 months | 0.81 (0.54 to 1.24) | 78% | 1194 | > 49,000 |
| | Unclear duration | 0.41 (0.02 to 7.73) | 71% | 13 | > 200 |

**Table 12. Myocardial infarction (fatal and non-fatal), subgroup data** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **Subgroup by baseline SFA, P = 0.50** | Up to 12%E SFA | | N/A | | |
| | > 12 to 15%E SFA | 0.96 (0.87 to 1.07) | 0% | 1392 | > 51,000 |
| | > 15 to 18%E SFA | 0.52 (0.05 to 5.39) | N/A | 3 | 55 |
| | > 18%E SFA | 0.76 (0.55 to 1.05) | N/A | 125 | 846 |
| **Subgroup by SFA change, P = 0.50** | Up to 4%E SFA difference | 0.96 (0.87 to 1.07) | 0% | 1392 | > 51,000 |
| | > 4 to 8%E SFA difference | 0.52 (0.05 to 5.39) | N/A | 3 | 55 |
| | > 8%E SFA difference | 0.76 (0.55 to 1.05) | N/A | 125 | > 800 |
| **Subgroup by sex, P = 0.35** | Men | 0.85 (0.73 to 0.98) | 0% | 592 | > 3000 |
| | Women | 0.97 (0.86 to 1.09) | N/A | 1106 | > 48,000 |
| | Mixed, men and women | 0.75 (0.13 to 4.47) | 51% | 16 | > 500 |
| **Subgroup by CVD risk, P = 0.96** | Low CVD risk | 0.90 (0.72 to 1.13) | 49% | 1231 | > 49,000 |
| | Moderate CVD risk | 0.75 (0.13 to 4.47) | 51% | 16 | > 500 |
| | Existing CVD | 0.87 (0.74 to 1.03) | 0% | 467 | > 2000 |
| **Subgroup by serum TC reduction, P = 0.12** | TC reduced by ≥ 0.2 mmol/L | 0.83 (0.70 to 0.98) | 9% | 592 | > 4000 |
| | TC reduced by < 0.2 mmol/L | 0.98 (0.87 to 1.10) | 0% | 1122 | > 49,000 |
| | Unclear TC change | | | | |
| **Subgroup by decade of publication, P = 0.23** | 1960s | 0.80 (0.64, 1.00) | 10% | 313 | 1731 |
| | 1970s | 0.08(0.0, 1.33) | N/A | 6 | 102 |
| | 1980s | 0.91 (0.73, 1.14) | N/A | 276 | 2033 |
| | 1990s | 0.52 (0.05, 5.39) | N/A | 3 | 55 |
| | 2000s | 0.98 (0.87, 1.10) | 0% | 1116 | > 49,000 |

CHO: carbohydrate
CVD: cardiovascular disease

MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 13. Non-fatal myocardial infarction, sensitivity analyses**

| **Analysis** | | **RR (95% CI) of non-fatal MI** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.95 (0.80 to 1.13) | 27% | 1348 | > 52,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.95 (0.80 to 1.13) | 27% | 1348 | > 52,000 |
| | SFA significantly reduced | 0.91 (0.72 to 1.25) | 60% | 1225 | > 51,000 |
| | TC significantly reduced | 0.97 (0.79 to 1.19) | 45% | 1296 | > 51,000 |
| | Minus WHI | 0.81 (0.64 to 1.04) | 0% | 242 | > 3000 |
| | Mantel-Haenszel fixed-effect | 0.94 (0.85 to 1.05) | 27% | 1348 | > 52,000 |
| | Peto fixed-effect | 0.94 (0.84 to 1.05) | 27% | 1348 | > 52,000 |

SFA: saturated fatty acid
TC: total cholesterol

**Table 14. Non-fatal myocardial infarction, subgroup analyses**

| **Analysis, P value for subgroup differences** | | **RR (95% CI) of non-fatal MI** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.62** | PUFA replacement | 0.80 (0.63 to 1.03) | 0% | 233 | > 3000 |
| | MUFA replacement | 1.20 (0.42 to 3.45) | N/A | 11 | 52 |
| | CHO replacement | 0.99 (0.73 to 1.35) | 75% | 1188 | > 50,000 |
| | Protein replacement | 0.99 (0.73 to 1.35) | 75% | 1188 | > 50,000 |
| **Subgroup by duration, P = 0.64** | Up to 24 months | 0.83 (0.57 to 1.22) | 0% | 103 | > 2000 |

**Table 14. Non-fatal myocardial infarction, subgroup analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | > 24 to 48 months | 0.82 (0.53 to 1.27) | 10% | 84 | > 1000 |
| | > 48 months | 1.01 (0.74 to 1.38) | 73% | 1161 | > 49,000 |
| | Unclear duration | | | | |
| **Subgroup by baseline SFA, P = 0.43** | Up to 12%E SFA | | N/A | | |
| | > 12 to 15%E SFA | 1.00 (0.75 to 1.35) | 64% | 1191 | > 51,000 |
| | > 15 to 18%E SFA | | | | |
| | > 18%E SFA | 0.62 (0.31 to 1.21) | N/A | 34 | 846 |
| **Subgroup by SFA change, P = 0.43** | Up to 4%E SFA difference | 1.00 (0.75 to 1.35) | 64% | 1191 | > 51,000 |
| | > 4 to 8%E SFA difference | | | | |
| | > 8%E SFA difference | 0.62 (0.31 to 1.21) | N/A | 34 | > 800 |
| **Subgroup by sex, P = 0.35** | Men | 0.81 (0.63 to 1.03) | 0% | 239 | > 3000 |
| | Women | 1.10 (0.73 to 1.64) | 85% | 1106 | > 48,000 |
| | Mixed, men and women | 2.02 (0.19 to 21.94) | N/A | 3 | > 200 |
| **Subgroup by CVD risk, P = 0.61** | Low CVD risk | 0.87 (0.68 to 1.12) | 19% | 968 | > 47,000 |
| | Moderate CVD risk | 2.02 (0.19 to 21.94) | N/A | 3 | > 200 |
| | Existing CVD | 1.00 (0.76 to 1.31) | N/A | 377 | > 5000 |
| **Subgroup by serum TC reduction, P = 0.14** | TC reduced by ≥ 0.2 mmol/L | 0.80 (0.62 to 1.03) | 0% | 234 | > 3000 |
| | TC reduced by < 0.2 mmol/L | 1.11 (0.77 to 1.60) | 71% | 1114 | > 48,000 |
| | Unclear TC change | | | | |
| **Subgroup by decade of publication, P = 0.34** | 1960s | 0.84 (0.62, 1.13) | 0% | 157 | 1743 |
| | 1970s | | | | |
| | 1980s | 0.74 (0.48, 1.14) | NA | 82 | 2033 |

**Table 14. Non-fatal myocardial infarction, subgroup analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | 1990s | | | | |
| | 2000s | 1.11 (0.76, 1.61) | 71% | 1109 | > 49,000 |

CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 15. Stroke (any type and outcome), sensitivity analyses**

| **Analysis** | | **RR (95% CI) of stroke** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 1.00 (0.89 to 1.12) | 0% | 1125 | > 50,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 1.00 (0.90 to 1.12) | 0% | 1119 | > 50,000 |
| | SFA significantly reduced | 0.99 (0.88 to 1.12) | 2% | 1120 | > 50,000 |
| | TC significantly reduced | 1.02 (0.91 to 1.14) | 0% | 1084 | > 49,000 |
| | Minus WHI | 0.63 (0.35 to 1.14) | 0% | 49 | > 2000 |
| | Mantel-Haenszel fixed-effect | 0.99 (0.89 to 1.11) | 0% | 1125 | > 50,000 |
| | Peto fixed-effect | 0.99 (0.88 to 1.13) | 18% | 1125 | > 50,000 |

SFA: saturated fatty acid
TC: total cholesterol

**Table 16. Stroke (any time and outcome), subgroup analyses**

| **Analysis, P value for subgroup differences** | | **RR (95% CI) of stroke** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.69** | PUFA replacement | 0.68 (0.37 to 1.27) | 0% | 41 | > 1700 |

**Table 16. Stroke (any time and outcome), subgroup analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | MUFA replacement | | | | |
| | CHO replacement | 1.01 (0.90 to 1.13) | 0% | 1083 | > 49,000 |
| | Protein replacement | 1.01 (0.89 to 1.15) | 11% | 1082 | > 49000 |
| **Subgroup by duration, P = 0.17** | Up to 24 months | 1.01 (0.06 to 15.93) | N/A | 2 | > 200 |
| | > 24 to 48 months | 0.57 (0.30 to 1.11) | 0% | 36 | > 900 |
| | > 48 months | 1.02 (0.91 to 1.14) | 0% | 1079 | > 49,000 |
| | Unclear duration | 0.20 (0.02 to 1.68) | N/A | 6 | 196 |
| **Subgroup by baseline SFA, P = 0.36** | Up to 12%E SFA | | N/A | | |
| | > 12 to 15%E SFA | 1.01 (0.90 to 1.13) | 0% | 1084 | > 49,000 |
| | > 15 to 18%E SFA | 0.35 (0.01 to 8.12) | N/A | 1 | 55 |
| | > 18%E SFA | 0.59 (0.30 to 1.15) | N/A | 35 | 846 |
| **Subgroup by SFA change, P = 0.36** | Up to 4%E SFA difference | 1.01 (0.90 to 1.13) | 0% | 1084 | > 49,000 |
| | > 4 to 8%E SFA difference | 0.35 (0.01 to 8.12) | N/A | 1 | 55 |
| | > 8%E SFA difference | 0.59 (0.30 to 1.15) | N/A | 35 | > 800 |
| **Subgroup by sex, P = 0.35** | Men | 0.63 (0.33 to 1.18) | 0% | 39 | > 1300 |
| | Women | 1.02 (0.91 to 1.14) | 0% | 1076 | > 48,000 |
| | Mixed, men and women | 0.37 (0.07 to 1.97) | 0% | 8 | > 400 |
| **Subgroup by CVD risk, P = 0.42** | Low CVD risk | 0.86 (0.52 to 1.42) | 59% | 597 | > 47,000 |
| | Moderate CVD risk | 0.37 (0.07 to 1.97) | 0% | 8 | > 400 |
| | Existing CVD | 1.01 (0.86 to 1.18) | 0% | 518 | > 2000 |
| **Subgroup by serum TC reduction, P = 0.24** | TC reduced by ≥ 0.2 mmol/L | 0.70 (0.38 to 1.28) | 0% | 43 | > 1900 |

**Table 16. Stroke (any time and outcome), subgroup analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | TC reduced by < 0. 2 mmol/L | 1.01 (0.89 to 1.15) | 11% | 1082 | > 49,000 |
| | Unclear TC change | | | | |
| **Subgroup by decade of publication, P=0.79** | 1960s | 0.92 (0.31, 2.69) | 23% | 40 | 1651 |
| | 1970s | | | | |
| | 1980s | | | | |
| | 1990s | 0.35 (0.01, 8.12) | N/A | 1 | 55 |
| | 2000s | 1.01 (0.90, 1.13) | 0% | 1084 | > 49,000 |

CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 17. CHD mortality, sensitivity analyses**

| **Analysis** | | **RR (95% CI) of CHD mortality** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.98 (0.84 to 1.15) | 21% | 886 | > 53,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.98 (0.84 to 1.15) | 21% | 886 | > 53,000 |
| | SFA significantly reduced | 1.02 (0.87 to 1.20) | 17% | 735 | > 52,000 |
| | TC significantly reduced | 1.00 (0.83 to 1.20) | 33% | 786 | > 52,000 |
| | Minus WHI | 0.97 (0.76 to 1.24) | 37% | 494 | > 4000 |
| | Mantel-Haenszel fixed-effect | 0.98 (0.86 to 1.12) | 21% | 886 | > 53,000 |
| | Peto fixed-effect | 0.98 (0.85 to 1.13) | 39% | 886 | > 53,000 |

SFA: saturated fatty acid
TC: total cholesterol

**Table 18. CHD mortality, subgroup data**

| Analysis, P value for subgroup differences | | RR (95% CI) of CHD mortality | $I^2$ | No. of events | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.80** | PUFA replacement | 0.98 (0.74 to 1.28) | 49% | 491 | > 4000 |
| | MUFA replacement | 3.00 (0.33 to 26.99) | N/A | 4 | 52 |
| | CHO replacement | 1.01 (0.86 to 1.18) | 0% | 586 | > 50,000 |
| | Protein replacement | 1.01 (0.86 to 1.18) | 0% | 586 | > 50,000 |
| **Subgroup by duration, P = 0.33** | Up to 24 months | 1.02 (0.78 to 1.33) | 0% | 203 | > 2000 |
| | > 24 to 48 months | 0.87 (0.64 to 1.19) | N/A | 141 | > 1000 |
| | > 48 months | 1.03 (0.79 to 1.34) | 52% | 537 | > 49,000 |
| | Unclear duration | 0.09 (0.01 to 1.60) | N/A | 5 | > 100 |
| **Subgroup by baseline SFA, P = 0.35** | Up to 12%E SFA | | N/A | | |
| | > 12 to 15%E SFA | 1.06 (0.90 to 1.25) | 11% | 644 | > 51,000 |
| | > 15 to 18%E SFA | | | | |
| | > 18%E SFA | 0.82 (0.55 to 1.21) | N/A | 91 | > 800 |
| **Subgroup by SFA change, P = 0.35** | Up to 4%E SFA difference | 1.06 (0.90 to 1.25) | 11% | 644 | > 51,000 |
| | > 4 to 8%E SFA difference | | | | |
| | > 8%E SFA difference | 0.82 (0.55 to 1.21) | N/A | 91 | > 800 |
| **Subgroup by sex, P = 0.26** | Men | 0.98 (0.79 to 1.23) | 30% | 489 | > 4000 |
| | Women | 1.01 (0.83 to 1.24) | 0% | 392 | > 48,000 |
| | Mixed, men and women | 0.09 (0.01 to 1.60) | N/A | 5 | > 100 |
| **Subgroup by CVD risk, P = 0.23** | Low CVD risk | 0.95 (0.78 to 1.16) | 0% | 400 | > 47,000 |
| | Moderate CVD risk | 0.09 (0.01 to 1.60) | N/A | 5 | > 100 |
| | Existing CVD | 1.03 (0.83 to 1.27) | 22% | 481 | > 5000 |

