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Reduction in saturated fat intake for cardiovascular disease (Review)

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TABLE OF CONTENTS

[Intervention Review]

Reduction in saturated fat intake for cardiovascular disease

Lee Hooper[1], Nicole Martin[2], Oluseyi F Jimoh[1], Christian Kirk[1], Eve Foster[1], Asmaa S Abdelhamid[1]

[1]Norwich Medical School, University of East Anglia, Norwich, UK. [2]Institute of Health Informatics Research, University College London, London, UK

Contact address: Lee Hooper, l.hooper@uea.ac.uk.

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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 eliminated from the diet are more helpfully replaced by polyunsaturated fats, monounsaturated fats, carbohydrate or protein.

Objectives

To assess the effect of reducing saturated fat intake and replacing it with carbohydrate (CHO), polyunsaturated (PUFA), 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 15 October 2019, and searched Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) on 17 October 2019.

Selection criteria

Included trials fulfilled the following criteria: 1) randomised; 2) intention to reduce saturated fat intake OR intention to alter dietary fats and achieving a reduction in saturated fat; 3) compared with higher saturated fat intake or usual diet; 4) not multifactorial; 5) in adult humans with or without cardiovascular disease (but not acutely ill, pregnant or breastfeeding); 6) intervention duration at least 24 months; 7) mortality or cardiovascular morbidity data available.

Data collection and analysis

Two review authors independently assessed inclusion, extracted study data and assessed risk of bias. We performed random-effects meta-analyses, meta-regression, subgrouping, sensitivity analyses, funnel plots and GRADE assessment.

Main results

We included 15 randomised controlled trials (RCTs) (16 comparisons, 56,675 participants), that used a variety of interventions from providing all food to advice on reducing saturated fat. The included long-term trials suggested that reducing dietary saturated fat reduced the risk of combined cardiovascular events by 17% (risk ratio (RR) 0.83; 95% confidence interval (CI) 0.70 to 0.98, 12 trials, 53,758 participants of whom 8% had a cardiovascular event, $I^2 = 67\%$, GRADE moderate-quality evidence). Meta-regression suggested that greater reductions in saturated fat (reflected in greater reductions in serum cholesterol) resulted in greater reductions in risk of CVD events, explaining most heterogeneity between trials. The number needed to treat for an additional beneficial outcome (NNTB) was 56 in primary prevention trials, so 56 people need to reduce their saturated fat intake for ~four years for one person to avoid experiencing a CVD event. In secondary prevention trials, the NNTB was 53. Subgrouping did not suggest significant differences between replacement of saturated fat calories with polyunsaturated fat or carbohydrate, and data on replacement with monounsaturated fat and protein was very limited.

We found little or no effect of reducing saturated fat on all-cause mortality (RR 0.96; 95% CI 0.90 to 1.03; 11 trials, 55,858 participants) or cardiovascular mortality (RR 0.95; 95% CI 0.80 to 1.12, 10 trials, 53,421 participants), both with GRADE moderate-quality evidence.

There was little or no effect of reducing saturated fats on non-fatal myocardial infarction (RR 0.97, 95% CI 0.87 to 1.07) or CHD mortality (RR 0.97, 95% CI 0.82 to 1.16, both low-quality evidence), but effects on total (fatal or non-fatal) myocardial infarction, stroke and CHD events (fatal or non-fatal) were all unclear as the evidence was of very low quality. There was little or no effect on cancer mortality, cancer diagnoses, diabetes diagnosis, HDL cholesterol, serum triglycerides or blood pressure, and small reductions in weight, serum total cholesterol, LDL cholesterol and BMI. There was no evidence of harmful effects of reducing saturated fat intakes.

Authors' conclusions

The findings of this updated review suggest that reducing saturated fat intake for at least two years causes a potentially important reduction in combined cardiovascular events. Replacing the energy from saturated fat with polyunsaturated fat or carbohydrate appear to be useful strategies, while effects of replacement with monounsaturated fat are unclear. The reduction in combined cardiovascular events resulting from reducing saturated fat did not alter by study duration, sex or baseline level of cardiovascular risk, but greater reduction in saturated fat caused greater reductions in cardiovascular events.

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 and hard vegetable fats with plant oils, unsaturated spreads or starchy foods).

Background

Health guidance suggests that 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 for at least two years on health outcomes including dying, heart disease and stroke. We only looked at studies of adults (18 years or older). They 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 56,000 participants. The evidence is current to October 2019. 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 had little effect on the risk of dying. The review found that health benefits arose from replacing saturated fats with polyunsaturated fat or starchy foods. The greater the decrease in saturated fat, and the more serum total cholesterol is reduced, the greater the protection from cardiovascular events. 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 difference in effect between men and women.

This means that, if 56 people without cardiovascular disease, or 53 people who already have cardiovascular disease, reduce their saturated fat for around 4 years, then one person will avoid a cardiovascular event (heart attack or stroke) they would otherwise have experienced.

Quality of the evidence

There is a large body of evidence assessing effects of reducing saturated fat for at least two years. These studies provide moderate-quality evidence that reducing saturated fat reduces our risk of cardiovascular disease.

SUMMARY OF FINDINGS

Summary of findings 1. 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)

Low saturated fat compared with usual saturated fat for CVD risk

Patient or population: people at any baseline risk of CVD

Intervention: lower saturated fat intake

Comparison: higher saturated fat intake

Settings: Any, including community-dwelling and institutions. Included RCTs were conducted in North America, Europe and Australia/New Zealand, no studies were carried out in industrialising or developing countries.

Outcomes	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
		Risk with higher SFA intake	Risk with lower SFA intake			
All-cause mortality follow-up mean duration 56 months[1]	**RR 0.96** (0.90 to 1.03)	62 per 1000	60 per 1000 (56 to 64)	55,858 (12)	⊕⊕⊕⊝ **Moderate**[2,3,4,5,6]	Critical importance. Reducing saturated fat intake probably makes little or no difference to all-cause mortality.
Cardiovascular mortality follow-up mean duration 53 months[1]	**RR 0.94** (0.78 to 1.13)	19 per 1000	18 per 1000 (15 to 22)	53,421 (11)	⊕⊕⊕⊝ **Moderate**[2,3,4,6,7]	Critical importance. Reducing saturated fat intake probably makes little or no difference to cardiovascular mortality.
Combined cardiovascular events follow-up mean duration 52 months[1]	**RR 0.83** (0.70 to 0.98)	85 per 1000	70 per 1000 (59 to 83)	53,758 (13)	⊕⊕⊕⊝ **Moderate**[4,8,9,10,11]	Critical importance. Reducing saturated fat intake probably reduces cardiovascular events (to a greater extent with greater cholesterol reduction).
Myocardial infarctions follow-up mean duration 55 months	**RR 0.90** (0.80 to 1.01)	32 per 1000	29 per 1000 (25 to 32)	53,167 (11)	⊕⊝⊝⊝ **Very Low**[3,4,5,11,12]	Critical importance. The effect of reducing saturated fat intake on risk of myocardial infarction is unclear as the evidence is of very low quality.

Non-fatal MI follow-up mean duration 55 months[1]	**RR 0.97** (0.87 to 1.07)	26 per 1000	25 per 1000 (23 to 28)	52,834 (8)	⊕⊕⊝⊝ **Low**[3,4,5,6,13]	Critical importance. Reducing saturated fat may have little or no effect on risk of non-fatal myocardial infarction.
Stroke follow-up mean duration 59 months[1]	**RR 0.92** (0.68 to 1.25)	22 per 1000	20 per 1000 (15 to 27)	50,952 (7)	⊕⊝⊝⊝ **Very Low** [3,4,6,13,14]	Critical importance. The effect of reducing saturated fat on the risk of stroke is unclear as the evidence was of very low quality.
CHD mortality follow-up mean duration 65 months[1]	**RR 0.97** (0.82 to 1.16)	16 per 1000	16 per 1000 (13 to 19)	53,159 (9)	⊕⊕⊝⊝ **Low**[2,3,4,6,14]	Critical importance. Reducing saturated fat intake may have little or no effect on CHD mortality.
CHD events follow-up mean duration 59 months[1]	**RR 0.83** (0.68 to 1.01)	42 per 1000	35 per 1000 (29 to 43)	53,199 (11)	⊕⊝⊝⊝ **Very low** [4,5,6,12,15]	Critical importance. The effect of reducing saturated fat on risk of CHD events is unclear as the evidence is of very low quality.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
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] **Risk of bias.** Limiting trials to those at low summary risk of bias also suggested little or no effect. Not downgraded.
[3] **Inconsistency**. We found no important heterogeneity; $I^2 \leq 30\%$. Not downgraded.
[4] **Indirectness**. These RCTs directly assessed the effect of lower vs higher 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). However, no trials included participants from developing countries. Not downgraded.
[5] **Imprecision**. The 95% CI includes both no effect and a benefit. Downgraded once.
[6] **Publication bias**. The funnel plot, and comparison of fixed- and random-effects meta-analyses did not suggest major small-study (publication) bias. Not downgraded.
[7] **Imprecision**. The 95% CI includes both harm and benefit. Downgraded once.
[8] **Risk of bias.** Limiting trials to those at low summary risk of bias suggested a smaller and non-statistically significant effect (RR 0.96, 95% CI 0.76 to 1.20) suggesting little or no effect on risk of CVD events. Downgraded once (along with publication bias).
[9] **Inconsistency**. Although heterogeneity was high, $I^2 = 65\%$, this was mostly explained by the degree of cholesterol-lowering (a dose effect). Not downgraded.
[10] **Imprecision**. The 95% CI includes only benefit or minimal effect. Not downgraded.

[11] **Publication bias**. The funnel plot did not suggest publication bias, but comparison of fixed- and random-effects meta-analyses suggested possible small-study (publication) bias. Downgraded once (along with risk of bias, downgraded once in total).

[12] **Risk of bias.** Limiting trials to those at low summary risk of bias moved the RR slightly towards 1.0, suggesting little or no effect on total MI. Downgraded once.

[13] **Risk of bias.** Limiting trials to those at low summary risk of bias moved the RR slightly away from 1.0, suggesting that reducing SFA reduces the risk of non-fatal MI. This was also seen in several other sensitivity analyses. Downgraded once.

[14] **Imprecision**. The 95% CI includes both important benefits and important harms. Downgraded twice.

[15] **Inconsistency**. Heterogeneity was high, I^2 = 65%. Downgraded once.

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 plasma cholesterol levels (Oliver 1953).

Meanwhile in 1949 in the USA, 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. 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. The equation suggests 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 100 mg/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, systematic reviews of the observational data have not confirmed these early studies. Skeaff 2009 included 28 USA 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 effects 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. 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. There are also systematic 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, MUFAs or protein 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 (Abdelhamid 2020; Abdelhamid 2018; Abdelhamid 2019; Brainard 2020; Brown 2019; Deane 2019; Hanson 2020; Hooper 2018; Hooper 2019; Hooper 2012). A recent very large trial, 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 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 USA 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 minimise intake of partially hydrogenated fats" (Lichtenstein 2006). Current 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 a healthy diet including low saturated fat intake (Mach 2019), referencing a variety of evidence including several recent systematic reviews. This is reflected in UK Scientific Advisory Committee on Nutrition recommendations that "dietary reference value for saturated fats remains unchanged: the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%", and that "saturated fats are substituted with unsaturated fats. More evidence is available supporting substitution with PUFA than substitution with MUFA" (SACN 2019).

Recent UK National Institute for Health and Care Excellence(NICE) guidance suggests that for people at high risk of or with CVD that they "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". This statement was based on long-term randomised controlled trials reporting hard outcomes, and NICE separately assessed effects of high polyunsaturated diets, including 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 macronutrients the saturated fats were replaced by, updating Hooper 2015a. This update also supports a 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 noncommunicable 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 included 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

We included 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, compared to higher saturated fat intake which could be usual diet, higher saturated fat, placebo or a control diet. Intended duration of the dietary intervention was at least two years (24 months or 104 weeks).

We excluded multiple risk factor interventions other than diet or supplementation (unless effects of diet or supplementation could be separated, as in a factorial design, so that the additional intervention was consistent or randomised between the intervention or control groups) and studies that aimed for weight loss in one arm but not the other. Atkins-type diets aiming to increase protein and fat intake were excluded, as were studies where fat was reduced by means of a fat-substitute (like Olestra). Enteral and parenteral feeds were excluded, as were formula weight reducing diets.

Examples: studies that reduced saturated fats and encouraged physical activity in one arm and compared with encouraging physical activity in the control were included; studies that reducedsaturated fats and encouraged physical activity in one arm and compared with no intervention in the control were excluded; studies that reduced saturated fats and encouraged fruit and vegetables in one arm and compared with no intervention in the control were included.

Types of outcome measures

Primary outcomes

- All-cause mortality (deaths from any cause)
- Cardiovascular (CVD) mortality (deaths from myocardial infarction, stroke, and/or sudden death)
- Combined CVD events. These included data available on number of people experiencing any of the following: cardiovascular death, 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).

To meet our inclusion criteria, trials had to report either deaths or CVD events. These could be reported as serious adverse events (SAEs) or via communication with authors.

Secondary outcomes

- Additional health events; the outcomes CHD mortality and CHD events were added at the request of the WHO NUGAG group, and were not present in the original overarching systematic review. For each of these, we assessed number of participants experiencing any of these:
  - Myocardial infarction, total (fatal and non-fatal)
  - Myocaridal infarction, non-fatal
  - Stroke
  - CHD mortality, which includes death from myocardial infarction or sudden CVD death
  - CHD events, which include any of the following: fatal or non-fatal myocardial infarction, angina or sudden CVD death
  - type II diabetes incidence
- Blood measures including serum blood lipids
  - total cholesterol (TC, mmol/L)
  - low-density lipoprotein (LDL) cholesterol, mmol/L
  - high-density lipoprotein (HDL) cholesterol, mmol/L
  - triglyceride (TG), mmol/L
  - TG/HDL ratio
  - LDL/HDL ratio
  - total/HDL ratio
  - lipoprotein (a) (Lp(a)), mmol/L
  - insulin sensitivity including glucose tolerance (homeostatic model assessment (HOMA), intravenous glucose tolerance test (IV-GTT), clamp, glycosylated haemoglobin (HbA1C))
- Other outcomes including adverse effects reported by study authors
  - cancer diagnoses
  - cancer deaths
  - body weight, kg
  - body mass index (BMI, kg/m^2)
  - systolic blood pressure (sBP, mmHg)
  - diastolic blood pressure (dBP, mmHg)
  - quality of life (any measure)

As all trials collect data on deaths and cardiovascular events (as serious adverse events if not as planned outcome measures), we only included trials where we knew that at least one primary outcome occurred, by communication with authors if necessary. Where we knew that at least one primary outcome occurred, we included the study even where we were unable to use that data in meta-analysis. We excluded studies where we knew that no primary outcome events occurred (for a study to be excluded in this way the paper needed to be very explicit about the lack of all outcomes or we received confirmation from the authors) and this was noted as the reason for exclusion. Lack of a single primary outcome only occurs in very small studies or in young cohorts, so omitting these studies will make no difference to effect sizes and very little difference to absolute effect sizes (NNTs etc). All other trials were considered unclear and where we could not gain clarification on events from authors, they were classified as “awaiting assessment”.

For composite outcomes (like CVD events), we worked to collect data on the number of participants in each arm who experienced any type of CVD event, and did not double-count people (so that a person experiencing a stroke and two heart attacks during a trial was counted as one person experiencing CVD events, not as three CVD events).

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 collected change data (with a measure of variance) for continuous outcomes where these were available, and end data where change data were not provided in usable format.

Search methods for identification of studies

Electronic searches

The updated searches were run on 15 October 2019 on the following databases:

- CENTRAL (Issue 10 of 12, 2019, Cochrane Library)
- MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE, Ovid, 1946 to October 14, 2019)
- Embase (Ovid, 1980 to 2019 week 41).

For this update, we introduced searches of two trials registers on 17 October 2019; Clinicaltrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). The searches are described in Appendix 1. The RCT filter for MEDLINE was the Cochrane sensitivity and precision-maximising RCT filter (Lefebvre 2011), and for Embase, terms as recommended in the Cochrane Handbook were applied (Lefebvre 2011).

As we were updating another Cochrane review relating to dietary fat (Hooper 2015b) at the same time, results of the searches for both reviews were combined and de-duplicated before assessment of titles and abstracts.

The search to 2014 is described in Hooper 2015a, and previous searches in Hooper 2012. .

Searching other resources

We searched for recent publications of the included studies, to ensure the best possible data set for each study.

Data collection and analysis

Selection of studies

Search results were loaded into Covidence software. All authors independently assessed titles and abstracts from the search, differences were resolved by discussion and, when the findings were not clear cut, the full text was collected for assessment. 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 a data extraction form designed for earlier versions of this review. 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. Those at low or moderate risk combined are primary prevention trials.

Data were extracted independently in duplicate by AA, FOJ and/or LH, alongside assessment of risk of bias.

Assessment of risk of bias in included studies

We carried out 'Risk of bias' assessment independently in duplicate as part of data extraction. We assessed trial risk of bias using the Cochrane tool for assessment of risk of bias (Higgins 2011). For included RCTs, we also assessed whether each study:

1. was free of systematic differences in care,
2. aimed to reduce SFA intake,
3. achieved SFA reduction, or
4. achieved total serum cholesterol reduction.

We used the category 'other bias' to note any further issues of methodological concern. Funding was not formally a part of our assessment of bias in RCTs as it is not a core part of the Cochrane 'Risk of bias' tool, but was reported in the Characteristics of included studies.

Two authors (LH, NM) independently extracted validity data from studies identified by the previous search, and resolved differences by discussion.