**Table 18. CHD mortality, subgroup data** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **Subgroup by serum TC reduction, P = 0.73** | TC reduced by ≥ 0.2 mmol/L | 0.96 (0.75 to 1.24) | 42% | 491 | > 4000 |
| | TC reduced by < 0.2 mmol/L | 1.02 (0.83 to 1.25) | 0% | 395 | > 48,000 |
| | Unclear TC change | | | | |
| **Subgroup by decade of publication, P = 0.62** | 1960s | 0.84 (0.66, 1.06) | 23% | 40 | 1651 |
| | 1970s | 0.54 (0.03, 9.26) | 75% | 63 | 560 |
| | 1980s | 1.00 (0.76, 1.30) | N/A | 194 | 2033 |
| | 1990s | | | | |
| | 2000s | 1.01 (0.83, 1.24) | 0% | 392 | > 48,000 |

CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 19. CHD events, sensitivity analyses**

| **Analysis** | | **RR (95% CI) of CHD events** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Main analysis** | | 0.87 (0.74 to 1.03) | 66% | 3307 | > 53,000 |
| **Sensitivity analyses** | Stated aim to reduce SFA | 0.87 (0.74 to 1.03) | 66% | 3307 | > 53,000 |
| | SFA significantly reduced | 1.95 (0.82 to 1.10) | 49% | 2988 | > 52,000 |
| | TC significantly reduced | 0.85 (0.70 to 1.03) | 75% | 3034 | > 52,000 |
| | Minus WHI | 0.80 (0.61 to 1.03) | 59% | 758 | > 4000 |
| | Mantel-Haenszel fixed-effect | 0.93 (0.87 to 0.99) | 66% | 3307 | > 53,000 |

**Table 19. CHD events, sensitivity analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | Peto fixed-effect | 0.92 (0.86 to 0.99) | 72% | 3307 | > 53,000 |

SFA: saturated fatty acid
TC: total cholesterol

**Table 20. CHD events, subgroup analyses**

| **Analysis, P value for subgroup differences** | | **RR (95% CI) of CHD events** | **$I^2$** | **No. of events** | No. of participants |
|---|---|---|---|---|---|
| **Subgroup by replacement P = 0.28** | PUFA replacement | 0.76 (0.57 to 1.00) | 71% | 737 | > 3000 |
| | MUFA replacement | 1.50 (0.62 to 3.61) | N/A | 15 | 52 |
| | CHO replacement | 0.98 (0.83 to 1.14) | 55% | 2846 | > 51,000 |
| | Protein replacement | 0.99 (0.88 to 1.12) | 41% | 2833 | > 51,000 |
| **Subgroup by duration, P = 0.72** | Up to 24 months | 1.01 (0.76 to 1.35) | 5% | 307 | > 2000 |
| | > 24 to 48 months | 0.79 (0.55 to 1.14) | 50% | 251 | > 1000 |
| | > 48 months | 0.93 (0.76 to 1.14) | 79% | 2703 | > 49,000 |
| | Unclear duration | 0.60 (0.10 to 3.58) | 81% | 46 | > 200 |
| **Subgroup by baseline SFA, P = 0.09** | Up to 12%E SFA | | N/A | | |
| | > 12 to 15%E SFA | 0.99 (0.88 to 1.12) | 34% | 2837 | > 51,000 |
| | > 15 to 18%E SFA | 0.30 (0.09 to 0.98) | N/A | 13 | 60 |
| | > 18%E SFA | 0.77 (0.56 to 1.04) | N/A | 138 | > 800 |
| **Subgroup by SFA change, P = 0.09** | Up to 4%E SFA difference | 0.99 (0.88 to 1.12) | 34% | 2837 | > 51,000 |
| | >4 to 8%E SFA difference | 0.30 (0.09 to 0.98) | N/A | 13 | 60 |
| | >8%E SFA difference | 0.77 (0.56 to 1.04) | N/A | 138 | > 800 |
| **Subgroup by sex, P = 0.39** | Men | 0.84 (0.70 to 1.02) | 35% | 708 | > 3000 |

**Table 20. CHD events, subgroup analyses** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| | Women | 1.02 (0.84 to 1.23) | 77% | 2549 | > 48,000 |
| | Mixed, men and women | 0.88 (0.18 to 4.36) | 76% | 50 | > 500 |
| **Subgroup by CVD risk, P = 0.95** | Low CVD risk | 0.90 (0.76 to 1.05) | 33% | 2236 | > 47,000 |
| | Moderate CVD risk | 0.88 (0.18 to 4.36) | 76% | 50 | > 500 |
| | Existing CVD | 0.94 (0.75 to 1.17) | 61% | 1021 | > 5000 |
| **Subgroup by serum TC reduction, P = 0.06** | TC reduced by ≥ 0.2 mmol/L | 0.75 (0.58 to 0.99) | 65% | 738 | > 4000 |
| | TC reduced by < 0.2 mmol/L | 1.03 (0.87 to 1.21) | 44% | 2569 | > 49,000 |
| | Unclear TC change | | | | |
| **Subgroup by decade of publication, P < 0.001** | 1960s | 0.84 (0.68, 1.05) | 30% | 419 | 1731 |
| | 1970s | 0.27 (0.14, 0.52) | N/A | 38 | 102 |
| | 1980s | 0.91 (0.73, 1.14) | N/A | 276 | 2033 |
| | 1990s | 0.33 (0.10, 1.09) | N/A | 13 | 57 |
| | 2000s | 1.03 (0.86, 1.23) | 48% | 2561 | > 49,000 |

CHO: carbohydrate
CVD: cardiovascular disease
MUFA: mon-unsaturated fatty acid
N/A: not applicable
PUFA: polyunsaturated fatty caid
SFA: saturated fatty acid
TC: total cholesterol

**Table 21. Process outcome data (secondary outcomes)**

| Outcome | Effect (95% CI) | $I^2$ | No. of studies (participants) | Differential effect by replacement? | Summary |
|---|---|---|---|---|---|
| **TC, mmol/L** | -0.24 (-0.36 to -0.13) | 60% | 13 (7115) | No, P = 0.20 | TC reduced |
| **LDL, mmol/L** | -0.19 (-0.33 to -0.05) | 37% | 5 (3291) | No, P = 0.16 | LDL reduced |

**Table 21. Process outcome data (secondary outcomes)** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **HDL, mmol/L** | -0.01 (-0.02 to 0.01) | 0% | 7 (5183) | No, P = 0.99 | No effect |
| **TG, mmol/L** | -0.08 (-0.21 to 0.04) | 51% | 7 (3845) | No, P = 0.12 | No effect |
| **TG/HDL ratio** | N/A | N/A | N/A | N/A | No data |
| **TC/HDL ratio** | -0.10 (-0.33 to 0.13) | 24% | 3 (2985) | No, P = 0.45 | No effect |
| **LDL/HDL ratio** | -0.36 (-0.92 to 0.20) | N/A | 1 (50) | N/A | Unclear |
| **Lipoprotein (a), mmol/L** | 0.00 (-0.00 to 0.00) | 0% | 2 (2882) | No, P = 1.00 | No effect |
| **Diabetes diagnosis** | RR 0.96 (0.90 to 1.02) | N/A | 1 (> 48,000; 3342 diagnoses) | No, P = 1.00 | No effect |
| **HbA1c, %** | N/A | N/A | N/A | N/A | No data |
| **Glucose 2 hrs post GTT, mmol/L** | -1.69 (-2.55 to -0.82) | 45% | 3 (249) | N/A | Reduced |
| **HOMA** | 0.00 (-0.04 to 0.04) | NA | 1 (2832) | N/A | No effect |

GTT: glucose tolerance test
HOMA: homeostatic model assessment
TC: total cholesterol
TG: triglyceride

**Table 22. Potential harms (secondary outcomes)**

| Outcome | Effect (95% CI) | $I^2$ | No. of studies (participants) | Differential effect by replacement? | Summary |
|---|---|---|---|---|---|
| **Cancer diagnoses** | RR 0.94 (0.83 to 1.07) | 33% | 4 (> 52,000; 5476 diagnoses) | No, P = 0.33 | No effect |
| **Cancer deaths** | RR 1.00 (0.61 to 1.64) | 49% | 5 (> 52,000; 2472 deaths) | No, P = 0.94 | No effect |
| **Body weight, kg** | MD -1.97 (-3.67 to -0.27) | 72% | 6 (4541) | No, P = 1.00 | Weight loss |

**Table 22. Potential harms (secondary outcomes)** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **BMI, kg/m²** | MD -0.50 (-0.82 to -0.19) | 55% | 6 (5553) | No, P = 0.41 | BMI reduced |
| **Systolic BP, mmHg** | MD -0.19 (-1.36 to 0.97) | 0% | 5 (3812) | No, P = 0.97 | No effect |
| **Diastolic BP, mmHg** | MD -0.36 (-1.03 to 0.32) | 0% | 5 (3812) | No, P = 1.00 | No effect |

BMI: body mass index
MD: mean difference
RR: risk ratio

**Table 23. SFA cut-off data**

| Cut- off | RR of all-cause mortality | RR of CVD mortality | RR of CVD events | RR of MI | RR of non-fatal MI | RR of stroke | RR of CHD mortality | RR of CHD events |
|---|---|---|---|---|---|---|---|---|
| **7%E** | 1.11 (0.58 to 2.12) | 0.20 (0.01 to 4.15) | 0.20 (0.01 to 4.15) | N/A | N/A | N/A | N/A | N/A |
| **8%E** | 1.11 (0.58 to 2.12) | 0.20 (0.01 to 4.15) | 0.20 (0.01 to 4.15) | N/A | N/A | N/A | N/A | N/A |
| **9%E** | 0.99 (0.84 to 1.15) | 0.69 (0.51 to 0.94) | 0.79 (0.62 to 0.99) | 0.76 (0.55 to 1.05) | 0.62 (0.31 to 1.21) | 0.59 (0.30 to 1.15) | 0.82 (0.55 to 1.21) | 0.77 (0.56 to 1.04) |
| **10%E** | 0.99 (0.90 to 1.09) | 0.97 (0.74 to 1.26) | 0.89 (0.74 to 1.07) | 0.93 (0.80 to 1.08) | 0.99 (0.69 to 1.41) | 1.00 (0.89 to 1.12) | 1.05 (0.83 to 1.32) | 0.93 (0.75 to 1.14) |
| **11%E** | 1.00 (0.88 to 1.12) | 0.95 (0.73 to 1.24) | 0.88 (0.74 to 1.05) | 0.94 (0.84 to 1.06) | 0.99 (0.69 to 1.41) | 0.98 (0.83 to 1.14) | 1.02 (0.87 to 1.20) | 0.94 (0.77 to 1.15) |
| **12%E** | 0.99 (0.91 to 1.07) | 0.96 (0.79 to 1.18) | 0.91 (0.79 to 1.04) | 0.94 (0.85 to 1.04) | 0.95 (0.72 to 1.25) | 0.99 (0.88 to 1.12) | 1.02 (0.87 to 1.20) | 0.95 (0.82 to 1.10) |
| **13%E** | 1.02 (0.83 to 1.25) | 0.93 (0.63 to 1.38) | 0.78 (0.61 to 1.00) | 0.87 (0.73 to 1.04) | 0.72 (0.50 to 1.03) | 0.54 (0.29 to 1.00) | 1.06 (0.76 to 1.48) | 0.84 (0.63 to 1.12) |

CHD coronary heart disease
CVD cardiovascular disease
MI myocardial infarction
N/A not applicable (no relevant studies)
RR: risk ratio
SFA saturated fat, as percentage of energy

**Table 24. GRADE profile: What is the effect of replacing some saturated fat with other fats, protein or CHO in adults?**

| Quality assessment | | | | | | | No of participants (study event rate%) | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design [1] | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Reduced saturated fat intake | Usual saturated fat intake | Relative effect (95% CI) | Absolute effects (per 10,000) | | |
| **All-cause mortality (follow-up mean 56 months[1])** | | | | | | | | | | | | |
| 12 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 1377/22819 (6%) | 1899/33039 (5.7%) | **RR 0.97** (0.9 to 1.05) | **17 fewer** (from 57 fewer to 29 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Cardiovascular mortality (follow-up mean 53 months[1])** | | | | | | | | | | | | |
| 12 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 483/21844 (2.2%) | 613/31577 (1.9%) | **RR 0.95** (0.8 to 1.12) | **10 fewer** (from 39 fewer to 23 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Cardiovascular events (follow-up mean 52 months[1])** | | | | | | | | | | | | |
| 13 | RCTs | no serious risk of bias[2] | serious inconsistency[7] | no serious indirectness[4] | no serious imprecision[8] | none[6] | 1774/21791 (8.1%) | 2603/31509 (8.3%) | **RR 0.83** (0.72 to 0.96) | **138 fewer** (from 33 fewer to 228 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Fatal and non-fatal myocardial infarction (follow-up mean 55 months[1])** | | | | | | | | | | | | |
| 11 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 717/21725 (3.3%) | 997/31442 (3.2%) | **RR 0.90** (0.8 to 1.01) | **32 fewer** (from 63 | ⊕⊕⊕◯ MODERATE | CRITICAL |

**Table 24. GRADE profile: What is the effect of replacing some saturated fat with other fats, protein or CHO in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 3 more) | | |
| **Non-fatal myocardial infarction (follow-up mean 55 months[1])** | | | | | | | | | | | | |
| 9 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[9] | 547/ 21559 (2.5%) | 801/ 31275 (2.6%) | **RR 0. 95** (0.8 to 1.13) | **13 fewer** (from 51 fewer to 33 more) | ⊕⊕⊕ O MODERATE | CRITICAL |
| **Stroke (follow-up 59 mean months[1])** | | | | | | | | | | | | |
| 8 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[9] | 453/ 20602 (2.2%) | 672/ 30350 (2.2%) | **RR 1. 00** (0.89 to 1.12) | **0 fewer** (from 25 fewer to 25 more) | ⊕⊕⊕ O MODERATE | CRITICAL |
| **CHD mortality (follow-up mean 65 months[1])** | | | | | | | | | | | | |
| 10 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none [6] | 401/ 21714 (1.8%) | 485/ 31445 (1.5%) | **RR 0. 98** (0.84 to 1.15) | **30 fewer** (from 25 fewer to 23 more) | ⊕⊕⊕ O MODERATE | CRITICAL |
| **CHD events (follow-up mean 59 months[1])** | | | | | | | | | | | | |
| 12 | RCTs | no serious risk of bias[2] | serious inconsistency[10] | no serious indirectness[4] | serious imprecision[5] | none [6] | 1346/ 21743 (6.2%) | 1961/ 31456 (6.2%) | **RR 0. 87** (0.74 to 1.03) | **80 fewer** (from 160 fewer to 19 more) | ⊕⊕ OO LOW | CRITICAL |

[1]Minimum study duration was 24 months.