Poorly concealed allocation is associated with a 40% greater effect size (Schulz 1995), so randomisation and allocation concealment are core issues for all trials. Lack of blinding is associated with bias, though smaller levels of bias than lack of allocation concealment (Savovic 2012), especially in studies with objectively measured outcomes (Wood 2008).

For this review, we introduced the concept of summary risk of bias for whole trials. We considered dietary advice or all-food-provided type trials to be at low summary risk of bias where we judged randomisation, allocation concealment, and blinding of outcome assessors to be adequate. Summary risk of bias was considered moderate to high in all other included trials.

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 pairwise 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.

In the previous version of this review, data for WHI 2006 were presented separately for those without baseline CVD, and with baseline CVD, for most outcomes. This has been altered in this version of the review, so that both sets of data are presented as a single trial except when subgrouping by CVD risk. This has the effect of representing this study in the same way others are represented (which is appropriate), and slightly reducing the weight of the WHI 2006 study in random-effects meta-analysis, altering the numbers in the analysis.

When assessing event data, we aimed to assess number of participants experiencing an event (rather than numbers of events), 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 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.

Where included studies used methods to infer missing data (such as carrying the latest measurement forward), then we used these data in analyses. Where this was not done, we used the data as presented.

Assessment of heterogeneity

We examined heterogeneity using the I^2 test, and considered it important where greater than 50% (Higgins 2003; Higgins 2011). Where we identified important clinical or unexplained statistical heterogeneity, we did not pool but instead summarised the studies in a narrative format. We used the assessment of heterogeneity in our GRADE assessments, so that the quality of evidence was downgraded where heterogeneity was important, and not explained by subgrouping or meta-regression.

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. For this update, we also compared findings of fixed- and random-effects meta-analysis since the two methods weight small trials differently, and different effect sizes suggest potential small study bias (Page 2019).

Data synthesis

We carried out data synthesis in the absence of clinical heterogeneity. 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 noncommunicable 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 (refined or unrefined), protein, trans fats, a mixture of these, or unclear. However, when we presented these data to the WHO NUGAG group, they suggested that this subgrouping be altered. They suggested that we use 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, or on refined and unrefined carbohydrates, we did not include a trans group or distinguish by carbohydrate type. 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 dropouts, 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 mean assessed intervention SFA intake was < 10%E and the mean control SFA intake 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 a mean intervention SFA intake < 7%E and mean control SFA intake > 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 2006)
5. Analysis run with Mantel-Haenszel fixed-effect model
6. Analysis run with Peto fixed-effect model

For this update we also introduced sensitivity analysis excluding trials not at low summary risk of bias. We used results of these analysis to inform GRADE assessment of risk of bias.

GRADE

All primary outcomes, and secondary additional health events, were represented in the 'Summary of findings' table, and underwent GRADE assessment. The GRADE Working Group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations (www.gradeworkinggroup.org/; GRADE 2004). 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.

Outcome data were interpreted as follows:

1. Is there an effect? (options were 'increased risk', 'decreased risk', or 'little or no effect'). Our main outcome measure was RR so we decided on existence of an effect using RR. RR > 8% (RR < 0.92 or > 1.08) for the highest quality evidence suggested increased or decreased risk (otherwise little or no effect). The presence or not of an effect was decided on the RR for the main analysis and sensitivity analyses, the highest quality evidence (the main analysis, the sensitivity analyses of trials at low summary risk of bias and at low risk of compliance problems).
2. For continuous outcomes, reducing SFA was considered to have little or no effect unless effect sizes represented at least 5% change from baseline (or 2% in the case of cumulative outcomes such as adiposity).
3. Quality of evidence was assessed using GRADE assessment (GRADE 2004) for key outcomes. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), plus GRADEpro GDT software (GRADEpro 2015). We justified all decisions to downgrade the quality of studies using footnotes and made comments to aid reader's understanding of the review.
4. Where there was a suggested effect, the size of effect was assessed using the number needed to treat for an additional beneficial outcome (NNTB), number needed to treat for an additional harmful outcome (NNTH) or absolute risk reduction (ARR).

RESULTS

Description of studies

Results of the search

Figure 1 displays the flow diagram for inclusion of studies. We assessed the 7991 titles and abstracts from the updated electronic search, as well as assessing the 8930 titles and abstracts from the search for our sister review (Hooper 2015b), which de-duplicated to 15,314 titles and abstracts. Of these, 530 were considered potentially relevant to one or both reviews, so were collected as full text. Ten publications were considered relevant for this systematic review, and these were grouped into:

Figure 1. Study flow diagram for this systematic review (update searches run October 2019).

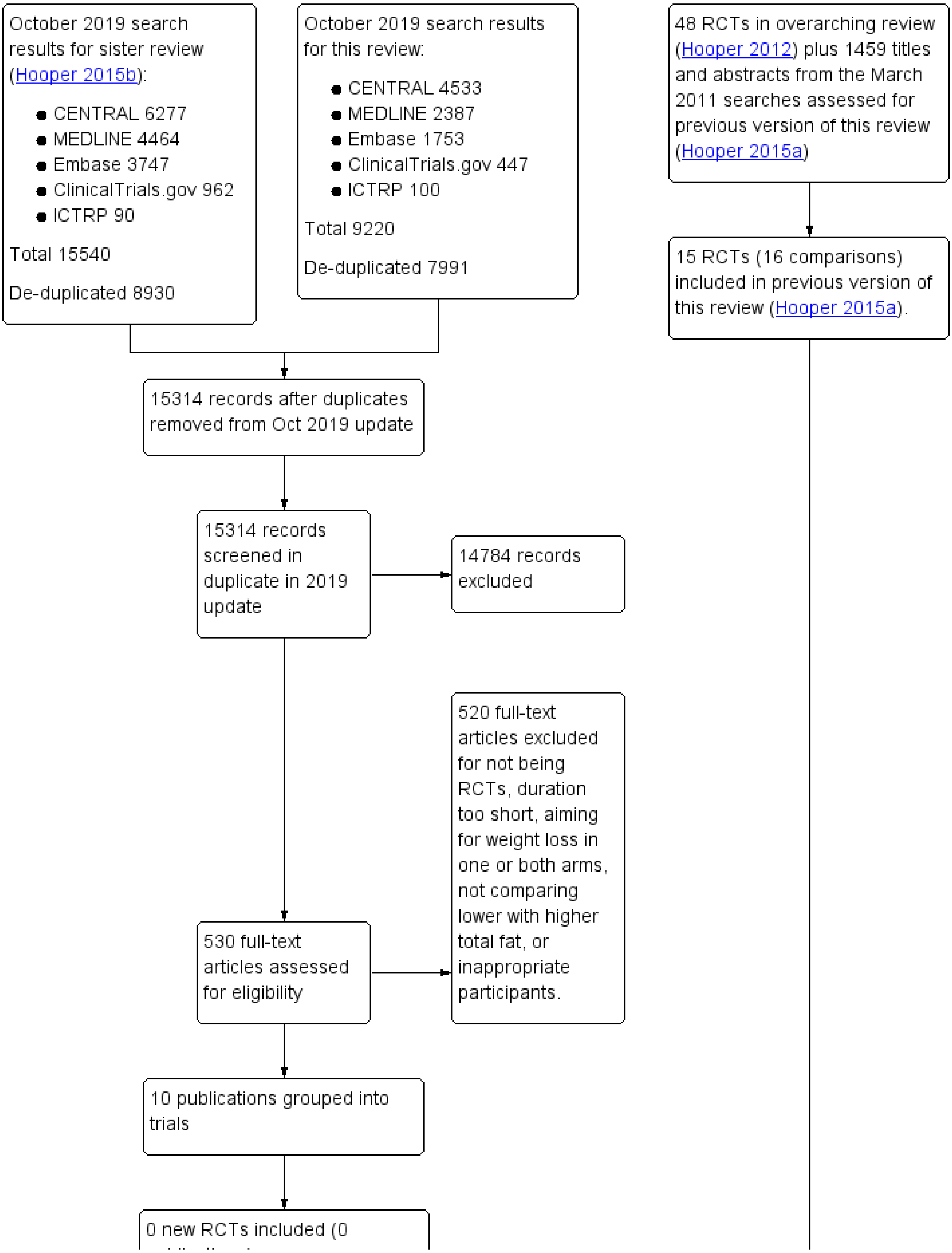
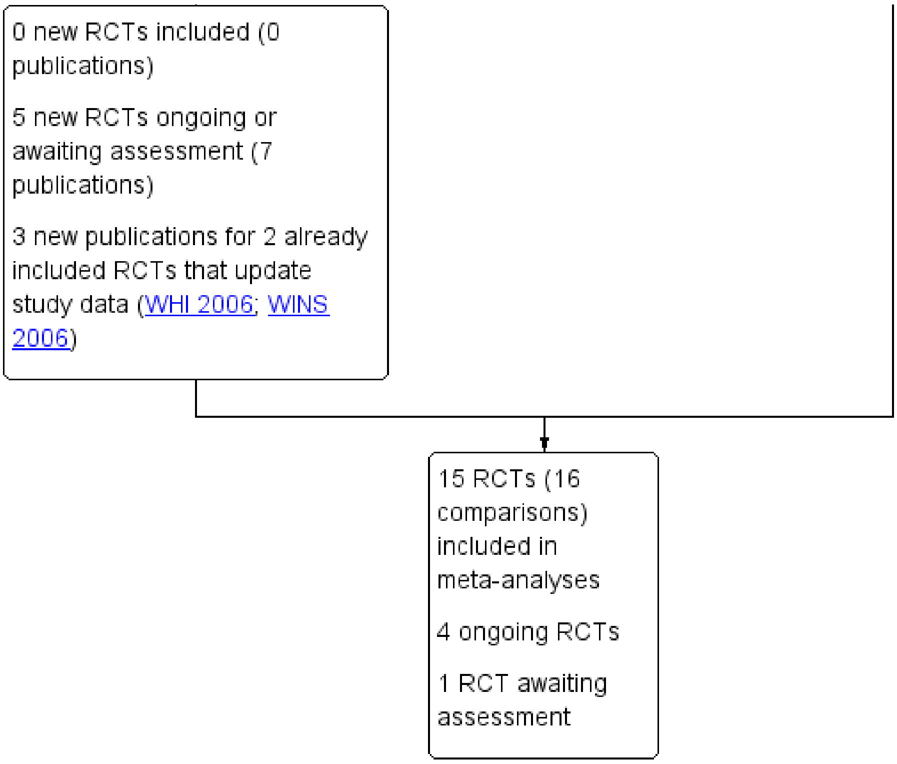


Figure 1. (Continued)



- three new publications for two already included trials (WHI 2006; WINS 2006),
- two publications for one study awaiting assessment (not enough details to confirm inclusion, ICFAMED), and
- five publications for four ongoing trials (ENAbLE due unclear; NCT02481466 due 2020; NCT02938832 due 2023; NEW Soul Study due 2022).

There were no new included trials, but there were new data for WHI 2006 and WINS 2006, as well as the ongoing studies and the study awaiting assessment. This resulted in an updated review including 15 RCTs (16 comparisons as the Rose trial has two comparisons, Rose corn oil 1965 and Rose olive 1965).

Included studies

We included 15 randomised controlled trials (RCTs) randomising 56,675 participants in the review (Included studies), and describe them in Characteristics of included studies. The interventions are compared in Table 1.

The main study papers ranged in publication date from 1965 to 2006, but with supplementary publications included up to 2019. The RCTs were conducted in North America (six), Europe (seven), and Australia/New Zealand (two); no studies were carried out in industrialising or developing countries. Six RCTs included only people at high risk of cardiovascular disease, four at moderate risk, and four at low risk (three with raised cancer risk or cancer diagnosis, one with no specific health risks), while one trial included participants at low and high CVD risk (WHI 2006, Table 1; this trial made assessments in each of these groups). Seven studies included only men, three only women, and five both men and women. However, as the largest trial (WHI 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 15 of the 16 intervention arms, and additional supplements such as oil or other foods were provided in three trials (four arms: MRC 1968; Oslo Diet-Heart 1966; Rose corn oil 1965; Rose olive 1965), while all food was provided in a residential facility in one RCT (Veterans Admin 1969). Of the 15 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 two trials (Ley 2004; WHI 2006), and was unclear in three RCTs (Black 1994; Houtsmuller 1979; Rose corn oil 1965; Rose olive 1965). Advice was provided by a dietitian in nine arms, a nutritionist in one, 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 (16 intervention arms), 11 RCTs (12 comparisons) provided data on all-cause mortality (including 55,858 participants and 3518 deaths), 10 RCTs (11 comparisons) on CV mortality (53,421 participants and 1096 cardiovascular deaths), and 11 RCTs (12 comparisons) on combined cardiovascular CVD events (53,300 participants, of whom 4476 participants experienced at least one CVD event) (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 and 15 studies reported on any single outcome, see Table 2 and Table 3).

Excluded studies

We excluded 520 full-text publications at this update, having assessed the full texts in duplicate. We describe the reasons for some of 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) appears twice in this

summary, it is a single trial. Rose 1965 was a 3-arm trial and we have used the two intervention arms separately in the review.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): CVD outcomes	Blinding of outcome assessment (detection bias): All-cause mortality	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Free of systematic difference in care?	Stated aim to reduce SFA	Achieved SFA reduction	Achieved TC reduction	Other bias
Black 1994	+	?	-	+	+	+	+	-	-	+	?	+
DART 1989	+	?	-	+	+	+	+	-	+	+	+	+
Houtsmuller 1979	+	?	-	?	+	?	+	?	+	?	+	-
Ley 2004	+	+	-	+	+	?	+	-	-	+	-	+
Moy 2001	+	?	-	-	+	?	+	-	+	+	+	+
MRC 1968	+	?	-	+	+	?	+	-	+	?	+	+
Oslo Diet-Heart 1966	+	+	-	?	+	+	+	-	+	?	+	+
Oxford Retinopathy 1978	+	+	-	?	+	?	+	+	-	+	-	+
Rose corn oil 1965	+	?	-	+	+	?	+	+	+	?	-	+
Rose olive 1965	+	?	-	+	+	?	+	+	+	?	-	+
Simon 1997	+	?	-	?	+	?	+	-	-	+	+	+
STARS 1992	+	+	-	?	+	?	+	-	+	+	+	+
Sydney Diet-Heart 1978	+	+	-	+	+	+	+	-	+	+	+	+
Veterans Admin 1969	+	+	+	+	+	+	+	+	+	+	-	+
WHI 2006	+	+	-	+	+	+	+	-	+	+	+	+
WINS 2006	+	+	-	+	+	+	+	-	-	+	-	+

Allocation

All the included trials were randomised controlled trials, and some detail of the randomisation process was provided for all studies, so all were considered at low risk of bias. 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 eight RCTs (eight comparisons, Ley 2004; Oslo Diet-Heart 1966; Oxford Retinopathy 1978; STARS 1992; Sydney Diet-Heart 1978; Veterans Admin 1969; WHI 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. It can also be achieved 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 of participants to be inadequate in the remaining studies.

Blinding of outcome assessment was assessed separately for mortality and CVD outcomes. Blinding is not relevant in assessing all-cause mortality, so all trials were considered at low risk of bias for detection bias for this outcome. For CVD outcomes, nine trials were at low risk of detection bias, one was at high risk and the remainder were unclear.

Incomplete outcome data

Assessing whether incomplete outcome data had been addressed was difficult, as the primary outcomes for this review (mortality and cardiovascular events) were often reported as dropouts and exclusions from the original studies, rather than as the primary outcomes of these trials. 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 tracking of medical records, with assessment of health status by blinded trained adjudicators (WHI 2006), so few major events were likely to have been missed. In the other eight 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 dropouts 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 at low risk of selective reporting.

Other potential sources of bias

Systematic differences in care. We assessed the studies for risk of bias in relation to systematic differences in care. The three RCTs (four comparisons) that appeared at low risk 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 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).

Aim to reduce saturated fat. 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 (11 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 2006), while the remaining five did not (although they did achieve SFA reduction).

Successful saturated fat reduction. Eleven RCTs (11 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 2006; WINS 2006). The remaining studies did not report SFA intake, so we rated them as unclear.

Successful cholesterol reduction. We would expect saturated fat reduction to be reflected in total or LDL cholesterol reductions, which may be more accurate assessments than self-reported saturated fat intake. Nine RCTs (10 comparisons) provided information on serum total 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 in lower saturated fat arms compared with higher saturated fat arms were DART 1989; Houtsmuller 1979; Simon 1997; STARS 1992; Sydney Diet-Heart 1978; WHI 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 by at least 0.2 mm0l/L. One study (Black 1994) did not report lipid levels during the study, while five others did report lipid levels but did not suggest clear differences between lower and higher saturated fat arms (Ley 2004; Oxford Retinopathy 1978; Rose corn oil 1965; Rose olive 1965; Veterans Admin 1969; WINS 2006).

Dietary changes other than saturated fat. Some trials were partially confounded by aiming to make 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. In these studies, any effect on outcomes could be a result of other dietary changes, not of changes in saturated fat intake. The 11 studies (12 comparisons) that appeared free of such differences included Black 1994; DART 1989; Houtsmuller 1979; Ley 2004; MRC 1968; Oxford Retinopathy 1978; Rose corn oil 1965; Rose olive 1965; Simon 1997; Sydney Diet-Heart 1978; Veterans Admin 1969; WINS 2006. This factor was not considered alongside others in the formal risk of bias assessment (Figure 2) so is described here. We did not identify any further methodological issues.

Summary risk of bias. We considered dietary advice or all-food-provided type trials to be at low summary risk of bias where we judged randomisation, allocation concealment, and blinding of outcome assessors to be adequate. For CVD outcomes, five trials were assessed as at low summary risk of bias: Ley 2004; Sydney Diet-Heart 1978; Veterans Admin 1969; WHI 2006; WINS 2006. For all-cause mortality (and lipid outcomes) where blinding of outcome assessors is not important, a further three trials were also at low summary risk of bias, eight in total: Ley 2004; Oslo Diet-Heart 1966; Oxford Retinopathy 1978; STARS 1992; Sydney Diet-Heart 1978; Veterans Admin 1969; WHI 2006; WINS 2006.