[2]These large RCTs of relatively long duration were well randomised and almost half had good allocation concealment (the rest were unclear). Blinding was only well-conducted in 1 RCT, however blinding is very difficult in trials of dietary fat intake. Incomplete outcome data were variable, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group). These risks to validity were combined with risks from imprecision, and outcomes were downgraded once for a combination of both issues. We noted no other biases. We noted that the level of compliance with interventions involving

long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.

[3]No important heterogeneity; $I^2 \leq 30\%$

[4]These RCTs directly assessed the effect of lower vs usual saturated fat intake on health outcomes of interest. Participants included men and women with and without CVD at baseline (also some participants with CVD risk factors like diabetes, or at risk of cancers).

[5] The 95% CI crosses 1.0 and does not exclude important benefit or harm

[6]The funnel plot did not suggest any small study (publication) bias

[7]Potentially important heterogeneity was identified; $I^2$ = 65%. However, the heterogeneity was partly explained by the degree of saturated fat reduction, and the degree of cholesterol lowering achieved (in subgrouping and in meta-regression).

[8]The 95% CI does not cross 1.0 or a threshold of important harm.

[9]Too few studies to reliably assess publication bias (< 10 RCTs).

[10]Important heterogeneity; $I^2$ = 66%

**Table 25. GRADE profile: What is the effect of replacing some saturated fat with PUFA* on risk of CVD in adults?**

| Quality assessment | | | | | | | No of participants (study event rate %) | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Reduced saturated fat intake** | **Usual saturated fat intake** | **Relative effect (95% CI)** | **Absolute effects (per 10,000)** | | |
| **All-cause mortality (follow-up mean 56 months[1])** | | | | | | | | | | | | |
| 7 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 406/2123 (19.1%) | 418/2115 (19.8%) | **RR 0.96** (0.82 to 1.13) | **79 fewer** (from 360 fewer to 256 more) | ⨁⨁◯◯ MODERATE | CRITICAL |
| **Cardiovascular mortality (follow-up mean 55 months[1])** | | | | | | | | | | | | |
| 7 | RCTs | no serious risk of bias[2] | serious inconsistency[7] | no serious indirectness[4] | serious imprecision[5] | none[6] | 266/2123 (12.5%) | 287/2128 (13.5%) | **RR 0.95** (0.73 to 1.25) | **67 fewer** (from 364 fewer to 337 more) | ⨁◯◯◯ LOW | CRITICAL |
| **Cardiovascular events (follow-up mean 53 months[1])** | | | | | | | | | | | | |

**Table 25. GRADE profile: What is the effect of replacing some saturated fat with PUFA* on risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | RCTs | no serious risk of bias[2] | serious inconsistency[8] | no serious indirectness[4] | no serious imprecision[9] | none[6] | 390/1953 (20%) | 494/1942 (25.4%) | **RR 0.73** (0.58 to 0.92) | **687 fewer** (from 204 fewer to 1068 fewer) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Fatal and non-fatal myocardial infarction (follow-up mean 53 months[1])** | | | | | | | | | | | | |
| 7 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 269/1953 (13.8%) | 322/1942 (16.6%) | **RR 0.83** (0.67 to 1.02) | **282 fewer** (from 547 fewer to 33 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Non-fatal myocardial infarction (follow-up mean 53 months[1])** | | | | | | | | | | | | |
| 5 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 104/1875 (5.5%) | 129/1863 (6.9%) | **RR 0.8** (0.63 to 1.03) | **138 fewer** (from 256 fewer to 21 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Stroke (follow-up mean 63 months[1])** | | | | | | | | | | | | |
| 4 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | very serious[10] | none[6] | 17/856 (2%) | 24/850 (2.8%) | **RR 0.68** (0.37 to 1.27) | **90 fewer** (from 178 fewer to 76 more) | ⊕OOO VERY LOW | CRITICAL |
| **CHD mortality (follow-up mean 36 months[1])** | | | | | | | | | | | | |
| 7 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 240/2147 (11.2%) | 251/2151 (11.7%) | **RR 0.98** (0.74 to 1.28) | **23 fewer** (from 303 fewer to 327 more) | ⊕⊕⊕O MODERATE | CRITICAL |

**Table 25. GRADE profile: What is the effect of replacing some saturated fat with PUFA* on risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CHD events (follow-up mean 53 months[1])** | | | | | | | | | | | | |
| 7 | RCTs | no serious risk of bias[2] | serious inconsistency [11] | no serious indirectness[4] | serious imprecision[5] | none[6] | 329/1956 (16.8%) | 408/1944 (21%) | **RR 0.76** (0.57 to 1.0) | **504 fewer** (from 902 fewer to 0 more) | ⊕⊕ LOW | CRITICAL |

* Polyunsaturated fatty acids replacing saturated fatty acids in individual studies were predominantly of plant origin.
[1] Minimum study duration was 24 months.
[2] These large RCTs of relatively long duration were well randomised but fewer than half had good allocation concealment (the rest were unclear). Blinding was only well-conducted in 1 RCT, however blinding is very difficult in trials of dietary fat intake. In about half the included studies, it was unclear if outcome data were incomplete and most studies had systematic differences in care (i.e. intervention group had more time or attention than the control group). We noted no other biases. Not downgraded for bias, however we note that the level of compliance with interventions involving long-term behaviour change, such as those used in many of these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[3] No important heterogeneity; $I^2 < 50\%$
[4] These RCTs directly assessed the effect of reducing saturated fat, and replacing it with other dietary sources of energy, compared to usual diet, on health outcomes of interest. Participants included men and women with and without CVD at baseline.
[5] The 95% CI crosses 1.0 and does not exclude important benefit or harm.
[6] Too few studies to reliably assess publication bias (< 10 RCTs).
[7] Important heterogeneity; $I^2 = 55\%$
[8] Important heterogeneity; $I^2 = 69\%$.Subgrouping suggested greater effects on cardiovascular events with greater reduction in SFA intake, higher baseline SFA intake and greater serum total cholesterol reduction (meta-regression not carried out).
[9] 95% CI does not cross threshold of important benefit or harm.

**Table 26. GRADE profile: What is the effect of replacing some saturated fat with MUFA on risk of CVD in adults?**

| **Quality assessment** | | | | | | | **No of participants (study event rate%)** | | **Effect** | | **Quality** | **Importance** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Reduced saturated fat intake** | **Usual saturated fat intake** | **Relative effect (95% CI)** | **Absolute effects (per 10,000)** | | |
| **All-cause mortality (follow-up mean 24 months)** | | | | | | | | | | | | |

**Table 26. GRADE profile: What is the effect of replacing some saturated fat with MUFA on risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | RCTs | serious risk of bias[1] | no serious inconsistency [2] | no serious indirectness[3] | very serious imprecision[4] | none [5] | 3/26 (11.5%) | 1/26 (3.8%) | **RR 3.0** (0.33 to 26.99) | **769 more** (from 258 fewer to 9996 more) | ⊖ OOO VERY LOW | CRITICAL |
| **Cardiovascular mortality (follow-up mean 24 months)** | | | | | | | | | | | | |
| 1 | RCTs | serious risk of bias[1] | no serious inconsistency [2] | no serious indirectness[3] | very serious imprecision[4] | none [5] | 3/26 (11.5%) | 1/26 (3.8%) | **RR 3.0** (0.33 to 26.99) | **769 more** (from 258 fewer to 9996 more) | ⊖ OOO VERY LOW | CRITICAL |
| **Cardiovascular events (follow-up mean 24 months)** | | | | | | | | | | | | |
| 1 | RCTs | serious risk of bias[1] | no serious inconsistency [2] | no serious indirectness[3] | very serious imprecision[4] | none [5] | 11/26 (42.3%) | 11/26 (42.3%) | **RR 1.0** (0.53 to 1.89) | **0 fewer** (from 1988 fewer to 3765 more) | ⊖ OOO VERY LOW | CRITICAL |
| **Fatal and non-fatal myocardial infarction (follow-up mean 24 months)** | | | | | | | | | | | | |
| 1 | RCTs | serious risk of bias[1] | no serious inconsistency [2] | no serious indirectness[3] | very serious imprecision[4] | none [5] | 7/26 (26.9%) | 5/26 (19.2%) | **RR 1.4** (0.51 to 3.85) | **769 more** (from 942 fewer to 5481 more) | ⊖ OOO VERY LOW | IMPORTANT |
| **Non-fatal myocardial infarction (follow-up mean 24 months)** | | | | | | | | | | | | |
| 1 | RCTs | serious risk of bias[1] | no con- | no serious indirect- | very serious im- | none [5] | 6/26 (23.1%) | 5/26 (19.2%) | **RR 1.2** (0.42 to 3.45) | **385 more** (from | ⊖ OOO | IMPORTANT |

**Table 26. GRADE profile: What is the effect of replacing some saturated fat with MUFA on risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | sistency [2] | ness[3] | precision[4] | | | | | 1115 fewer to 4711 more) | VERY LOW | |
| **Stroke** | | | | | | | | | | | | |
| 0 | No studies identified reporting this outcome | | | | | | | | | | | |
| **CHD mortality (follow-up mean 24 months)** | | | | | | | | | | | | |
| 1 | RCTs | serious risk of bias[1] | no serious inconsistency [2] | no serious indirectness[3] | very serious imprecision[4] | none [5] | 3/26 (11.5%) | 1/26 (3.8%) | **RR 3** (0.33 to 26.99) | **769 more** (from 258 fewer to 9996 more) | ⊕OOO VERY LOW | IMPORTANT |
| **CHD events (follow-up mean 24 months)** | | | | | | | | | | | | |
| 1 | RCTs | serious risk of bias[1] | no serious inconsistency [2] | no serious indirectness[3] | very serious imprecision[4] | none [5] | 9/26 (34.6%) | 6/26 (23.1%) | **RR 1.5** (0.62 to 3.61) | **1154 more** (from 877 fewer to 6023 more) | ⊕OOO VERY LOW | IMPORTANT |

[1]This single, very small RCT of relatively long duration was well randomised, but had an unclear risk of bias in terms of allocation concealment and incomplete outcome data, and lacked participant blinding; however blinding is very difficult in trials of dietary fat intake. We downgraded it for serious risk of bias.

[2]Only one trial

[3]This RCT directly assessed the effect of reducing saturated fat, and replacing it with other dietary sources of energy, compared to usual diet, on health outcomes of interest. Participants included men with CVD at baseline.

[4]The 52 participants in the relevant arms of this trial experienced relatively few events. As a result, there were wide to very wide confidence intervals. In addition, the 95% CI crosses 1.0 and does not exclude important benefit or harm.

[5]Too few studies to reliably assess publication bias (< 10 RCTs).

**Table 27. GRADE profile: What is the effect of replacing some saturated fat with CHO on risk of CVD in adults?**

| Quality assessment | | | | | | | No of participants (study event rate %) | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design[1] | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Reduced saturated fat intake | Usual saturated fat intake | Relative effect (95% CI) | Absolute effects (per 10,000) | | |
| **All-cause mortality (follow-up mean 48 months[2])** | | | | | | | | | | | | |
| 6 | RCTs | no serious risk of bias[3] | no serious inconsistency[4] | no serious indirectness[5] | serious imprecision[6] | none[7] | 1080/21715 (5%) | 1597/31954 (5%) | **RR 0.98** (0.91 to 1.05) | **10 fewer** (from 45 fewer to 25 more) | ⨁⨁◯◯ MODERATE | CRITICAL |
| **Cardiovascular mortality (follow-up mean 46 months[2])** | | | | | | | | | | | | |
| 6 | RCTs | no serious risk of bias[3] | no serious inconsistency[4] | no serious indirectness[5] | serious imprecision[6] | none[7] | 316/20740 (1.5%) | 429/30492 (1.4%) | **RR 0.99** (0.86 to 1.14) | **1 fewer** (from 20 fewer to 20 more) | ⨁⨁◯◯ MODERATE | CRITICAL |
| **Cardiovascular events (follow-up mean 46 months[2])** | | | | | | | | | | | | |
| 6 | RCTs | no serious risk of bias[3] | serious inconsistency[9] | no serious indirectness[5] | serious imprecision[6] | none[7] | 1512/20740 (7.3%) | 2273/30492 (7.5%) | **RR 0.93** (0.79 to 1.08) | **52 fewer** (from 157 fewer to 60 more) | ⨁◯◯◯ LOW | CRITICAL |
| **Fatal and non-fatal myocardial infarction (follow-up mean 51 months[2])** | | | | | | | | | | | | |
| 4 | RCTs | no serious risk of bias[3] | no serious inconsis- | no serious indirect- | serious impreci- | none[7] | 572/20674 (2.8%) | 820/30425 (2.7%) | **RR 0.96** (0.86 to 1.06) | **11 fewer** (from 38 | ⨁⨁◯◯ | IMPORTANT |