Effects of interventions

See: **Summary of findings 1** 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

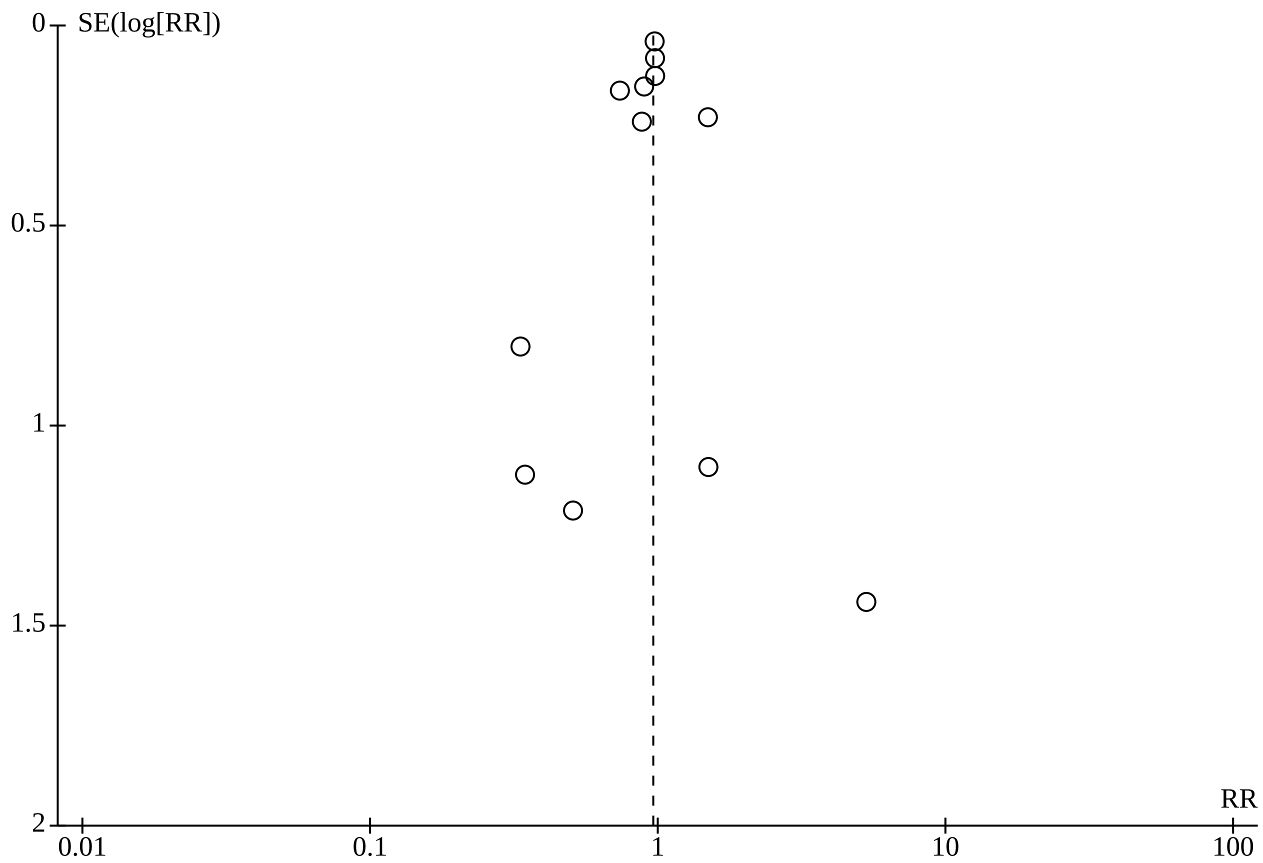
All-cause mortality

GRADE assessment suggests that reducing saturated fat intake probably makes little or no difference to all-cause mortality (moderate-quality evidence, downgraded once for imprecision).

There was little or no effect of lower saturated fat compared to higher saturated fat intake on mortality (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.90 to 1.03, I^2 = 2%, 55,858 participants, 3518 deaths, 11 RCTs, P_{effect} = 0.42, Analysis 1.1). This lack of effect was confirmed in sensitivity analyses including only trials at low summary risk of bias (Analysis 1.2), that aimed to reduce saturated fat (Analysis 1.3), that significantly reduced saturated fat intake (Analysis 1.4), that achieved a reduction in total or LDL cholesterol (Analysis 1.5), excluding the largest trial (WHI 2006, Analysis 1.6), or analysing using Mantel-Haenszel or Peto fixed-effect analysis (Analysis 1.7; Analysis 1.8).

Small study bias was assessed using a funnel plot and comparing the results of fixed- and random-effects meta-analysis. The funnel plot did not suggest any small study bias (Figure 3), and the results of fixed- and random-effects meta-analyses were very similar, suggesting that small study bias was not an issue.

Figure 3. Funnel plot of comparison: fat modification or reduction vs usual diet - total mortality.



There was little or no effect, regardless of what nutrients were used to replace the saturated fat removed, including replacement with PUFA, MUFA, CHO and/or protein (Analysis 1.9). Effects did not differ by main substitution (Analysis 1.10), study duration (Analysis 1.11), baseline saturated fat intake (Analysis 1.12), degree of difference in saturated fat between arms (Analysis 1.13), participant sex

(Analysis 1.14), by baseline CVD risk (Analysis 1.15), by degree of cholesterol reduction (Analysis 1.16) or by decade of publication (Analysis 1.17, Chi^2 test for differences between subgroups all P > 0.05).

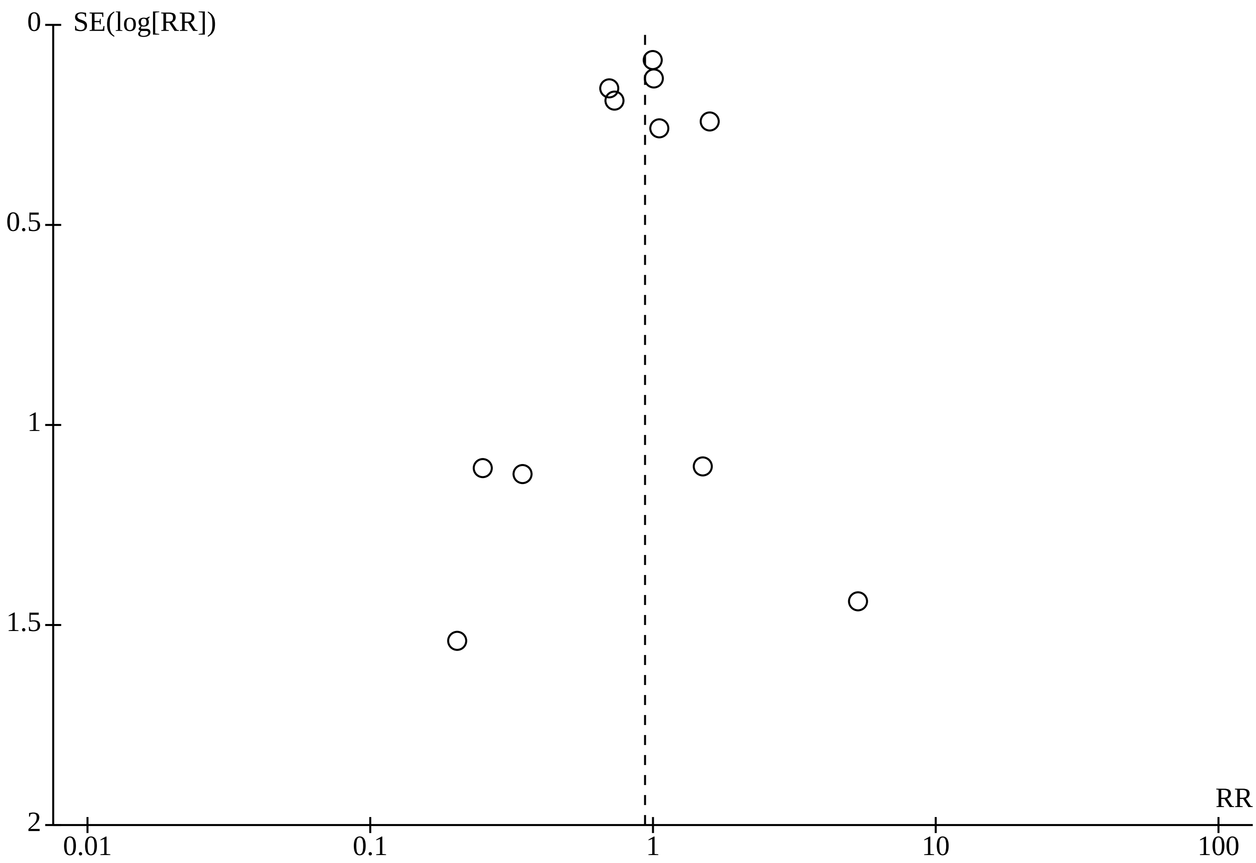
Cardiovascular mortality

GRADE assessment suggests that reducing saturated fat intake probably makes little or no difference to cardiovascular mortality (moderate-quality evidence, downgraded once for imprecision).

There was little or no effect of SFA reduction 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 1.18). This lack of effect was confirmed in sensitivity analyses limiting to trials at low summary risk of bias (Analysis 1.19), explicitly aiming to reduce saturated fat (Analysis 1.20), achieving statistically significant saturated fat reduction (Analysis 1.21), achieving cholesterol reduction (Analysis 1.22), or running fixed-effect analysis (Analysis 1.24; Analysis 1.25). However, excluding the largest single trial (WHI 2006) suggested that reducing saturated fat intake reduced the risk of CVD mortality (Analysis 1.23).

The funnel plot did not suggest small study bias (Figure 4), and the similarity in effect sizes between fixed- and random-effects analysis suggests that small study bias is not important here.

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



Subgrouping did not suggest important effects of reduced SFA on cardiovascular mortality, regardless of what was substituted for SFA (Analysis 1.26). When subgrouping by main substitution (Analysis 1.27), duration (Analysis 1.28), baseline SFA intake (Analysis 1.29), by difference in SFA (Analysis 1.30), participant sex (Analysis 1.31), baseline CVD risk (Analysis 1.32), or degree of cholesterol reduction (Analysis 1.33), there were no statistically significant differences between subgroups. There was a marginally significant difference between subgroups when ordered by decade of publication, but no clear pattern of effect, so we assumed the effect was probably spurious (Analysis 1.34). Additionally, effects 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

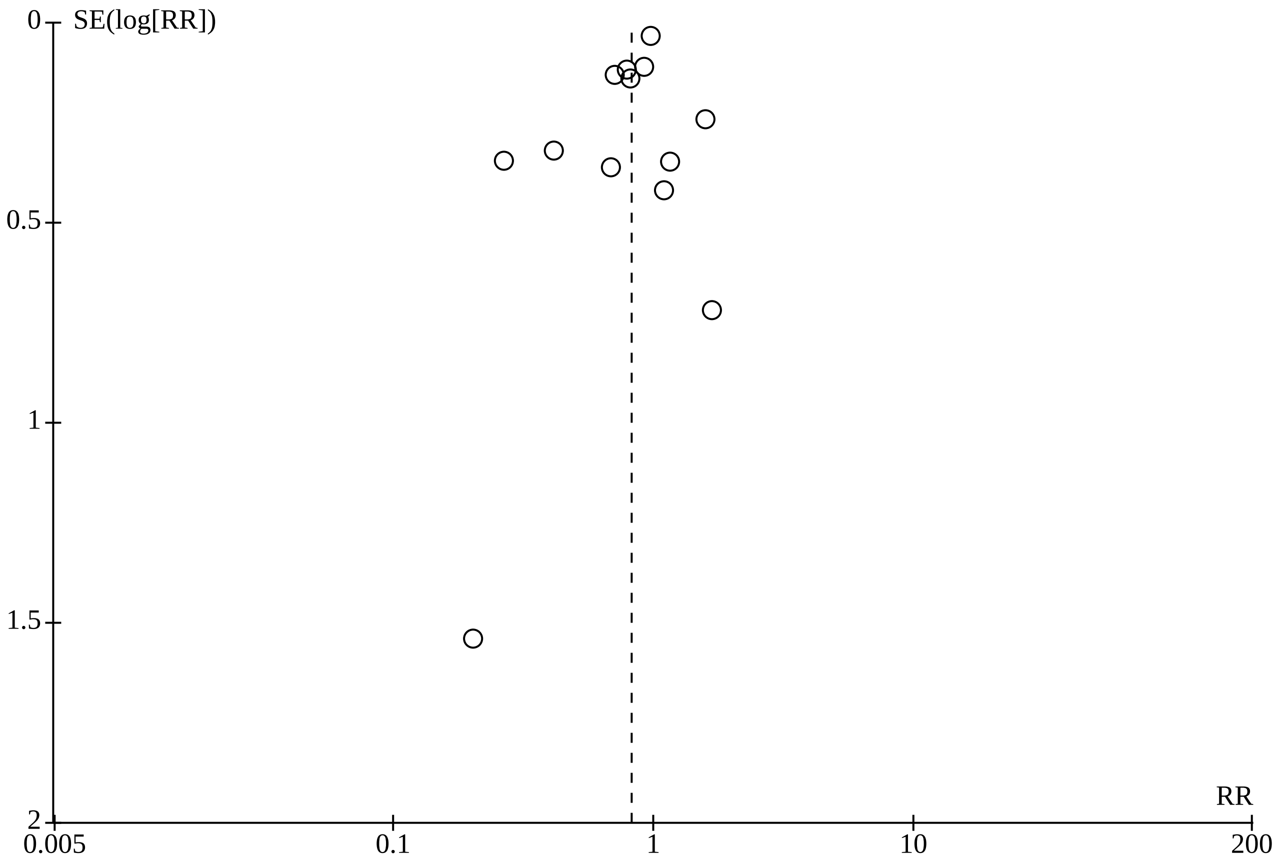
GRADE assessment suggests that reducing SFA intake probably reduces cardiovascular events, to a greater extent with greater cholesterol reduction (moderate-quality evidence, downgraded once for risk of bias and publication bias combined).

There was a 17% reduction in cardiovascular events in people who had reduced SFA compared with those on higher SFA (RR

0.83, 95% CI 0.70 to 0.98, I^2 = 67%, 12 RCTs, 53,758 participants, 4538 people with cardiovascular events, P_{effect} = 0.03, Analysis 1.35). This protective effect was confirmed in sensitivity analyses including only trials that aimed to reduce saturated fat (Analysis 1.37), that significantly reduced saturated fat intake (Analysis 1.38), that achieved a reduction in total or LDL cholesterol (Analysis 1.39), or excluding the largest trial (WHI 2006, Analysis 1.40). Analysing including only trials at low summary risk of bias, or using Mantel-Haenszel or Peto fixed-effect analysis suggested more marginal protection(Analysis 1.36; Analysis 1.41; Analysis 1.42).

A funnel plot did not suggest severe small-study bias (Figure 5), but fixed-effect analyses suggested slightly smaller effects (Analysis 1.41; Analysis 1.42), suggesting that smaller studies with more cardiovascular events in the intervention groups may be missing. Adding any such studies back would tend to moderate the protective effect of reducing SFA.

Figure 5. Funnel plot of comparison: fat modification or reduction vs usual diet - combined cardiovascular events.



Sensitivity analysis omitting trials which included dietary interventions in addition to changes to dietary fat (for example, changes to fruit and vegetable or fibre intake) we excluded three trials (Oslo Diet-Heart 1966; STARS 1992; WHI 2006). This analysis also suggested that reducing saturated fat (rather than other dietary changes) reduced risk of cardiovascular events: RR 0.86 (95% CI 0.67 to 1.09, Analysis 1.43).

When we subgrouped according to replacement for SFA, the PUFA replacement group suggested a 21% reduction in cardiovascular events, a 16% reduction in studies replacing SFA with carbohydrate, and little or no effect of other replacements, but without statistically significant effects between subgroups (Analysis 1.44). Similarly, there were no statistically significant differences between subgroups by main replacement (Analysis 1.45), by study duration (Analysis 1.46), in men or women (Analysis 1.49) or by baseline CVD risk (Analysis 1.50). When subgrouping, there was a suggestion of greater effects when baseline SFA was higher (Analysis 1.47), with greater reduction of SFA (Analysis 1.48), and with greater cholesterol reduction (Analysis 1.51). There were different effects by decade of publication, but no suggestion of a trend or a change following wider introduction of statins in the mid-1990s (Analysis 1.52).

We further 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 4). 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 total serum cholesterol levels reduced CVD events more. Greater baseline SFA intake and greater reduction in SFA were also associated with greater improvement in CVD events with SFA reduction, and increases in PUFA and MUFA intakes were slightly protective of CVD events, but none of these relationships were statistically significant. Overall, 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. Apparent heterogeneity was accounted for by a dose-effect; where SFA reduction resulted in greater serum cholesterol reduction, the reduction in CVD events was greater.

This 17% reduction in risk of CVD events translated into a number needed to treat for an additional beneficial outcome (NNTB) of 56 in primary prevention trials, so that 56 people need to reduce their saturated fat intake over around four years for one person to avoid experiencing a CVD event. In secondary prevention trials, the NNTB was 53.

Secondary outcomes - health events

Myocardial Infarction (fatal and non-fatal)

GRADE assessment suggested that the effect of reducing saturated fat intake on risk of myocardial infarction is unclear as the evidence was of very low-quality (downgraded once each for risk of bias, imprecision and publication bias).

There was a small protective effect of SFA reduction on myocardial infarction (fatal and non-fatal, RR 0.90, 95% CI 0.80 to 1.01, I^2 = 10%, 10 RCTs (11 comparisons) including 53,167 participants, 1714 people experiencing MI, Analysis 2.1). This protective effect was slightly modified in sensitivity analyses, and confirmed in analyses limited to trials that aimed to reduce saturated fat (Analysis 2.3), that achieved a reduction in total or LDL cholesterol (Analysis 2.5), and excluding the largest trial (WHI 2006, Analysis 2.6). Sensitivity analyses including only trials at low summary risk of bias (RR 0.93, 95% CI 0.81 to 1.08, Analysis 2.2), that significantly reduced saturated fat intake (Analysis 2.4), analysed using Mantel-Haenszel or Peto fixed-effect analysis (Analysis 2.7; Analysis 2.8) suggested little or no effect, though risk ratios were still all < 1.0.

The funnel plot was difficult to interpret, but did not raise major concerns about small-study bias (not shown). While effects of random- and fixed-effect meta-analysis were only slightly different, they fell each side of the line suggesting an effect (Analysis 2.7; Analysis 2.8). There may be a small amount of small study bias.

The protective effect of replacing SFA with PUFA appeared to explain the reduction in MI (Analysis 2.9), but there were no statistically significant differences between subgroups by replacement (Analysis 2.10), duration (Analysis 2.11), baseline SFA intake (Analysis 2.12), change in SFA intake (Analysis 2.13), participant sex (Analysis 2.14), baseline CVD risk (Analysis 2.15), cholesterol reduction (Analysis 2.16) or decade of publication (Analysis 2.17).

Myocardial Infarction (non-fatal only)

GRADE assessment suggests that reducing saturated fat may have little or no effect on risk of non-fatal myocardial infarction (low-quality evidence, downgraded once each for risk of bias and imprecision).

There was no clear effect of SFA reduction compared to usual diet on non-fatal myocardial infarction (RR 0.97, 95% CI 0.87 to 1.07, I^2 = 0%, 7 RCTs, 52,834 participants, 1385 people with at least one non-fatal MI, Analysis 2.18). This lack of effect was not altered in sensitivity analyses retaining only those that aimed to reduce SFA (Analysis 2.20), those showing a reduction in serum cholesterol (Analysis 2.22), or fixed-effect analysis (Analysis 2.24; Analysis 2.25). However, sensitivity analyses retaining only trials at low summary risk of bias (RR 0.89, 95% CI 0.58 to 1.35, Analysis 2.19), those showing a significant reduction in SFA (Analysis 2.21), and omitting the largest trial (WHI 2006, Analysis 2.23) all suggested a reduction in non-fatal MI with reduced SFA.

The funnel plot did not raise major concerns about small-study bias (not shown), and effects of fixed- and random-effects analyses were very similar, reinforcing the lack of small study bias.

Subgrouping by any replacement for SFA suggested reductions in non-fatal MI when replaced by PUFA, but not other replacements (Analysis 2.26). Subgrouping by main substitution (Analysis 2.27), duration (Analysis 2.28), baseline SFA intake (Analysis 2.29), degree of SFA reduction (Analysis 2.30), sex (Analysis 2.31), baseline CVD risk (Analysis 2.32), degree of cholesterol reduction (Analysis 2.33) and decade of publication (Analysis 2.34) did not suggest significant differences between subgroups.

Stroke (any type, fatal or non-fatal)

GRADE assessment suggests that the effect of reducing SFA intake on stroke is unclear as the evidence is of very low-quality (downgraded twice for imprecision and once for risk of bias).

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 little or no effect of SFA reduction compared to usual diet on stroke of any type with any outcome (RR 0.92, 95% CI 0.68 to 1.25, I^2 = 9%, 7 RCTs, 50,952 participants, 1118 people with stroke, Analysis 2.35). This lack of effect was not altered in sensitivity analyses retaining only those that aimed to reduce SFA (Analysis 2.37), those showing a reduction in serum cholesterol (Analysis 2.39), or fixed-effect analysis (Analysis 2.41; Analysis 2.42). However, for sensitivity analyses retaining only trials at low summary risk of bias (RR 0.76, 95% CI 0.42 to 1.38, Analysis 2.36), those showing a significant reduction in SFA (Analysis 2.38), and omitting the largest trial (WHI 2006, Analysis 2.40) the best estimate of effect always suggested a reduction in stroke with reduced SFA, though they were not statistically significant.

We did not create a funnel plot as the analysis only included data from seven RCTs, however RRs generated using fixed-effect analyses were much closer to 1.0 than the random-effects meta-analysis (suggesting a small amount of publication bias), though both suggested little or no effect.

Subgrouping by any substitution for SFA suggested reduction in risk of stroke whether SFA was replaced by PUFA, CHO or protein (Analysis 2.43). Subgrouping did not suggest significant differences between subgroups by main substitution (Analysis 2.44), duration (Analysis 2.62), baseline SFA (Analysis 2.46), SFA change (Analysis 2.47), sex (Analysis 2.48), CVD risk (Analysis 2.49), cholesterol reduction (Analysis 2.50) or decade of publication (Analysis 2.51).

Coronary heart disease (CHD) mortality

GRADE assessment suggests that reducing saturated fat intake may have little or no effect on CHD mortality (low-quality evidence, downgraded twice for imprecision).

Eight RCTs (9 comparisons) suggest little or no effect of reducing saturated fat on risk of CHD mortality (RR 0.97, 95% CI 0.82 to 1.16, I^2 = 28%, 53,159 participants, 927 people died of coronary heart disease, Analysis 2.52), and this was not altered in any sensitivity analyses (Analysis 2.53; Analysis 2.54; Analysis 2.55; Analysis 2.56; Analysis 2.57; Analysis 2.58; Analysis 2.59).

We did not create a funnel plot as the analysis only included data from seven RCTs, but the results of fixed- and random-effects analyses were nearly identical, suggesting that small study bias is not an issue here.

There was no suggestion of an effect of reducing SFA on CHD mortality regardless of what replaced the SFA (Analysis 2.60). There were no statistically significant differences between subgrouping in any analysis (Analysis 2.61; Analysis 2.62; Analysis 2.63; Analysis 2.64; Analysis 2.65; Analysis 2.66; Analysis 2.67; Analysis 2.68).

Coronary heart disease events

GRADE assessment suggested that the effect of reducing saturated fat on CHD events is unclear as the evidence is of very low-quality (downgraded once each for imprecision, risk of bias and inconsistency).

There was the suggestion of a 17% reduction in CHD events as a result of saturated fat reduction in the main analysis (RR 0.83, 95% CI 0.68 to 1.01, I^2 = 62%, 53,199 participants, 2261 people had at least one coronary heart disease event in 10 RCTs, Analysis 2.69). This did not differ in sensitivity analyses (Analysis 2.74; Analysis 2.72; Analysis 2.73; Analysis 2.71; Analysis 2.75; Analysis 2.76) except when limiting to trials at low summary risk of bias (RR 0.92, 95% CI 0.77 to 1.10, Analysis 2.70).

The funnel plot did not appear unbalanced, and the results of fixed- and random-effects analyses were different, though both suggested that reducing SFA resulted in lower risk of CHD.

Subgrouping by any replacement for SFA suggested that replacement by PUFA may lead to reduced risk of CHD events (Analysis 2.77). There were no statistically significant differences between any other subgroups (Analysis 2.78; Analysis 2.79; Analysis 2.80; Analysis 2.81; Analysis 2.82; Analysis 2.83; Analysis 2.84) except by decade of publication, though this did not suggest any sequence or step change (Analysis 2.85).

Type 2 diabetes, new diagnoses

Only one RCT reported on diagnosis of diabetes (WHI 2006). There was little or no effect of reducing SFA intakes on diagnosis of diabetes in this study (RR 0.96, 95% CI 0.90 to 1.02, 48,835 participants, 3342 developed diabetes, Analysis 2.86). WHI 2006 was assessed at low summary risk of bias, aimed to reduce SFA, and demonstrated significant SFA and cholesterol reduction. With only one trial, we were not able to assess publication bias or carry out subgrouping.

Secondary outcomes - blood levels

Serum blood lipids

Total cholesterol (TC): There was a reduction in TC in participants with reduced SFA compared to higher SFA (mean difference (MD) -0.24 mmol/L, 95% CI -0.36 to -0.13, I^2 = 60%, 13 RCTs, 7115 participants, Analysis 3.1). We did not conduct sensitivity analyses or 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, Analysis 3.2; Analysis 3.3). 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 higher SFA (MD -0.19 mmol/L, 95% CI -0.33 to -0.05, I^2 = 37%, 5 RCTs, 3291 participants, Analysis 3.4). There was no clear differential effect on LDL depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture, Analysis 3.5; Analysis 3.6). We could not interpret the funnel plot due to sparsity of studies (not shown).

High-density lipoprotein (HDL): There was little or no effect of reducing SFA intakes on HDL (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, I^2 = 0%, 7 RCTs, 5147 participants, Analysis 3.7). There was no clear differential effect on HDL depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture, Analysis 3.8; Analysis 3.9). We could not interpret the funnel plot due to sparsity of studies (not shown).

Triglycerides (TG): There was little or no effect of reducing SFA intakes on TG (MD -0.08 mmol/L, 95% CI -0.21 to 0.04, I^2 = 51%, 7 RCTs, 3845 participants, Analysis 3.10). There was no clear differential effect on TG depending on the replacement for SFA (PUFA, MUFA, CHO or a mixture, Analysis 3.11; Analysis 3.12). 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 little or no effect of reducing SFA intakes on TC/HDL (MD -0.10, 95% CI -0.33 to 0.13, I^2 = 24%, 2985 participants, Analysis 3.13). There were no clear differential effects of replacement on TC/HDL (Analysis 3.14; Analysis 3.15). 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 on LDL/HDL in this study (MD -0.36, 95% CI -0.92 to 0.20, 50 participants, Analysis 3.16). This study replaced SFA with CHO (mainly) and PUFA.

Lipoprotein (a) (Lp(a)): Only two RCTs reported on lipoprotein (a), but these included 28,820 participants. There was little or no effect of reducing SFA intakes on Lp(a) (MD 0.00, 95% CI -0.00 to 0.00, I^2 = 0%, Analysis 3.17). There was no suggestion of differential effects of replacement on Lp(a) (Analysis 3.18; Analysis 3.19). 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 little or no 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, Analysis 3.20).

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, Analysis 3.20). We could not interpret the funnel plot due to sparsity of studies (not shown).

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

Secondary outcomes - other outcomes and potential harms

There was little or 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, Analysis 4.1); **cancer deaths** (RR 1.00, 95% CI 0.61 to 1.64, I^2 = 49%, 5 RCTs, 52,283 participants, 2472 cancer deaths, Analysis 4.2); **systolic blood pressure** (MD -0.19 mmHg, 95% CI -1.36 to 0.97, I^2 = 0%, 5 RCTs, 3812 participants, Analysis 4.5); **diastolic blood pressure** (MD -0.36 mmHg, 95% CI -1.03 to 0.32, I^2 = 0%, 5 RCTs, 3812 participants, Analysis 4.6).

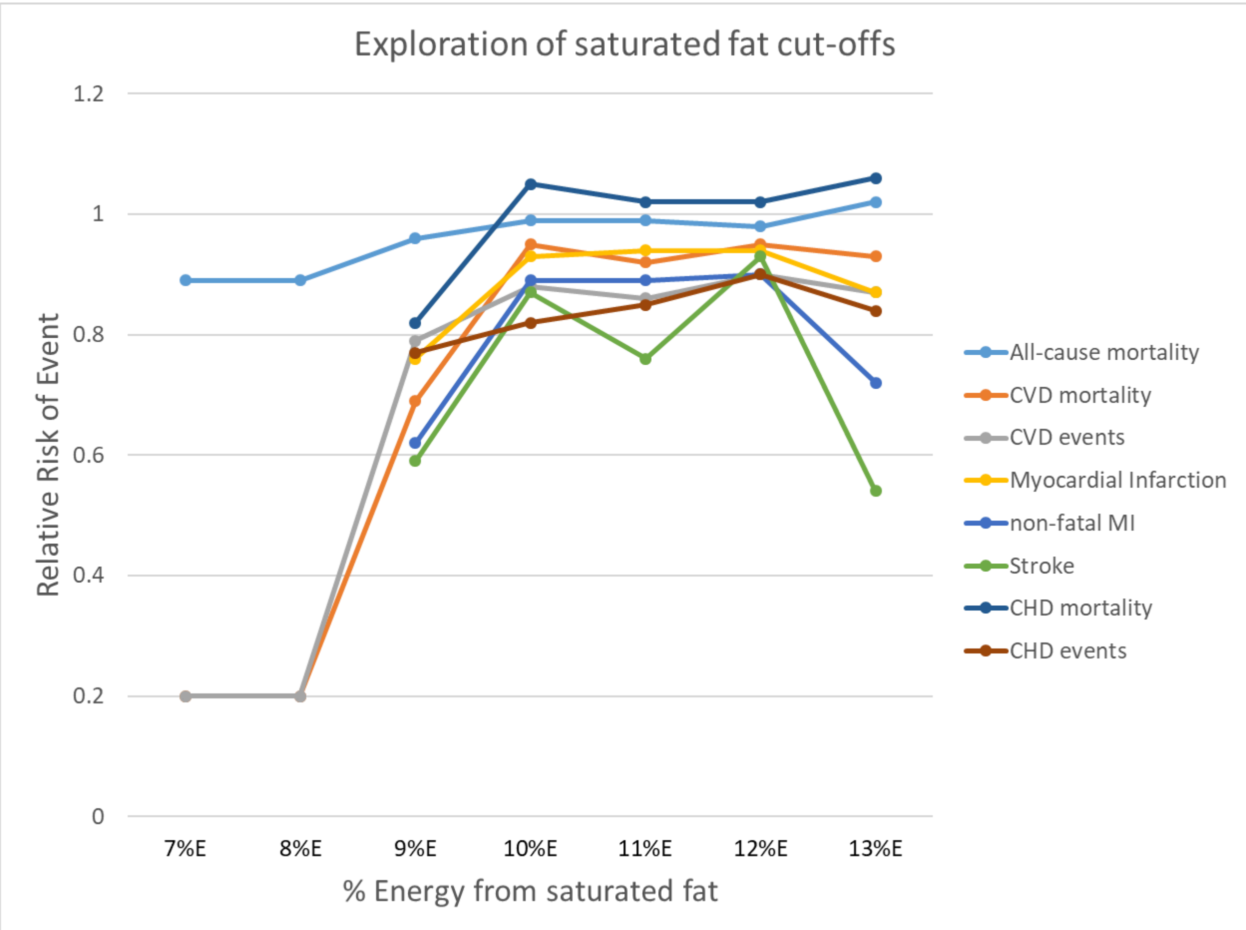
There was evidence that reducing SFA intake resulted in small reductions in **body weight** (MD -1.97 kg, 95% CI -3.67 to -0.27, I^2 = 72%, 6 RCTs, 4541 participants, Analysis 4.3), and **body mass index** (MD -0.50, 95% CI -0.82 to -0.19, I^2 = 55%, 6 RCTs, 5553 participants, Analysis 4.4).

Only one RCT reported assessing **quality of life**. The Women's Health Initiative (WHI 2006) assessed quality of life at baseline using the SF-36 tool). They found that being in the lower SFA arm resulted in a small improvement in Global Quality of Life at trial close-out (on a scale of 0 worst to 10 best, MD 0.04, 95% CI 0.01 to 0.07, Analysis 4.7). This very small effect (less than 1% change) was statistically significant but unlikely to be relevant to individuals. However, it suggests no reduction in quality of life in those reducing their saturated fat.

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 noncommunicable 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 5, and were plotted for a visual overview (Figure 6). The figure suggests reductions in cardiovascular outcomes in studies where saturated fat intake was greater than 10%E in control groups, and less than 10%E in intervention groups.

Figure 6. Exploration of saturated fat cut-offs



Additional WHO NUGAG specific questions:

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 noncommunicable diseases (NCDs)?

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 reductions in cardiovascular events in studies with greater serum total cholesterol reductions (implying greater reductions in SFA intake). Effects of reducing SFA on other cardiovascular and cancer outcomes were either very small or unclear (as the evidence was of very low quality), but it should be noted that risk ratios were all 1.0 or lower - no harm was indicated. Effects on NCD risk factors were small but positive (serum total cholesterol, LDL cholesterol, systolic and diastolic blood pressure, weight and BMI) or neutral (HDL cholesterol and TGs).

What is the effect of reducing SFA on coronary heart disease mortality and coronary heart disease events?

We found little or no effect of reducing SFA on non-fatal MI and CHD events, but the evidence on MI, stroke and CHD events was of very low quality. However, all risk ratios were less than 1.0.

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 in cardiovascular events in studies that replaced saturated fats by PUFAs or CHO than in studies with replacement with MUFAs 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 probably reduces the risk of CVD events. Replacing SFA with PUFA also appears to reduce the risk of total MI, non-fatal MI, stroke and CHD events, but has little or no effect on all-cause mortality, CVD mortality and CHD mortality.

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

The evidence for effects of replacing SFA with MUFA was very limited, so assessment of health effects was not possible.

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

While studies that replaced SFA with CHO reduced CVD events and stroke, effects on all-cause mortality and other CVD outcomes suggested little or no effect.

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

There was no evidence suggesting that replacing SFA with protein reduced all-cause mortality or any CVD outcomes, but the evidence was limited.

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 10%E in control groups, and less than 10%E in intervention groups (see Figure 6).