**Table 27. GRADE profile: What is the effect of replacing some saturated fat with CHO on risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | tency[4] | ness[5] | sion[6] | | | | | fewer to 16 more) | MOD-ER-ATE | |
| **Non-fatal myocardial infarction (follow-up mean 60 months[2])** | | | | | | | | | | | | |
| 3 | RCTs | no serious risk of bias[3] | serious inconsistency[9] | no serious indirectness[5] | serious imprecision[6] | none[7] | 470/20559 (2.3%) | 718/30309 (2.4%) | **RR 0.99** (0.73 to 1.35) | 2 fewer (from 64 fewer to 83 more) | ⨁◯◯◯ LOW | IMPORTANT |
| **Stroke (follow-up mean 60 months[2])** | | | | | | | | | | | | |
| 4 | RCTs | no serious risk of bias[3] | no serious inconsistency[4] | no serious indirectness[5] | serious imprecision[6] | none[7] | 435/19656 (2.2%) | 648/29410 (2.2%) | **RR 1.01** (0.9 to 1.13) | **2 more** (from 22 fewer to 29 more) | ⨁⨁◯◯ MODERATE | IMPORTANT |
| **CHD mortality (follow-up mean 60 months[2])** | | | | | | | | | | | | |
| 3 | RCTs | no serious risk of bias[3] | no serious inconsistency[4] | no serious indirectness[5] | serious imprecision[6] | none[7] | 255/20559 (1.2%) | 331/30309 (1.1%) | **RR 1.01** (0.86 to 1.18) | **1 more** (from 15 fewer to 20 more) | ⨁⨁◯◯ MODERATE | IMPORTANT |
| **CHD events (follow-up mean 51 months[2])** | | | | | | | | | | | | |
| 5 | RCTs | no serious risk of bias[3] | serious inconsistency[8] | no serious indirectness[5] | serious imprecision[6] | none[7] | 1140/20677 (5.5%) | 1706/30427 (5.6%) | **RR 0.98** (0.83 to 1.14) | **11 fewer** (from 95 fewer to 79 more) | ⨁◯◯◯ LOW | IMPORTANT |

[1]There was insufficient information across all studies to make any determination about the type of carbohydrate used as replacement.
[2]Minimum study duration was 24 months.
[3]These large RCTs of relatively long duration were well randomised, most had good allocation concealment (the rest were unclear) and most were not at risk for bias in terms of incomplete outcome data. In no studies was blinding well-conducted; however blinding is very difficult in trials of dietary fat intake. All studies had systematic differences in care (i.e. intervention group had more time or

attention than the control group). No other biases noted. Not downgraded for bias, however we note that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[4]No important heterogeneity; $I^2$ = 0%.
[5]These RCTs directly assessed the effect of reducing saturated fat, and replacing it with other dietary sources of energy, compared to usual diet, on health outcomes of interest. Participants included men and women with and without CVD at baseline.
[6]The 95% CI crosses 1.0 and does not exclude important benefit or harm.
[7]Too few studies to reliably assess publication bias (< 10 RCTs).
[8]Important heterogeneity; $I^2$ = 55%.

**Table 28. GRADE profile: What is the effect of replacing some saturated fat with protein on the risk of CVD in adults?**

| Quality assessment | | | | | | | No of participants (study event rate%) | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Reduced saturated fat intake** | **Usual saturated fat intake** | **Relative effect (95% CI)** | **Absolute effects (per 10, 000)** | | |
| **All-cause mortality (follow-up mean 50 months[1])** | | | | | | | | | | | | |
| 5 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 1079/21688 (5%) | 1594/31926 (5%) | **RR 0.98** (0.91 to 1.06) | **10 fewer** (from 45 fewer to 30 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Cardiovascular mortality (follow-up mean 48 months[1])** | | | | | | | | | | | | |
| 5 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 315/20713 (1.5%) | 426/30464 (1.4%) | **RR 0.99** (0.86 to 1.14) | **1 fewer** (from 20 fewer to 20 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Cardiovascular events (follow-up mean 48 months[1])** | | | | | | | | | | | | |
| 5 | RCTs | no serious risk of bias[2] | no serious inconsis- | no serious indirect- | serious imprecis- | none[6] | 1504/20713 (7.3%) | 2253/30464 (7.4%) | **RR 0.98** (0.9 to 1.06) | **15 fewer** (from | ⊕⊕⊕O | CRITICAL |

**Table 28. GRADE profile: What is the effect of replacing some saturated fat with protein on the risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | tency[3] | ness[4] | sion[5] | | | | | 74 fewer to 44 more) | MOD-ER-ATE | |
| **Fatal and non-fatal myocardial infarction (follow-up mean 56 months[1])** | | | | | | | | | | | | |
| 3 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 571/20647 (2.8%) | 818/30397 (2.7%) | **RR 0.96** (0.86 to 1.07) | **11 fewer** (from 38 fewer to 19 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Non-fatal myocardial infarction (follow-up mean 60 months[1])** | | | | | | | | | | | | |
| 3 | RCTs | no serious risk of bias[2] | serious inconsistency[7] | no serious indirectness[4] | serious imprecision[5] | none[6] | 470/20559 (2.3%) | 718/30309 (2.4%) | **RR 0.99** (0.73 to 1.35) | **2 fewer** (from 64 fewer to 83 more) | ⊕⊕OO LOW | IMPORTANT |
| **Stroke (follow-up mean 72 months[1])** | | | | | | | | | | | | |
| 3 | RCTs | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 435/19629 (2.2%) | 647/29382 (2.2%) | **RR 1.01** (0.89 to 1.15) | **2 more** (from 24 fewer to 33 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **CHD mortality (follow-up mean 60 months[1])** | | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 255/20559 (1.2%) | 331/30309 (1.1%) | **RR 1.01** (0.86 to 1.18) | **1 more** (from 15 fewer to 20 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **CHD events (follow-up mean 56 months[1])** | | | | | | | | | | | | |

**Table 28. GRADE profile: What is the effect of replacing some saturated fat with protein on the risk of CVD in adults?** (*Continued*)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | randomised trials | no serious risk of bias[2] | no serious inconsistency[3] | no serious indirectness[4] | serious imprecision[5] | none[6] | 1137/20647 (5.5%) | 1696/30397 (5.6%) | **RR 0.99** (0.88 to 1.12) | **6 fewer** (from 67 fewer to 67 more) | ⊕⊕ ⊕O MODERATE | IMPORTANT |

[1]Minimum study duration was 24 months.
[2]These large RCTs of relatively long duration were well randomised, most had good allocation concealment (the rest were unclear) and most were not at risk for bias in terms of incomplete outcome data. In no studies was blinding well-conducted, however blinding is very difficult in trials of dietary fat intake. All studies had systematic differences in care (i.e. intervention group had more time or attention than the control group). We noted no other biases. Not downgraded for bias; however we note that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[3]No important heterogeneity; $I^2$ <50%.
[4]These RCTs directly assessed the effect of reducing saturated fat, and replacing it with other dietary sources of energy, compared to usual diet, on health outcomes of interest. Participants included men and women with and without CVD at baseline.
[5]The 95% CI crosses 1.0 and does not exclude important benefit or harm.
[6]Too few studies to reliably assess publication bias (< 10 RCTs).
[7]Important heterogeneity; $I^2$ = 75%.