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 probably has little or no effect on all-cause or cardiovascular mortality, but probably caused a 17% (95% CI 2 to 30%, I^2 = 67%, moderate-quality evidence) reduction in people experiencing cardiovascular events. The heterogeneity in this relationship was explained by greater reduction in CVD events in trials with greater serum cholesterol lowering. This effect on cardiovascular events was retained in most sensitivity analyses, but not when limiting to studies at low summary risk of bias. Subgrouping suggested that there was a 21% (95% CI 0 to 38%) reduction in cardiovascular events in studies that replaced saturated fats by PUFAs, and a 16% (95% CI -6 to 33%) reduction in studies replacing with CHO, with little information on the effect of replacing with MUFAs or protein. The difference between subgroups was not statistically significant. We could not explore data on trans fats due to lack of data. Meta-regression and subgrouping suggested that greater reductions in SFA intake, greater reductions in total serum cholesterol levels, higher baseline SFA intake and greater increases in PUFA and MUFA intakes reduced CVD events more, but the strongest factor was the degree of cholesterol lowering. This suggests that the cardiovascular effects of reducing saturated fat rely on changes in atherosclerosis via serum cholesterol. The degree of cholesterol lowering reflects greater reduction in SFA and greater increase in PUFA (Hegsted 2000).

There may be little or no effect of SFA reduction on non-fatal MI or CHD mortality (both low-quality evidence), and effects on fatal and non-fatal MI, stroke and CHD events were unclear (as the evidence was of very low-quality). However, risk ratios were less than 1.00 for all of these. While we found small reductions in body weight and body mass index with advice to reduce saturated fats, there was little or no effect on diabetes diagnoses, cancer diagnoses or cancer deaths, or on systolic or diastolic blood pressure.

Reducing saturated fat caused reductions in serum total and LDL cholesterol, which did not differ according to type of replacement. There was little or no effect of saturated fat reduction on serum HDL cholesterol or triglyceride. Data on lipid ratios, Lp(a) and HOMA were very limited and effects unclear, but SFA reduction appears to reduce glucose two hours after a glucose load.

Overall completeness and applicability of evidence

The review included adult participants at varying levels of risk of cardiovascular disease, men and women, with mean ages from 46 to 66 years at baseline, 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 all primary and secondary CVD outcomes. Three thousand five hundred and eighteen participants in the included trials died, 1096 died of a cardiovascular cause, and 4538 experienced at least one cardiovascular event.

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

All 15 trials (16 comparisons) included were randomised controlled trials, allocation concealment was judged well done in eight RCTs and blinding of outcome assessors adequate in nine trials assessing CVD outcomes (and all trials assessing all-cause mortality). Blinding of participants is difficult and expensive in dietary fat trials, but was adequate in one trial. 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. Five trials were at low summary risk of bias.

The lack of blinding of participants in most dietary trials is unlikely to alter outcome assessment when outcomes include death and cardiovascular events (although it could potentially affect assessment of worsening of angina, or increased dose of antianginals), but lack of blinding in 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 saturated 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 interventions that reduced dietary saturated fat intake reduced the risk of cardiovascular events.

Complex interventions

With complex interventions, such as dietary interventions, 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), as well as questions around whether the intended intervention was realised in study participants during the study.

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 to support generalisability for the effects of the interventions.

We aimed to identify all the relevant studies through use of a broad 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, to simplify decisions on inclusion, and the two independent assessors 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, it is difficult to measure actual saturated fat intake achieved. Some trials did not report it, either because they did not assess it, or did assess it but didn't report this relatively uninteresting outcome. Other trials 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. Assessment of change in total cholesterol is a way to get over self-reporting of dietary intake as reducing saturated fat reduces total and LDL cholesterol. This review suggests that the relationship between saturated fat reduction and CVD events is moderated by the degree of cholesterol lowering, which is exactly what would be expected of a true effect.

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 different 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 dropouts. 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 2500 deaths, over 500 cardiovascular deaths, and over 3000 participants experiencing at least one cardiovascular event (all within WHI 2006, the largest single study with almost 50,000 female participants for many years).

The number of cardiovascular deaths across the review was relatively small (1096), so while we can be quite confident in reporting a reduction in participants experiencing cardiovascular events (4476 events) with SFA reduction, and a lack of effect on total mortality (3518 deaths) within the studies' time scales, the effect on cardiovascular mortality is less clear. The risk ratio of 0.94 (95% CI 0.78 to 1.13, Analysis 1.18) 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 people experiencing MIs, 1118 strokes and 1385 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, and to relatively small reductions in saturated fat (and serum cholesterol) in some trials. Some of the events included within combined cardiovascular events, such as new or worsening angina or increased anti-anginal treatment, could potentially be influenced by allocated study arm, and so might increase bias within unblinded trials (although they also add power to see potential effects). There are difficulties in finding data on the number of people experiencing composite end points such as cardiovascular events. This end point represents the number of people experiencing any of the following: cardiovascular death, 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). Adding up the number of events is easy, but a single participant may have experienced a stroke, an MI and atrial fibrillation during a trial - and we need to take care not to count this individual three times. So finding such composite end point data involves using the best published composite end point data and supplementing this with author contact where possible. We have underestimated such composite end points rather than overestimated them where exact data are not available. Added to this complex picture, it needs to be remembered that definitions and diagnoses of some end points have altered over time.

Where the funnel plots and comparison of fixed- and random-effects meta-analyses suggest small-study bias, we have downgraded the quality of the evidence in GRADE, but effects of any such small study bias appear small.

Some trials were partially confounded by aiming to make 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, fibre or salt intakes. In these studies, any effect on outcomes could be a result of other dietary changes, not of changes in saturated fat intake. The 11 studies (12 comparisons) that appeared free of such differences included Black 1994; DART 1989; Houtsmuller 1979; Ley 2004; MRC 1968; Oxford Retinopathy 1978; Rose corn oil 1965; Rose olive 1965; Simon 1997; Sydney Diet-Heart 1978; Veterans Admin 1969; WINS 2006. On the basis of reviewer comments, we assessed effects of reducing saturated fat intake on combined CVD events including only these trials free of additional interventions. Omitting trials with additional interventions (Oslo Diet-Heart 1966; STARS 1992; WHI 2006) leaves nine studies (ten arms) randomising 4456 participants of whom 812 experienced a CVD event, suggesting a similar reduction in CVD events (RR 0.86, 95% CI 0.67 to 1.09, I^2 = 59%, Analysis 1.43) to the main analysis (RR 0.83, 95% CI 0.70 to 0.98, I^2 = 67%, > 53,000 participants randomised, Analysis 1.35). This suggests that effects on combined CVD events are not driven by interventions other than reductions in saturated fats and any energy replacements.

One surprising element of this review is the lack of new trials identified in the 2019 update, and small numbers of potential ongoing trials. This is likely to be because well-powered trials on cardiovascular end points will need to be large and carried out over several years, so expensive. As the effects of saturated fats are felt to be established and understood, trialists and funders may feel that the money would be better invested in answering other questions. For most of the ongoing trials, information is limited and these trials may or may not be included when fully published. 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 little or no effect on all-cause or cardiovascular mortality but did appear to reduce the risk of 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). 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 issue of what factors should be adjusted for, and what not adjusted for, in observational studies when dietary factors are very tightly correlated is a thorny one, and one of the reasons why trial data may be helpful. 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 little or no relationship between saturated fat intake and coronary heart disease (RR 1.07, 95% CI 0.96 to 1.19) though their data did suggest a (non-statistically significant) reduction in stroke risk with higher saturated fat intake (RR 0.81, 95% CI 0.62 to 1.05, Siri-Tarino 2010).

In this review, we found that replacing saturated fat with PUFAs (a modified-fat diet) appeared more protective of cardiovascular events than replacement with carbohydrates (a low-fat diet, Analysis 1.44; Analysis 1.45). 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 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, 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 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 end points, 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 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 2006) we now have data on more people experiencing cardiovascular events who were originally 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 end points 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 0.96 (95% CI 0.90 to 1.03, Analysis 1.1), and for cardiovascular mortality RR 0.94 (95% CI 0.78 to 1.13, Analysis 1.18). Our best estimate is that SFA reduction results in a reduction of 6% in deaths due to cardiovascular disease, and a reduction of 4% in total deaths, but these are small effects with wide confidence intervals.

The high-risk participants all showed evidence of cardiovascular disease at baseline. Under current guidelines, most high-risk participants with raised lipid levels should be on lipid-lowering medication (Grundy 2019; 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. Recent guidelines recommend saturated fat reduction in general populations (SACN 2019).

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 large trials). 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, WHI 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence supports the reduction of saturated fat to reduce risk of combined cardiovascular events in people with and without existing cardiovascular disease, in men and women, over at least two years and in industrialised countries. Little or no effect of saturated fat reduction was seen on all-cause and cardiovascular mortality, at least on this timescale.

Practical ways to achieve reductions in dietary saturated fat include switching to lower fat dairy foods and cutting off meat fats, as well as reducing intake of foods high in saturated fats such as cakes, biscuits, pies and pastries, butter, ghee, lard, palm oil, sausages and cured meats, hard cheese, cream, ice cream, milkshakes and chocolate (for further details see NHS 2020).

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 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.

All future trials should be of at least 2 years duration (preferably longer), employ excellent methodology in terms of randomisation and allocation concealment, blinding of outcome assessors, high-quality assessment of macronutrients and micronutrients during the trial in both arms, and equivalent attention and health professional time to participants in both arms.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Black 1994

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	People with non-melanoma skin cancer (USA) CVD risk: low Control: randomised 67, analysed 58 Intervention: randomised 66, analysed 57 Mean years in trial: 1.9 % male: control 67%, intervention 54% Age: mean control 52.3 (SD 13.2), intervention 50.6 (SD 9.7) Ethnicity: white 100% (excluded from study if of Asian, Black, Hispanic or American Indian ancestry) Statins use allowed: Unclear % taking statins: Not reported
Interventions	Reduced fat vs usual diet Control aims: no dietary advice Intervention aims: total fat 20%E, protein 15%E, CHO 65%E Control methods: no dietary change, 4-month intervals clinic examination by dermatologist 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 Intervention delivered face-to-face by a dietitian 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 **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: Linoleic acid, cont 16.9 (SD 5.6) g, int 8.5 (SD 3.3) g 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 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 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 Trans fat intake: not reported **Replacement for saturated fat: CHO and protein (by dietary aims and achievements), main is CHO**

Black 1994 *(Continued)*

	Style: diet advice Setting: community
Outcomes	Stated trial outcomes: incidence of actinic keratosis and non-melanoma skin cancer Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths Secondary outcomes: cancer deaths (none) Tertiary outcomes: none (weight data provided, but no variance info)
Notes	**Study duration** 24 months. **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. **SFA reduction achieved.** **Total serum cholesterol: not reported** At 2 years control -1.5 kg n = 50?, intervention -1 kg n = 51? Trial dates: Study dates not reported (but still recruiting at first publication in 1994) Funding: National Cancer Institute 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	"list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice provided, so participants not blinded
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	"examined .... by dermatologists unaware of their treatment assignments". Deaths (all-cause and CVD) not considered relevant to the intervention
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk for all-cause and CVD mortality. Unclear for other outcomes
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data

Black 1994 *(Continued)*

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

Study characteristics	
Methods	Factorial RCT Diet And Reinfarction Trial (DART) Summary risk of bias: moderate to high
Participants	Men recovering from an MI (UK) CVD risk: high Control: randomised 1015, analysed unclear Intervention: randomised 1018, analysed unclear Mean years in trial: control 1.9, randomised 1.9 % male: 100% Age: mean control 56.8, intervention 56.4 (< 70) Ethnicity: not stated 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". % 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 Control aims: no dietary advice on fat, weight reducing advice if BMI > 30 Intervention aims: reduce fat intake to 30%E, increase P/S to 1.0, weight-reducing advice if BMI > 30 Note: This was a factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre. Control methods: dietitians provided 'sensible eating' advice without specific information on fats. 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. Intervention delivered individually face-to-face by a dietitian 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 **Saturated fat intake, %E (through study): cont 15 (SD3), int 11 (SD3), (mean difference -4.00, 95% CI -4.26 to -3.74) significant reduction**

DART 1989 *(Continued)*

	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 PUFA n-3 intake: EPA, cont 0.6 (SD 0.7) g/wk, Int 2.4 (SD 1.4) g/wk PUFA n-6 intake: not reported 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 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 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 Trans fat intake: not reported **Replacement for saturated fat: PUFA and CHO (by dietary aims), PUFA, CHO and protein (by dietary achievements), main PUFA** Style: diet advice Setting: community ⁑Estimated by subtraction (assuming total fat = SFA + PUFA + MUFA) or using the ratio (assuming P/S = PUFA/SFA)
Outcomes	Stated trial outcomes: mortality, reinfarction Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths (including stroke deaths) plus non-fatal MI Secondary outcomes: cancer deaths, total MI, non-fatal MI, CHD mortality, CHD events (total MI) Tertiary outcomes: total and HDL cholesterol
Notes	**Study duration:** 24 months **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. **SFA reduction aimed and achieved.** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.26 (95% CI -0.36 to -0.16), statistically significant reduction** Trial dates: Study dates not reported (published in 1989) 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) 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

DART 1989 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	Quote: "outcome assessors were not aware of study allocation" (Prof Burr, personal communication). Method of blinding not stated
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality
Incomplete outcome data (attrition bias) 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 the 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

Houtsmuller 1979

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Adults with newly-diagnosed diabetes (the Netherlands) CVD risk: moderate Control: 51 randomised, unclear how many analysed (all analysed re deaths) Intervention: 51 randomised, unclear how many analysed (all re deaths) Mean years in trial: unclear (max duration 6 years) % male: 56% overall Age: mean unclear Baseline total fat intake: unclear

Houtsmuller 1979 *(Continued)*

	Baseline saturated fat intake: unclear Ethnicity: not stated Statins use allowed? Unclear % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat vs usual diet Control aims: SFA 35%E, CHO 50%E, protein 15%E Intervention aims: total fat 40%E, 1/3 linoleic acid, CHO 45%E, protein 15%E Control methods: unclear, surveyed by dietitian Intervention methods: unclear, surveyed by dietitian Intervention appears to be delivered by dietitian but no clear details on format or frequency Total fat intake: not reported **Saturated fat intake: not reported (mean difference unclear)** PUFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported MUFA intake: not reported CHO intake: not reported Protein intake: not reported Trans fat intake: not reported **Replacement for saturated fat: mainly PUFA (based on dietary aims)** Style: diet advice? Setting: community
Outcomes	Stated trial outcomes: progression of diabetic retinopathy Data available on total mortality? no Cardiovascular mortality? no Events available for combined cardiovascular events: total MI and angina 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 **SFA reduction aimed (unclear whether achieved).** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.47(95% CI -0.76 to -0.18), statistically significant reduction** Trial dates: Study recruitment 1973 to (unclear) Funding: Dutch Heart Foundation

Houtsmuller 1979 *(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	Participants matched in pairs then randomised
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear, though unlikely as dietary advice provided
Blinding of outcome assessment (detection bias) CVD outcomes	Unclear risk	Blinding of outcome assessors not mentioned
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, 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 the 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	High risk	Some concerns around fraud in the first authors later research on diet in cancer. No allegations found regarding his research in diabetes (but much information is in Dutch). Numbers of events are not clear by arm and assumed from adding across various publications

Ley 2004

Study characteristics

Methods	RCT Summary risk of bias: low
Participants	People with impaired glucose intolerance or high normal blood glucose (New Zealand)

	CVD risk: moderate Control: unclear how many randomised (176 between both groups), unclear how many analysed (112 between both groups at 5 years) Intervention: as above Mean years in trial: 4.1 over whole trial % male: control 80%, intervention 68% Age: mean control 52.0 (SE 0.8), intervention 52.5 (SE 0.8) 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) Statins use allowed? Unclear % taking statins: Not reported
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: reduced fat diet (no specific goal stated) 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 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 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 Intervention delivered in small face-to-face groups but unclear by whom **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 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 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 Trans fat intake: not reported **Replacement for saturated fat: carbohydrate and protein (based on dietary achievements)** Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids, glucose, blood pressure Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: MI, angina, stroke, heart failure Secondary outcomes: total MI, stroke, cancer diagnoses, cancer deaths, CHD events (MI or angina)

Ley 2004 *(Continued)*

	Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs, BP
Notes	**Study duration** over 4 years **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. **SFA reduction achieved** **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** Trial dates: Recruitment 1988 to 1990 Funding: National Heart Foundation of New Zealand, Auckland Medical Research Foundation, Lotteries Medical Board and the Health Research Council of New Zealand 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 (trial author stated in their reply to us that randomisation and preparation of the envelopes was by people not involved in recruitment).
Allocation concealment (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter allocation later.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice, not blinded
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	Trial authors stated that outcome assessors were blinded.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, 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 the 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

Ley 2004 *(Continued)*

Other bias	Low risk	None noted

Moy 2001

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Middle-aged siblings of people with early CHD, with at least 1 CVD risk factor (USA) CVD risk: moderate Control: randomised 132, analysed 118 Intervention: randomised 135, analysed 117 Mean years in trial: 1.9 % male: control 49%, intervention 55% Age: control mean 45.7 (SD 7), intervention 46.2 (SD 7) Ethnicity: African-American 18% int, 25% control (remainder of group ethnicity not described, and outcomes not presented by ethnicity) Statins use allowed? Unclear (raised LDL cholesterol was a condition of entry, so use of statins probably minimal) % taking statins: Not reported
Interventions	Reduced fat intake vs usual diet Control aim: usual care Intervention aim: total fat 40 g/d or less Control methods: usual physician care with risk factor management at 0, 1 and 2 years Intervention methods: Individualised counselling by trained nurse, appointments 6 - 8 weekly for 2 years Intervention delivered individually, face-to-face by a trained nurse. 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 **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** PUFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported MUFA intake: not reported CHO intake: not reported Protein intake: not reported Trans fat intake: not reported **Replacement for saturated fat: unclear** Style: diet advice

Moy 2001 *(Continued)*

	Setting: community
Outcomes	Stated trial outcomes: dietary intake Data available on total mortality? yes, no deaths Cardiovascular mortality? yes, no deaths Events available for combined cardiovascular events: total MI, stroke, unstable angina, PVD and PTCA Secondary outcomes: cancer diagnoses (no events), cancer deaths (none), stroke, total and non-fatal MI, CHD mortality (none), CHD events (MI or angina) Tertiary outcomes: BMI, HDL and LDL cholesterol, TG
Notes	Study duration 2 years **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 saturated fat intake was significantly lower than in the control group **SFA reduction aimed and achieved** **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** Trial dates: Study recruitment 1991 to 1994 Funding: National Institute of Nursing Research, General Clinical Research Center of the National Institutes of Health 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	Randomly assigned via computerised schema after all eligible siblings from a family had been screened
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants clear about their allocation
Blinding of outcome assessment (detection bias) CVD outcomes	High risk	Trialists clear about allocation
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, 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

Moy 2001 *(Continued)*

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

Study characteristics	
Methods	RCT Medical Research Council (MRC) Summary risk of bias: moderate to high
Participants	Free-living men who have survived a first MI (UK) CVD risk: high Control: randomised 194, analysed 181 at 2 years Intervention: randomised 199, analysed 172 at 2 years Mean years in trial: control 3.7, intervention 3.8 % male: 100 Age: unclear (all < 60) Ethnicity: not stated Statins use allowed? Unclear (anti-coagulants allowed, but few other medications appear to have been used) % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat vs usual diet Control aims: usual diet Intervention aims: reduce dietary fat to 35 g fat per day, add 84 g soya oil per day Control methods: usual diet plus reducing diet (reduced CHO) for weight management for overweight men 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 Intervention appears to be delivered and supervised by trial dietitian but unclear how often. 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 **Saturated fat intake: not reported (mean difference unclear)** PUFA intake: not reported PUFA n-3 intake: not reported

MRC 1968 *(Continued)*

	PUFA n-6 intake: not reported MUFA intake: not reported CHO intake: not reported Protein intake: not reported Trans fat intake: not reported **Replacement for saturated fat: mainly PUFA (based on dietary goals)** Style: diet advice & supplement (soy oil) Setting: community
Outcomes	Stated trial outcomes: MI or sudden death Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths and fatal or non-fatal MI Secondary outcomes: total and non-fatal MI, stroke, cancer deaths, CHD mortality, CHD events (CHD mortality or non-fatal MI) Tertiary outcomes: none (data for weight, total cholesterol and BP, but no variance info)
Notes	Study duration over 6 years **Study aim:** for intervention "saturated fats were replaced by polyunsaturated fats", but saturated fat intakes during trial were not reported. **SFA reduction aimed** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.64 (95% CI unclear), reduction > 0.20** For all, data at 4 years, control n = 89, intervention n = 88 Weight change: control -3 kg, intervention 0 kg Total cholesterol change: control -0.47 mmol/L, intervention -1.11 mmol/L Systolic BP change: control 0 mmHg, intervention +2 mmHg Diastolic BP change: control +3 mmHg, intervention -1 mmHg Trial dates: Study recruitment 1960 to 1965, analysed 1967 Funding: Medical Research Council 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	Quote: "using random numbers, by blocks within hospitals"
Allocation concealment (selection bias)	Unclear risk	Not described

MRC 1968 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Big changes to fat intake in intervention group while control group ate their usual diet
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	Quote: "Suspected relapses were assessed at regular intervals by a review committee unaware of the patients diet group".
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) 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 the 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

Study characteristics	
Methods	RCT Oslo Diet-Heart Trial Summary risk of bias: moderate to high for CVD outcomes, low for all-cause mortality
Participants	Men with previous MI (Norway) CVD risk: high Control: randomised 206, analysed 148 (at 5 years) Intervention: randomised 206, analysed 152 (at 5 years) Mean years in trial: control 4.3, intervention 4.3 % male: 100 Age: mean control 56.3, intervention 56.2 (all 30 - 67) Ethnicity: ethnicity not mentioned Statins use allowed? Unclear (medications not mentioned as exclusion criteria, most appeared to be on anti-coagulant medications, statins not mentioned)

	% taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat diet vs control Control aims: no dietary advice but direct questions answered, supplement = 1 vitamin tablet daily 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) Control methods: usual diet Intervention methods: continuous instruction and supervision by dietitian, including home visits, letters and phone calls 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 was not reported here as unlikely to be representative, and lacking control group data) **Saturated fat intake: unclear (mean difference unclear)** PUFA intake: unclear PUFA n-3 intake: not reported PUFA n-6 intake: not reported MUFA intake: unclear CHO intake: unclear Protein intake: unclear Trans fat intake: unclear **Replacement for saturated fat: PUFA (based on dietary goals)** Style: diet advice and supplement (food) Setting: community
Outcomes	Stated trial outcomes: coronary heart disease morbidity and mortality Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: total MI, sudden death, stroke, angina Secondary outcomes: non-fatal and total MI, stroke, CHD mortality (fatal MI and sudden death), CHD events (MI, angina and sudden death) Tertiary outcomes: weight, total cholesterol, systolic and diastolic BP (but no variance information was provided)
Notes	Study duration over 4 years **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 **SFA reduction aimed (reduction unclear as not measured except in a highly compliant subgroup)** **Total serum cholesterol, difference between intervention and control, mmol/L: -1.07 (95% CI unclear), reduction > 0.20** Weight change from baseline was -0.5 kg in the control group (n ~ 155), -2.5 kg in the intervention group (n ~ 160) at 51 months

Oslo Diet-Heart 1966 *(Continued)*

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

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.

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

Trial dates: Recruitment 1956 to 1958

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.

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, so was not affected by participant characteristics and was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of their allocation as was the main trialist.
Blinding of outcome assessment (detection bias) CVD outcomes	Unclear risk	Outcomes were categorised by a diagnostic board, but their blinded status was unclear.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) 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
Free of systematic difference in care?	High risk	Dietetic input level very different, although medical care appeared similar. See control and intervention methods in the 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

Oslo Diet-Heart 1966 *(Continued)*

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

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high for CVD outcomes, low for all-cause mortality
Participants	Newly-diagnosed non-insulin-dependent diabetics (UK) CVD risk: moderate Control: number randomised unclear (249 split between the 2 groups, 125?), number analysed for mortality unclear (all but 2 overall at 16 years) Intervention: number randomised unclear (249 split between the 2 groups, 125?), number analysed as above Mean years in trial: overall 9.3? % male: overall 49% Age: mean overall 47.1 (all < 65) Ethnicity: not stated Statins use allowed? Unclear % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Reduced and modified dietary fat vs average diet Control aims: total fat 40%E, PUFA 12%E, protein 20%E, CHO 40%E (reducing simple sugars), 1500 kcal/day Intervention aims: total fat 26%E, PUFA 16%E, protein 20%E, CHO 54%E (reducing simple sugars), 1500 kcal/day Control methods: dietary advice from diabetes dietitian Intervention methods: dietary advice from diabetes dietitian 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 **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 Carbohydrate intake: not reported Protein intake: not reported

Oxford Retinopathy 1978 *(Continued)*

	Trans fat intake: not reported **Replacement for saturated fat: PUFA and CHO (based on dietary goals and achievements)** Style: diet advice Setting: community (outpatients clinic) §validity of these data is questionable as it represents only 3 intervention and 3 control participants. Source: Lopez-Espinoza 1984
Outcomes	Stated trial outcomes: retinopathy Data available on total mortality? yes, but unable to ascertain from which intervention groups (34 deaths at 10 years) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: BMI, total cholesterol
Notes	Study duration over 9 years **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 **SFA reduction achieved** **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** Trial dates: Recruitment 1973 to 1976 Funding: Oxford Diabetes Trust, British Diabetic Association, International Sugar Research Foundation Inc 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 of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) CVD outcomes	Unclear risk	Unclear whether physicians blinded to allocation
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.

Oxford Retinopathy 1978 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts - 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 the 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

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Men (?) with angina or following MI (UK) CVD risk: high Control: randomised 26, analysed 18 Intervention - corn: randomised 26, analysed 13 Mean years in trial: control 1.7, corn 1.5 % male: unclear (100%?) Age: mean control 58.8, corn 52.6 (all < 70) Ethnicity: not stated Statins use allowed? Unclear (anti-coagulants not allowed, but all participants received conventional treatments at the discretion of their physicians) % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat vs usual diet Control aims: usual diet Intervention aims - corn: restrict dietary fat, plus 80 g/day corn oil provided Control methods: usual physician care plus follow-up clinic monthly, then every 2 months, no dietary fat advice or oil provided Intervention methods: usual physician care plus follow-up clinic monthly, then every 2 months, dietary fat advice plus oil provided Unclear how the advice was delivered or by whom 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

Rose corn oil 1965 *(Continued)*

	Saturated fat intake: unclear (mean difference unclear) PUFA intake: unclear PUFA n-3 intake: not reported PUFA n-6 intake: not reported MUFA intake: unclear 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 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 Trans fat intake: unclear **Replacement for saturated fat: mainly PUFA (based on aims and achievements)** Style: diet advice and supplement (oil) Setting: community
Outcomes	Stated trial outcomes: cardiac events Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke Secondary outcomes: stroke (none), non-fatal and total MI, CHD mortality (fatal MI and sudden death), CHD events (all MI and sudden death) Tertiary outcomes: total cholesterol
Notes	Study duration 2 years **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. **SFA reduction aimed (but unclear whether achieved as SFA intake not reported)** **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** Trial dates: unclear, published in 1965 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) 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	Trial was stated as "randomised" but without further detail, apart from use of a sealed envelope as below.

Rose corn oil 1965 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	When a new participant was accepted for the trial a sealed envelope was opened containing the allocation instructions. In the case of participants allocated to an oil group, the instructions referred only to a code number.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The physicians in charge knew which participants were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving.
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	The electrocardiograms were assessed without the knowledge of the participant's treatment group.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some lost to follow-up by 2 years, 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?	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 the 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

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Men (?) with angina or following MI (UK) CVD risk: high Control: randomised 26, analysed 18 Intervention - olive: randomised 28, analysed 12 Mean years in trial: control 1.7, olive 1.5 % male: unclear (100%?) Age: mean control 58.8, olive 55.0 (all < 70) Ethnicity: Not stated

Rose olive 1965 *(Continued)*

	Statins use allowed? Unclear (anti-coagulants not allowed, but all participants received conventional treatments at the discretion of their physicians) % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat vs usual diet Control aims: usual diet Intervention aims - olive: restrict dietary fat, plus 80 g/day olive oil provided Control methods: usual physician care plus follow-up clinic monthly, then every 2 months, no dietary fat advice or oil provided Intervention methods: usual physician care plus follow-up clinic monthly, then every 2 months, dietary fat advice plus oil provided Unclear how the advice was delivered or by whom 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 **Saturated fat intake: unclear (mean difference unclear)** PUFA intake: unclear PUFA n-3 intake: not reported PUFA n-6 intake: not reported MUFA intake: unclear 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 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 Trans fat intake: unclear **Replacement for saturated fat: mainly MUFA (based on dietary aims)** Style: diet advice and supplement (oil) Setting: community
Outcomes	Stated trial outcomes: cardiac events Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke Secondary outcomes: stroke (none), non-fatal and total MI, CHD mortality (fatal MI and sudden death), CHD events (all MI and sudden death) Tertiary outcomes: total cholesterol
Notes	Study duration 2 years **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 **SFA reduction aimed (but unclear whether achieved as SFA intake not reported)**

Rose olive 1965 *(Continued)*

	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 Trial dates: unclear, published in 1965 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) 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	Trial was stated as "randomised" but without further detail, apart from use of a sealed envelope as below.
Allocation concealment (selection bias)	Unclear risk	When a new participant was accepted for the trial a sealed envelope was opened containing the allocation instructions. In the case of participants allocated to an oil group, the instructions referred only to a code number.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The physicians in charge knew which participants were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving.
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	The electrocardiograms were assessed without the knowledge of the participant's treatment group.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some lost to follow-up by 2 years, 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?	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 the 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

Simon 1997

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Women with a high risk of breast cancer (USA) CVD risk: low Control: randomised 96, analysed 75 Intervention: randomised 98, analysed 72 Mean years in trial: control 1.8, intervention 1.7 % male: 0 Age: mean control 46, intervention 46 Ethnicity: White 89%, African-American 9%, Hispanic 2% Statins use allowed? No (those on lipid-lowering medications were excluded) % taking statins: 0%
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: total fat 15%E 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 Intervention delivered face-to-face by a dietitian 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 **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 CHO intake: not reported Protein intake: not reported Trans fat intake: not reported **Replacement for saturated fat: unclear, either carbohydrate or protein (based on aims and achievements)** Style: diet advice Setting: community §Kasim 1993

Simon 1997 *(Continued)*

Outcomes	Stated trial outcomes: intervention feasibility Data available on total mortality? yes (2 deaths, but not clear in which arms) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: cancer diagnosis (8 diagnoses, but not clear in which arms) Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs
Notes	Study duration 2 years **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 **SFA reduction achieved** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.34 (95% CI -0.64 to -0.04), statistically significant reduction** Trial dates: Recruitment 1987 to 1989 Funding: Marilyn J Smith Fund, Harper-Grace Hospitals, the Wesley Foundation, National Cancer Institute, Karmanos Cancer Institute Core Grant, the United Foundation of Detroit 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
Random sequence generation (selection bias)	Low risk	Randomisation method not clearly described, but participants were stratified by age and randomised (block size 2).
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew their allocation.
Blinding of outcome assessment (detection bias) CVD outcomes	Unclear risk	Unclear whether physicians knew allocations
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts - 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

Simon 1997 *(Continued)*

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 the 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

Study characteristics	
Methods	RCT St Thomas' Atherosclerosis Regression Study (STARS) Summary risk of bias: moderate to high for CVD outcomes, low for all-cause mortality
Participants	Men with angina referred for angiography (UK) CVD risk: high Control: unclear how many randomised (30?), analysed 24 Intervention: unclear how many randomised (30?), analysed 26 Mean years in trial: control 2.9, intervention 3.0 % male: 100% Age: mean control 53.9, intervention 48.9 (all < 66) Ethnicity: not stated Statins use allowed? No (1 arm of the trial, not described here, prescribed cholestyramine) % taking statins: 0%
Interventions	Reduced and modified fat diet vs usual diet Control aims: no diet intervention but advised to lose weight if BMI > 25 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. 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 Initial intervention was delivered individually face-to-face by a dietitian and follow-up by a clinician. 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 **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** 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

STARS 1992 *(Continued)*

	PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 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 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 Trans fat intake: not reported **Replacement for saturated fat: CHO and PUFA (based on aims and achievements)** Style: diet advice Setting: community §Blann 1995
Outcomes	Stated trial outcomes: angiography Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke, CABG, angioplasty, stroke, total MI, CHD events, plus cancer deaths (none) 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 **Study aim** was to reduce saturated fats (to 8 - 10%E), and saturated fat intake in the intervention group was significantly reduced **SFA reduction aimed and achieved** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.76 (95% CI -1.19 to -0.33), statistically significant reduction** Trial dates: Study dates not reported (published in 1992) Funding: Unilever plc, the Chemical Pathology Fund of St Thomas' Hospital, and Bristol-Meyers Ltd 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	"blinded random cards issued centrally by statistician advisor"
Allocation concealment (selection bias)	Low risk	"blinded random cards issued centrally by statistician advisor"
Blinding of participants and personnel (performance bias)	High risk	Participant blinding: inadequate

STARS 1992 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) CVD outcomes	Unclear risk	Physician blinding: unclear
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts - 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 the 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

Study characteristics	
Methods	RCT Sydney Diet-Heart Trial Summary risk of bias: moderate to high
Participants	Men with previous MI (Australia) CVD risk: high Control: randomised 237, analysed 221 at 2 years Intervention: randomised 221, analysed 205 at 2 years Mean years in trial: control 4.3, intervention 4.3 % male: 100 Age: mean control 49.1 (SD 6.5), intervention 48.7 (SD 6.8) Ethnicity: not stated Statins use allowed? Unclear (use of medication did not appear to be an exclusion criteria) % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat diet vs usual diet Control aims: reduction in energy if overweight, no other specific dietary advice, allowed to use PUFA margarine instead of butter Intervention aims: SFA 10%E, PUFA 15%E, reduction in energy if overweight, dietary chol < 300 mg/day

Sydney Diet-Heart 1978 *(Continued)*

	Control methods: no specific dietary instruction (except re weight) Intervention methods: advised and tutored individually, diet assessed 3 times in 1st year and twice annually thereafter Intervention was delivered face-to-face individually but unclear by whom 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 **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 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 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 Trans fat intake: not reported **Primary replacement for saturated fat: mainly PUFA (based on dietary aims and achievements)** Style: diet advice Setting: community
Outcomes	Stated trial outcomes: cardiovascular mortality and morbidity Data available on total mortality? yes Cardiovascular mortality? yes (exact events included not stated) Events available for combined cardiovascular events: none Secondary outcomes: CHD deaths (exact events included not stated) Tertiary outcomes: total cholesterol, TG, BMI, sBP, dBP
Notes	Study duration 7 years **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%) **SFA reduction aimed and achieved** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.30 (95% CI -0.51 to -0.09), statistically significant reduction** Trial dates: Recruitment 1966 to [unclear] and followed for 2 to 7 years Funding: Life Insurance Medical Research Fund of Australia and New Zealand 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	Quote: "table of random numbers ... generated by a research assistant and was concealed until after medical evaluations and testing at baseline were completed".
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	Initially masked to group assignment (though success of blinding not checked)
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) 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 the 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

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Men living at the Veterans Administration Center (USA) CVD risk: low Control: randomised 422, analysed 422 Intervention: randomised 424, analysed 424 Mean years in trial: control 3.7, intervention 3.7 % male: 100 Age: mean control 65.6, intervention 65.4 (all 54 - 88)

Veterans Admin 1969 *(Continued)*

	Ethnicity: White 90%, African-American 7%, Asian 1%, Mexican 1%, other 1% Statins use allowed? Unclear (only 4 participants were taking nicotinic acid, 17 diuretics, 56 digitalis, none on heparin) % taking statins: Not reported (probably none as too early, pre-1980)
Interventions	Modified fat vs usual diet Control aims: provided, total fat 40%E Intervention aims: total fat 40%E, ⅔ of SFA replaced by unsaturated fats, dietary chol reduced Control methods: whole diet provided Intervention methods: whole diet provided 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 **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 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 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 Trans fat intake: not reported **Replacement for saturated fat: mainly PUFA (based on dietary aims and achievements)** Style: diet provided Setting: residential institution §Dayton 1965 ⁑Estimated by subtraction (assuming total fat = SFA + PUFA + MUFA or energy intake = energy from fat + CHO + protein)
Outcomes	Stated trial outcomes: mortality, heart disease Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: sudden death, definite MI, definite stroke, angina, PVD events 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) Tertiary outcomes: none (some data on total cholesterol, but no variance info)
Notes	Study duration over 8 years

Veterans Admin 1969 *(Continued)*

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

SFA reduction aimed and achieved

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

Trial dates: Recruitment 1959 to 1967

Funding: Veterans Administration, Arthur 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.