# APPENDICES

## Appendix 1. Search strategies March 2014

### CENTRAL

#1 lipid near (low* or reduc* or modifi*)
#2 cholesterol* near (low* or modifi* or reduc*)
#3 (#1 or #2)
#4 MeSH descriptor: [Nutrition Therapy] explode all trees
#5 diet* or food* or nutrition*
#6 (#4 or #5)
#7 (#3 and #6)
#8 fat* near (low* or reduc* or modifi* or animal* or saturat* or unsaturat*)
#9 MeSH descriptor: [Diet, Atherogenic] explode all trees
#10 MeSH descriptor: [Diet Therapy] explode all trees
#11 (#7 or #8 or #9 or #10)
#12 MeSH descriptor: [Cardiovascular Diseases] this term only
#13 MeSH descriptor: [Heart Diseases] explode all trees
#14 MeSH descriptor: [Vascular Diseases] explode all trees
#15 MeSH descriptor: [Cerebrovascular Disorders] this term only
#16 MeSH descriptor: [Brain Ischemia] explode all trees

#17 MeSH descriptor: [Carotid Artery Diseases] explode all trees
#18 MeSH descriptor: [Dementia, Vascular] explode all trees
#19 MeSH descriptor: [Intracranial Arterial Diseases] explode all trees
#20 MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#21 MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#22 MeSH descriptor: [Stroke] explode all trees
#23 coronar* near (bypas* or graft* or disease* or event*)
#24 cerebrovasc* or cardiovasc* or mortal* or angina* or stroke or strokes or tia or ischaem* or ischem*
#25 myocardi* near (infarct* or revascular* or ischaem* or ischem*)
#26 morbid* near (heart* or coronar* or ischaem* or ischem* or myocard*)
#27 vascular* near (peripheral* or disease* or complication*)
#28 heart* near (disease* or attack* or bypas*)
#29 (#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)
#30 (#11 and #29)

### MEDLINE OVID

1. (lipid$ adj5 (low$ or reduc$ or modifi$)).mp.
2. (cholesterol$ adj5 (low$ or modific$ or reduc$)).mp.
3. 1 or 2
4. exp Nutrition Therapy/
5. (diet$ or food$ or nutrition$).mp.
6. 4 or 5
7. 3 and 6
8. (fat adj5 (low$ or reduc$ or modifi$ or animal$ or saturat$ or unsatur$)).mp.
9. exp Diet, Atherogenic/
10. exp Diet Therapy/
11. 7 or 8 or 9 or 10
12. cardiovascular diseases/ or exp heart diseases/ or exp vascular diseases/
13. cerebrovascular disorders/ or exp brain ischemia/ or exp carotid artery diseases/ or exp dementia, vascular/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp stroke/
14. (coronar$ adj5 (bypas$ or graft$ or disease$ or event$)).mp.
15. (cerebrovasc$ or cardiovasc$ or mortal$ or angina$ or stroke or strokes).mp.
16. (myocardi$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).mp.
17. (morbid$ adj5 (heart$ or coronar$ or ischaem$ or ischem$ or myocard$)).mp.
18. (vascular$ adj5 (peripheral$ or disease$ or complication$)).mp.
19. (heart$ adj5 (disease$ or attack$ or bypass$)).mp.
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 11 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. drug therapy.fs.
27. randomly.ab.
28. trial.ab.
29. groups.ab.
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. exp animals/ not humans.sh.
32. 30 not 31
33. 21 and 32
34. 33
35. limit 34 to yr="2010 -Current"

36. limit 35 to "core clinical journals (aim)"

### EMBASE OVID

1. cardiovascular diseases/ or exp heart diseases/ or exp vascular diseases/
2. cerebrovascular disorders/ or exp brain ischemia/ or exp carotid artery diseases/ or exp dementia, vascular/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp stroke/
3. (coronar$ adj5 (bypas$ or graft$ or disease$ or event$)).mp.
4. (cerebrovasc$ or cardiovasc$ or mortal$ or angina$ or stroke or strokes).mp.
5. (myocardi$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).mp.
6. (morbid$ adj5 (heart$ or coronar$ or ischaem$ or ischem$ or myocard$)).mp.
7. (vascular$ adj5 (peripheral$ or disease$ or complication$)).mp.
8. (heart$ adj5 (disease$ or attack$ or bypass$)).mp.
9. or/1-8
10. (lipid$ adj5 (low$ or reduc$ or modifi$)).mp.
11. (cholesterol$ adj5 (low$ or modific$ or reduc$)).mp.
12. 10 or 11
13. (diet$ or food$ or eat$ or nutrition$).mp.
14. exp nutrition/
15. 13 or 14
16. 12 and 15
17. (fat adj5 (low$ or reduc$ or modifi$ or animal$ or saturat$ or unsatur$)).mp.
18. exp lipid diet/ or exp fat intake/ or exp low fat diet/
19. 16 or 17 or 18
20. 9 and 19
21. random$.tw.
22. factorial$.tw.
23. crossover$.tw.
24. cross over$.tw.
25. cross-over$.tw.
26. placebo$.tw.
27. (doubl$ adj blind$).tw.
28. (singl$ adj blind$).tw.
29. assign$.tw.
30. allocat$.tw.
31. volunteer$.tw.
32. crossover procedure/
33. double blind procedure/
34. randomized controlled trial/
35. single blind procedure/
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. (animal/ or nonhuman/) not human/
38. 36 not 37
39. 20 and 38
40. (2010* or 2011* or 2012* or 2013* or 2014*).em.
41. 39 and 40
42. limit 41 to priority journals

## WHAT'S NEW

Last assessed as up-to-date: 5 March 2014.

| Date | Event | Description |
|---|---|---|
| 27 March 2015 | New citation required and conclusions have changed | We split a previously published review (Reduced or modified dietary fat for preventing cardiovascular disease, DOI: 10.1002/14651858.CD002137.pub3) into six smaller review updates. The conclusions are therefore now focused on reduction in saturated fat intake instead of reducing or modifying fat intake overall on its effect on cardiovascular disease risk<br>This split review update includes 15 randomised controlled trials |
| 5 March 2014 | New search has been performed | The search has been updated to 5 March 2014. |

## CONTRIBUTIONS OF AUTHORS

All authors were active in the design of the review and in providing critical revisions of the manuscript.

LH was the principal author of earlier versions (Hooper 2000; Hooper 2001; Hooper 2012), originated and was primarily responsible for planning and carrying out this systematic review, liasing with WHO NUGAG, carrying out the statistical analyses, and writing the first draft of this review.

NM and LH were responsible for assessment of the results of the updated search, and assessment of inclusion of potentially relevant studies.

NM, AA and LH were responsible for data extraction and assessment of validity, as well as editing and proof-reading the review.

## DECLARATIONS OF INTEREST

Lee Hooper: None known

Nicole Martin: None known

Asmaa Abdelhamid: None known

George Davey Smith: None known

## SOURCES OF SUPPORT

### Internal sources


- University of East Anglia, UK.

Help with acquiring papers for the review, time for Lee Hooper to work on the review

- University of Manchester, UK.

Support with collection of papers for the review.


### External sources


- Studentship, Systematic Reviews Training Unit, Institute of Child Health, University of London, UK.

Funding to support Lee Hooper to carry out the first version of the systematic review


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is the result of updating the searches for *Reduced or modified dietary fat for preventing cardiovascular disease* (Hooper 2012) in March 2014, and splitting the review into several smaller, more manageable reviews. The objective and outcomes have been widened to address queries by WHO NUGAG and the inclusion criteria have changed to focus on saturated fat and long-term trials (24 months instead of six months).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Cardiovascular Diseases [mortality; *prevention & control]; Cause of Death; Dietary Carbohydrates [administration & dosage]; Dietary Fats [*administration & dosage]; Dietary Fats, Unsaturated [administration & dosage]; Dietary Proteins [administration & dosage]; Energy Intake; Fatty Acids [*administration & dosage]; Myocardial Infarction [mortality; prevention & control]; Randomized Controlled Trials as Topic; Stroke [prevention & control]

### MeSH check words

Adult; Humans