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	Quote: "table of random numbers used"
Allocation concealment (selection bias)	Low risk	Extensive baseline assessment before randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Institution provided diet in a masked fashion.
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	Physician knowledge of allocation was assessed and found similar to random.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding is not relevant in assessment of mortality.
Incomplete outcome data (attrition bias) 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 the 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 2006

Study characteristics	
Methods	RCT Women's Health Initiative (WHI) Summary risk of bias: low
Participants	Postmenopausal women aged 50 - 79 with or without CVD at baseline (USA) CVD risk: low in those without CVD at baseline, high in those with CVD Control without CVD at baseline: randomised 29,294, analysed 29,294 Intervention without CVD at baseline: randomised 19,541, analysed 19,541 Control with CVD at baseline: randomised 1369, analysed 1369 Intervention with CVD at baseline: randomised 908, analysed 908 Mean years in trial: control 8.1, intervention 8.1 % male: 0 Age: mean (both with and without CVD at baseline) int 62.3 (SD 6.9), control 62.3 (SD 6.9) 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. Statins use allowed? Yes % 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 Control: diet-related education materials Intervention: low-fat diet (20%E from fat), reduce saturated fat to 7%E with increased fruit and vegetables Control methods: given copy of 'Dietary Guidelines for Americans' Intervention methods: 18 group sessions with trained and certified nutritionists in the 1st year, quarterly maintenance sessions thereafter, focusing on diet and behaviour modification Intervention delivered face-to-face in a group by nutritionists Intake data all relate to the full WHI cohort (not divided by whether participants have CVD at baseline or not) 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 **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** 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 PUFA n-3 intake: not reported PUFA n-6 intake: not reported 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 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

WHI 2006 *(Continued)*

	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 Trans fat intake, %E (at 6 years)§: int 1.8 (SD?), cont 2.4 (SD?) (mean difference unclear, no SDs assumed) **Replacement for saturated fat: mainly carbohydrate, some protein (based on dietary achievement)** Style: dietary advice Setting: community §Amongst the 881 intervention and 1373 control participants with blood samples at baseline, with or without CVD at baseline (Howard 2010)
Outcomes	Stated trial outcomes: breast cancer, mortality, other cancers, cardiovascular events, diabetes Data available on total mortality? yes* Cardiovascular mortality? yes Events available for combined cardiovascular events: CHD, stroke, heart failure, angina, peripheral vascular disease, revascularisation, pulmonary embolism, DVT Secondary outcomes: cancer deaths*, cancer diagnoses*, stroke, non-fatal MI, diabetes diagnosis* Tertiary outcomes: weight, BMI, total, LDL and HDL cholesterol, TGs, systolic and diastolic BP (Lp(a) and HOMA reported as geometric means) * these are only available for the whole cohort, not split between low and high CVD risk groups
Notes	Study duration over 8 years **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 **SFA reduction aimed and achieved** **Total serum cholesterol, difference between intervention and control, mmol/L: -0.09 (95% CI -0.15 to -0.02), statistically significant reduction** Trial dates: Recruitment was between 1993 and 1998 Funding: National Heart, Lung and Blood Institute of the National Institutes of Health Declarations of Interest of primary researchers: Declarations varied 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 generated permuted block algorithm stratified by clinical centre and age
Allocation concealment (selection bias)	Low risk	Allocations developed by the WHI Clinical Coordinating Center

WHI 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants aware of allocation
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	Trained clinic staff, who were responsible for anthropometric assessments and administration of FFQs, were blinded to treatment assignments to the extent practical. The dietary intervention staff did not conduct clinical assessments, and clinic staff were not permitted to participate in any intervention activities; participants were instructed not to discuss nutrition activities with clinic staff.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Blinding not relevant for mortality assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Trials register 1999, study completion 2005, but outcomes not stated in trials register. However, outcomes were well published; 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 the 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

WINS 2006

Study characteristics	
Methods	RCT Women's Intervention Nutrition Study (WINS) Summary risk of bias: low
Participants	Women with localised resected breast cancer (USA) CVD risk: low Control: 1462 randomised, 1462 analysed Intervention: 975 randomised, 975 analysed Mean years in trial: overall 5.0 % men: 0 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)

WINS 2006 *(Continued)*

	Ethnicity: 85% white, 5% black, 4% Hispanic, 5% Asian or Pacific Islander, < 1% American Indian or unknown (no outcome data based on ethnicity) Statins use allowed? Not stated (statins not mentioned in inclusion or exclusion criteria within trial protocol) % taking statins: Not reported
Interventions	Reduced fat intake vs usual diet Control aims: minimal nutritional counselling focused on nutritional adequacy Intervention aims: total fat 15 - 20%E Control methods: 1 baseline dietetic session plus 3-monthly sessions 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 Intervention was delivered face-to-face individually by trained dietitian 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 intake, %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 **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** 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 PUFA n-3 intake: not reported by study arm PUFA n-6 intake: not reported by study arm 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 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 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 Trans fat intake: not reported **Replacement for saturated fat: CHO and protein (based on dietary achievement)** Style: dietary advice Setting: community *SDs appear incorrect, probably SEs?
Outcomes	Stated trial outcomes: dietary fat intake, total cholesterol, weight and waist measurement Data available on total mortality? yes Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: cancer diagnoses Tertiary outcomes: weight, BMI, total cholesterol

WINS 2006 *(Continued)*

Notes	Study duration 5 years **Study aim** was to reduce total fat to 15 - 20%E **SFA reduction achieved** **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** Trial dates: Recruitment 1994 to 2001 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 coordinating centre of WINS
Allocation concealment (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical coordinating centre of WINS
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not for dietary advice and participants
Blinding of outcome assessment (detection bias) CVD outcomes	Low risk	All outcomes assessed by the blinded outcome committee
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) 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 the 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
BMI: body mass index (weight in kg/ height in m, squared)
BP: blood pressure
CABG: coronary artery bypass graft
CHD: coronary heart disease
CHO: carbohydrate
chol: cholesterol
CI: confidence interval
cont: control group
CVD: cardiovascular disease
DART: Diet And Reinfarction Trial
dBP: diastolic blood pressure
DVT: deep vein thrombosis
EPA: eicosapentaenoic acid
GPs: general practitioners
HDL: high density lipoprotein
HOMA: homeostatic model assessment
int: intervention group
ITT: Intention to treat analysis
LDL: low density lipoprotein
Lp(a): lipoprotein (a)
MI: myocardial infarction
MRC: Medical Research Council
MUFA: monounsaturated fat
P/S: polyunsaturated/saturated fat ratio
PCTA: percutaneous transluminal coronary angioplasty
PUFA: polyunsaturated fat
PVD: peripheral vascular disease
RCT: randomised controlled trial
sBP: systolic blood pressure
SD: standard deviation
SE: standard error
SFA: saturated fats
STARS: St Thomas' Atherosclerosis Regression Study
TC: total cholesterol
TG: triglyceride
vs: versus
WHI: Women's Health Initiative
WINS: Women's Intervention Nutrition Study

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)

Study	Reason for exclusion
Aro 1990	Intervention and randomised follow-up less than 6 months
ASSIST 2001	Intervention was 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 stated 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
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 was 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
BREACPNT	Individual microbiome-based dietary advice vs Mediterranean diet (no suggestion of saturated fat reduction in either arm)

Study	Reason for exclusion
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 was 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
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 substudy 2002	Follow-up less than 24 months
Casas-Agustench 2013	Less than 24 months duration
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 was 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

Study	Reason for exclusion
Cox 1996	Multifactorial intervention
Croft 1986	Intervention was not dietary fat modification or low fat diet.
Curzio 1989	Follow-up less than 24 months
Da Qing IGT 1997	Intervention was not dietary fat modification or low-fat diet.
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 was 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 was 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
DIPI 2018	Less than 24 months duration
DIRECT 2009	Unable to establish contact with authors to establish whether relevant events occurred; multiple publications checked and no relevant outcomes found
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

Study	Reason for exclusion
Duffield 1982	Multifactorial intervention
Dullaart 1992	Study authors confirmed that no deaths or cardiovascular events occurred during the study.
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 was 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
Gaullier 2007	No appropriate control group (and not low fat vs modified fat)
Ginsberg 1988	Intervention and randomised follow-up less than 6 months

Study	Reason for exclusion
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 was 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
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

Study	Reason for exclusion
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 was 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)
King 2000	Intervention and randomised follow-up less than 6 months
Kingsbury 1961	Intervention and randomised follow-up less than 6 months
KNOTA	Numerous publications checked, but no relevant outcome data found. Trialists not contacted.
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

Study	Reason for exclusion
Kromhout 1987	No appropriate control group (and not low fat vs modified fat)
Kummel 2008	Intervention was 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 was not dietary fat modification or low-fat diet.
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 was 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 was 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 was not dietary fat modification or low-fat diet.

Study	Reason for exclusion
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
MEDINA	Less than 24 months duration
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
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 was 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
Mottalib 2018	Less than 24 months duration
MRFIT substudy 1986	Intervention and randomised follow-up less than 6 months
MSDELTA 1995	Intervention and randomised follow-up less than 6 months

Study	Reason for exclusion
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)
NCT01954472	Study withdrawn (not completed)
NCT03068078	Less than 24 months duration
Neil 1995	No appropriate control group (and not low fat vs modified fat)
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)
Nutri-AGEs 2015	Less than 24 months duration
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 was 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)

Study	Reason for exclusion
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 nonspecific (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.
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

Study	Reason for exclusion
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
SLIM 2008	Multifactorial intervention
Sopotsinskaia 1992	The study aimed for weight loss in 1 arm and not in the comparison arm.
Soul Food Light	Less than 24 months duration
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 was not dietary fat modification or low fat diet.
Søndergaard 2003	Follow-up less than 24 months
TAIM 1992	Intervention was 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 was 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

Study	Reason for exclusion
Troyer 2010	Longest duration only 12 months
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
VASTKOST 2012	Publications reported than no participants died or experienced CVD during the trial.
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
WAHA 2016	15%E from walnuts vs usual diet (neither arm aimed to reduce saturated fat intake)
Wass 1981	Intervention and randomised follow-up less than 6 months
Wassertheil 1985	Intervention was 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 was 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 was not dietary fat modification or low-fat diet.
Williams 1992	Intervention was not dietary fat modification or low-fat diet.
Williams 1994	Intervention was 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)
WINS UK 2011	Stated aim was to reduce total fat by 50%; no saturated fat aims

Study	Reason for exclusion
WOMAN 2007	Lifestyle intervention included exercise and weight as well as diet.
Wood 1988	Intervention was 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

CHO: carbohydrate
CV: cardiovascular
E: energy
vs: versus

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

ICFAMED

Methods	A Mediterranean diet for preventing heart failure and atrial fibrillation in hypertensive patients (ICFAMED) RCT, 24 months
Participants	People with hypertension aged 55 to 75 years at high cardiovascular risk, but without existing CVD
Interventions	MedDiet: Mediterranean-style diet, dietary advice (individual and group) every three months LFD: Low-fat diet according to American Heart Association guidelines, dietary advice (individual and group) every three months
Outcomes	Primary: heart failure and/or atrial fibrillation Secondary: echocardiographic variables & BP variables Actual outcomes from abstracts: MedDiet: 5 CVD events (atrial fibrillation (AF) 2; ischaemic heart disease (IHD) 2; stroke 1), LFD: 11 CVD events (AF 6, IHD 2, stroke 3). The crude rate for the occurrence of events per 1000 patient-months of follow-up was 197 (95% CI: 06–46) for MedDiet, 451 (95% CI: 3–8.1) for LFD. The HR for patients with MedDiet compared to LFD was 044 (95% CI: 015–126, P > 005).
Notes	Trials registration: ISRCTN27497769 Enrollment began in 2012; appears to have completed in 2017; abstract and poster publications only to date Awaiting assessment because: Unclear whether one arm was higher in saturated fat than the other, awaiting fuller publication to assess

AF: atrial fibrillation
CVD: cardiovascular disease
HR: hazard ratio
ICFAMED: A Mediterranean diet for preventing heart failure and atrial fibrillation in hypertensive patients
IHD: Ischaemic heart disease
LFD: low fat diet
MedDiet: Mediterranean style diet
RCT: randomised controlled trial

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

ENAbLE due unclear

Study name	ENAbLE
Methods	RCT, 2 x 2 diet and physical activity interventions, duration unclear
Participants	Stroke survivors able to walk independently
Interventions	AusMed diet, adaptation of the Mediterranean diet to the Australian context, including provision of starter foods, menu plans and regular counselling Comparator unclear Telehealth-delivered physical activity and diet interventions in both arms
Outcomes	Primary: sBP Secondary: lipid profiles and glycaemic control
Starting date	Mid 2019, planned completion date unclear
Contact information	Coralie English, University of Western Australia (first author of abstract)
Notes	Trial registration not found Unclear whether the intervention was truly lower vs higher saturated fat as saturated fat goals not provided, and duration unclear

NCT02481466 due 2020

Study name	Combined Portfolio diet and Exercise study (PortfolioEx)
Methods	RCT, 2 x 2 factorial design with exercise intervention, 36 months
Participants	Men and postmenopausal women with BMI up to 40 kg/m^2 with measurable arterial thickening
Interventions	Lower saturated fat: advice on a therapeutic diet appropriate for hypercholesterolemia (ie < 7% of energy from saturated fat, < 200 mg/d cholesterol) PLUS the combination of viscous fibres, soy protein, plant sterols and nuts, 5% extra monounsaturated fat, and selection of low glycemic index foods Higher saturated fat: advice to follow a DASH-like diet of whole grains, and low-fat dairy products with fruits and vegetables Both arms with or without instruction on the Laval exercise program — a standardised physical activity/exercise component supervised by trained kinesiologists (exercise physiologists)
Outcomes	Primary: maximum vessel wall volume of the carotid arteries Secondary: composite end point of myocardial infarction, revascularization, cardiovascular hospitalisation, cardiovascular mortality and stroke; atrial fibrillation; BP; and vessel outcomes
Starting date	Nov 2016, planned completion Dec 2022

NCT02481466 due 2020 *(Continued)*

Contact information	PI: David J Jenkins, MD, NutritionProject@smh.ca, Risk Factor Modification Centre, St. Michael's Hospital
Notes	Trials registration: NCT02481466 Unclear whether the intervention was truly lower vs higher saturated fat as saturated fat goals not provided for both arms

NCT02938832 due 2023

Study name	Does the advice to eat a mediterranean diet with low carbohydrate intake, compared with a low-fat diet, reduce diabetes and cardiovascular disease (CardioDiet)
Methods	RCT, 36 months
Participants	Adults with ischaemic heart disease followed up at cardiac rehabilitation units
Interventions	Mediterranean diet with an energy content (E%) from carbohydrates between 25-30% Traditional low-fat diet with 45-60 E% from carbohydrates
Outcomes	Primary: diabetes incidence Secondary: CVD disease, quality of life
Starting date	Oct 2016, planned completion Oct 2023
Contact information	PI: Fredrik H Nystrom, Professor, MD, University Hospital, Linkoeping, fredrik.nystrom@regionostergotland.se
Notes	Trials registration NCT02938832 Unclear whether the intervention was truly lower vs higher saturated fat as saturated fat goals not provided.

NEW Soul Study due 2022

Study name	Nutritious Eating With Soul (NEW Soul) study
Methods	RCT, 24 months
Participants	African-American adults aged 18-65 years with BMI 25- 49.9 kg/m^2
Interventions	Lower saturated fat: plant-based vegan diet, instructing participants to favour a diet built around whole grains, fruits, vegetables, and legumes, supplemented by the Oldways African Heritage and Health programme, which includes a food pyramid guide. A Taste of African Heritage (ATAH) six-lesson nutrition and cooking programme has an online course for health professionals and cooking instructors (all research and restaurant team members will complete this course). Interventions include intervention meetings, physical activity, and podcasts/mailings. Higher saturated fat: low-fat omnivorous diet, supplemented by the Oldways African Heritage and Health programme, which includes a food pyramid guide. A Taste of African Heritage (ATAH) six-lesson nutrition and cooking programme has an online course for health professionals and cooking

NEW Soul Study due 2022 *(Continued)*

	instructors (all research and restaurant team members will complete this course). Interventions include intervention meetings, physical activity, and podcasts/mailings.
Outcomes	Primary: CVD events Secondary: CVD risk factors (including LDL & BP), body weight
Starting date	May 2018, planned completion June 2022
Contact information	PI: Brie Turner-McGrievy, Associate Professor, University of South Carolina Trial website: https://newsoul.org/
Notes	Trials registration NCT03354377 Unclear whether the intervention was truly lower vs higher saturated fat as saturated fat goals not provided

ATAH: A Taste of African Heritage
AusMed: Australian style Mediterranean diet
BMI: body mass index
BP: blood pressure
CVD: cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
E: energy
LDL: low density lipoprotein
PorffolioEx: Combined Portfolio diet and Exercise study
RCT: randomised controlled trial
sBP: systolic blood pressure

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
1.1 ALL-CAUSE MORTALITY	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.2 All-cause mortality, SA low summary risk of bias	7	53219	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.08]
1.3 All-cause mortality, SA aim to reduce SFA	9	53112	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
1.4 All-cause mortality, SA statistically significant SFA reduction	8	54973	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
1.5 All-cause mortality, SA TC reduction	8	53073	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.07]
1.6 All-cause mortality, SA excluding WHI	11	7023	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 All-cause mortality, SA Mantel-Haenszel fixed-effect	12	55858	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.03]
1.8 All-cause mortality, SA Peto fixed-effect	12	55858	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.90, 1.04]
1.9 All-cause mortality, subgroup by any substitution	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 replaced by PUFA	7	4238	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.13]
1.9.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.99]
1.9.3 replaced by CHO	6	53669	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
1.9.4 replaced by protein	5	53614	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
1.9.5 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.10 All-cause mortality, subgroup by main substitution	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 replaced by PUFA	6	4183	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.14]
1.10.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.99]
1.10.3 replaced by CHO	5	51636	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
1.10.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.10.5 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.11 All-cause mortality, subgroup by duration	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.11.1 up to 24mo	4	2246	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.26]
1.11.2 >24 to 48mo	3	1294	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.12]
1.11.3 >48mo	4	52142	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.16]
1.11.4 unclear duration	1	176	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.61]
1.12 All-cause mortality, subgroup by baseline SFA	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.12.1 up to 12%E SFA baseline	1	2437	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.67, 1.21]
1.12.2 >12 to 15%E SFA baseline	5	51635	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.86, 1.19]
1.12.3 >15 to 18%E SFA baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.12]
1.12.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.83, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12.5 unclear	4	885	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.04]
1.13 All-cause mortality, subgroup by SFA change	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.13.1 up to 4%E difference	5	53939	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.13]
1.13.2 >4 to 8%E difference	2	188	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.07]
1.13.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.83, 1.15]
1.13.4 unclear	4	885	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.04]
1.14 All-cause mortality, subgroup by sex	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.14.1 Men	9	4410	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.11]
1.14.2 Women	2	51272	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
1.14.3 Mixed, men and women	1	176	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.61]
1.15 All-cause mortality, subgroup by CVD risk	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.15.1 Low CVD risk	4	52251	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.04]
1.15.2 Moderate CVD risk	1	176	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.61]
1.15.3 Existing CVD disease	7	3431	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.24]
1.16 All-cause mortality, subgroup by TC reduction	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.16.1 serum chol reduced by at least 0.2mmol/L	7	4238	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.14]
1.16.2 serum chol reduced by <0.2mmol/L	4	51487	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
1.16.3 serum chol reduction unclear	1	133	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.46]
1.17 All-cause mortality, subgroup decade of publication	12	55858	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]
1.17.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.07]
1.17.2 1970s	1	458	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.95, 2.34]
1.17.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.25]
1.17.4 1990s	2	188	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.07]
1.17.5 2000s	3	51448	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.05]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.18 CARDIOVASCULAR MORTALITY	11	53421	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.13]
1.19 CVD mortality, SA low summary risk of bias	4	50315	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.67, 1.38]
1.20 CVD mortality, SA aim to reduce SFA	9	53112	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.14]
1.21 CVD mortality, SA statistically significant SFA reduction	7	52536	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.21]
1.22 CVD mortality, SA TC reduction	8	53073	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.15]
1.23 CVD mortality, SA excluding WHI	10	4586	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.18]
1.24 CVD mortality, SA Mantel-Haenszel fixed-effect	11	53421	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
1.25 CVD mortality, SA Peto fixed-effect	11	53421	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.84, 1.08]
1.26 CVD mortality, subgroup by any substitution	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.26.1 replaced by PUFA	7	4251	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.25]
1.26.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.99]
1.26.3 replace by CHO	5	51232	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.14]
1.26.4 replaced by protein	4	51177	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
1.26.5 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.27 CVD mortality, subgroup by main substitution	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.27.1 replaced by PUFA	6	4196	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.28]
1.27.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.99]
1.27.3 replace by CHO	4	49199	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.42, 1.46]
1.27.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.27.5 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.28 CVD mortality, subgroup by duration	11	53447	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
1.28.1 up to 24mo	4	2272	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.54, 2.94]
1.28.2 >24 to 48mo	3	1294	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.08]
1.28.3 >48 mo	3	49705	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.73, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.28.4 unclear duration	1	176	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.19]
1.29 CVD mortality, subgroup by baseline SFA	11	53447	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
1.29.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.29.2 >12 to 15%E SFA baseline	5	51635	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.84, 1.32]
1.29.3 >15 to 18%E SFA baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.12]
1.29.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.96]
1.29.5 unclear	4	911	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.61, 1.66]
1.30 CVD mortality, subgroup by SFA change	11	53447	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
1.30.1 up to 4%E difference	4	51502	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.85, 1.33]
1.30.2 >4 to 8%E difference	2	188	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.05, 1.70]
1.30.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.96]
1.30.4 unclear	4	911	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.61, 1.66]
1.31 CVD mortality, subgroup by sex	11	53447	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
1.31.1 Men	9	4436	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.73, 1.25]
1.31.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.84, 1.19]
1.31.3 Mixed, men and women	1	176	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.19]
1.32 CVD mortality, subgroup by CVD risk	11	53447	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.80, 1.14]
1.32.1 Low CVD risk	3	47537	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.60, 1.16]
1.32.2 Moderate CVD risk	1	176	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.19]
1.32.3 Existing CVD disease	8	5734	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.83, 1.31]
1.33 CVD mortality, subgroup by TC reduction	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.33.1 serum chol reduced by at least 0.2mmol/L	7	4251	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.25]
1.33.2 serum chol reduced by <0.2mmol/L	3	49063	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.47, 2.01]
1.33.3 serum chol reduction unclear	1	133	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.15]

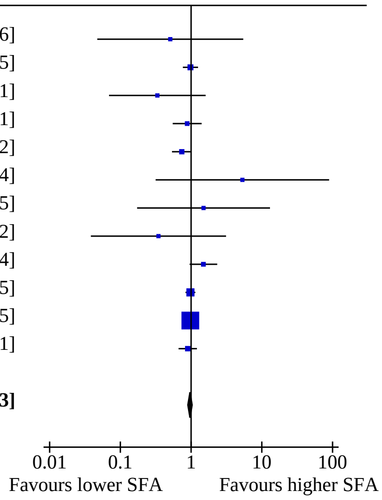
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.34 CVD mortality, subgroup decade of publication	11	53421	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.13]
1.34.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
1.34.2 1970s	1	458	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.99, 2.55]
1.34.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.77, 1.31]
1.34.4 1990s	2	188	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.05, 1.70]
1.34.5 2000s	2	49011	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.27, 2.21]
1.35 COMBINED CARDIOVASCULAR EVENTS	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.36 CVD events, SA low summary risk of bias	4	50315	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.76, 1.20]
1.37 CVD events, SA aim to reduce SFA	11	53449	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.00]
1.38 CVD events, SA statistically significant SFA reduction	8	52771	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.08]
1.39 CVD events, SA TC reduction	10	53410	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 1.00]
1.40 CVD events, SA excluding WHI	12	4923	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.64, 0.98]
1.41 CVD events, SA Mantel-Haenszel fixed-effect	13	53758	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 0.99]
1.42 CVD events, SA Peto fixed-effect	13	53758	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.88, 0.99]
1.43 CVD events, SA excluding trials with additional interventions	10	4456	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.09]
1.44 CVD events, subgroup by any substitution	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.44.1 replaced by PUFA	8	4353	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.62, 1.00]
1.44.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.53, 1.89]
1.44.3 replace by CHO	5	51232	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.06]
1.44.4 replaced by protein	4	51177	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.03]
1.44.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.41, 6.87]
1.45 CVD events, subgroup by main substitution	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.45.1 replaced by PUFA	7	4298	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.06]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.45.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.53, 1.89]
1.45.3 replace by CHO	4	49199	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.39, 1.16]
1.45.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.45.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.41, 6.87]
1.46 CVD events, subgroup by duration	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.46.1 up to 24mo	5	2481	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.16]
1.46.2 >24 to 48mo	3	1294	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.56, 0.95]
1.46.3 >48mo	3	49705	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.72, 1.33]
1.46.4 unclear duration	2	278	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.08]
1.47 CVD events, subgroup by baseline SFA	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.47.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.47.2 >12 to 15%E SFA baseline	6	51870	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.15]
1.47.3 >15 to 18%E SFA baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.22, 0.78]
1.47.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 1.00]
1.47.5 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.51, 1.03]
1.48 CVD events, subgroup by SFA change	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.48.1 up to 4%E difference	5	51737	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.16]
1.48.2 >4 to 8%E difference	2	188	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.22, 0.74]
1.48.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 1.00]
1.48.4 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.51, 1.03]
1.49 CVD events, subgroup by sex	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.49.1 Men	9	4410	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.03]
1.49.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
1.49.3 Mixed, men and women	3	513	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.49]
1.50 CVD events, subgroup by CVD risk	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.00]
1.50.1 Low CVD risk	3	47537	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.06]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.50.2 Moderate CVD risk	3	513	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.49]
1.50.3 Existing CVD disease	8	5708	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.12]
1.51 CVD events, subgroup by TC reduc-tion	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.51.1 serum chol reduced by at least 0.2mmol/L	9	4575	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 1.00]
1.51.2 serum chol reduced by <0.2mmol/L	3	49050	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.04]
1.51.3 serum chol reduction unclear	1	133	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.15]
1.52 CVD events, subgroup decade of publication	13	53758	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.52.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.69, 0.91]
1.52.2 1970s	2	560	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.12, 3.80]
1.52.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.15]
1.52.4 1990s	2	188	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.22, 0.74]
1.52.5 2000s	3	49246	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.04]

Analysis 1.1. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 1: ALL-CAUSE MORTALITY

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	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	7.6%	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	2.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	4.6%	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	2.3%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			

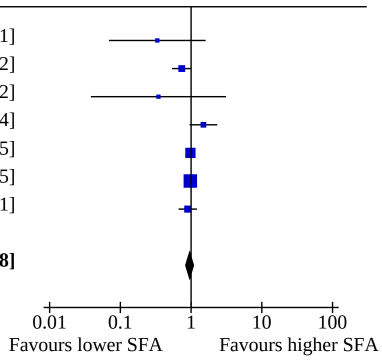


Heterogeneity: Tau² = 0.00; Chi² = 11.25, df = 11 (P = 0.42); I² = 2%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

Footnotes
(1) All-cause death during study, Prentice 2017
(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.2. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 2: All-cause mortality, SA low summary risk of bias

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	2	88	6	88	0.6%	0.33 [0.07 , 1.61]
Oslo Diet-Heart 1966	48	206	65	206	11.5%	0.74 [0.54 , 1.02]
STARS 1992	1	27	3	28	0.3%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	6.6%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	27.0%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	41.3%	0.98 [0.90 , 1.05]
WINS 2006	64	975	107	1462	12.7%	0.90 [0.67 , 1.21]
Total (95% CI)		**21482**		**31737**	**100.0%**	**0.95 [0.84 , 1.08]**
Total events:	1317		1906			



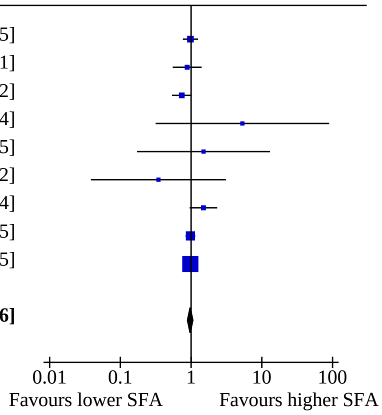
Heterogeneity: Tau² = 0.01; Chi² = 9.25, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable

Footnotes
(1) All-cause death during study, Prentice 2017

Analysis 1.3. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 3: All-cause mortality, SA aim to reduce SFA

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	111	1018	113	1015	10.8%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	3.2%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	6.8%	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	0.2%	1.50 [0.17 , 13.05]
STARS 1992	1	27	3	28	0.2%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	3.5%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	22.2%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	53.1%	0.98 [0.90 , 1.05]
Total (95% CI)		**21690**		**31422**	**100.0%**	**0.97 [0.89 , 1.06]**
Total events:	1398		1938			

Heterogeneity: Tau² = 0.00; Chi² = 8.94, df = 8 (P = 0.35); I² = 11%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

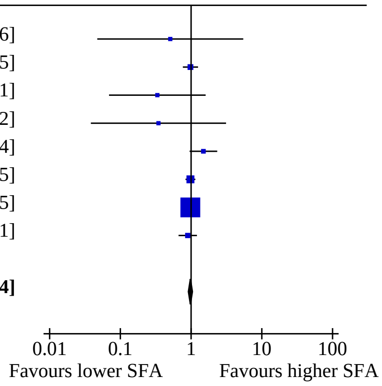


Footnotes
(1) All-cause death during study, Prentice 2017

Analysis 1.4. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 4: All-cause mortality, SA statistically significant SFA reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	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	6.9%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	2.1%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	16.5%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	69.4%	0.98 [0.90 , 1.05]
WINS 2006	64	975	107	1462	4.7%	0.90 [0.67 , 1.21]
Total (95% CI)		**22360**		**32613**	**100.0%**	**0.98 [0.92 , 1.04]**
Total events:	1381		1956			

Heterogeneity: Tau² = 0.00; Chi² = 6.69, df = 7 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

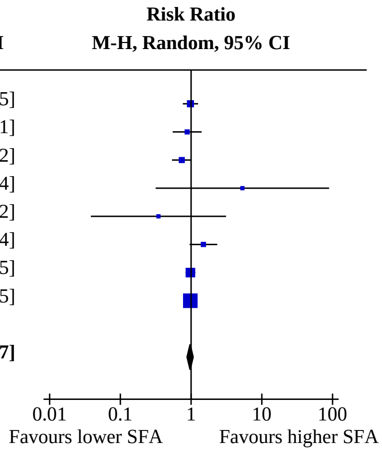


Footnotes
(1) All-cause death during study, Prentice 2017

Analysis 1.5. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 5: All-cause mortality, SA TC reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	111	1018	113	1015	12.8%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	4.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	8.3%	0.74 [0.54 , 1.02]
Rose corn oil 1965	5	28	0	13	0.1%	5.31 [0.32 , 89.44]
STARS 1992	1	27	3	28	0.2%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	4.5%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	23.9%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	46.0%	0.98 [0.90 , 1.05]
Total (95% CI)		**21664**		**31409**	**100.0%**	**0.97 [0.88 , 1.07]**
Total events:	1395		1937			

Heterogeneity: Tau² = 0.00; Chi² = 8.79, df = 7 (P = 0.27); I² = 20%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

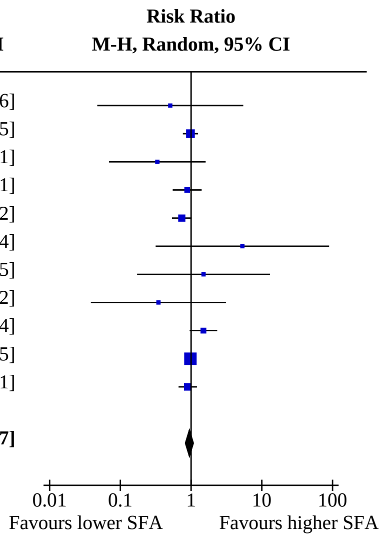


Footnotes
(1) All-cause death during study, Prentice 2017

Analysis 1.6. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 6: All-cause mortality, SA excluding WHI

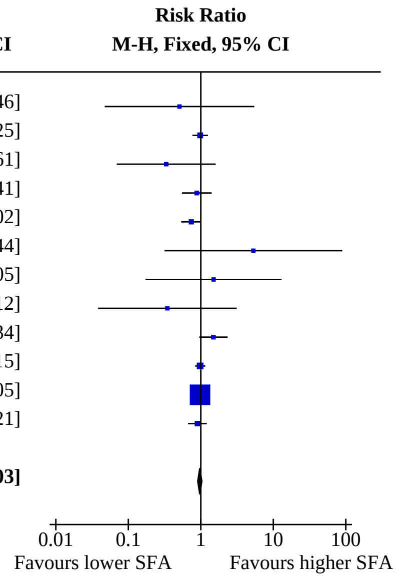
Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	1	66	2	67	0.3%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	20.0%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.6%	0.33 [0.07 , 1.61]
MRC 1968	28	199	31	194	6.6%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	13.2%	0.74 [0.54 , 1.02]
Rose corn oil 1965	5	28	0	13	0.2%	5.31 [0.32 , 89.44]
Rose olive 1965	3	26	1	13	0.3%	1.50 [0.17 , 13.05]
STARS 1992	1	27	3	28	0.3%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	7.2%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	36.6%	0.98 [0.83 , 1.15]
WINS 2006	64	975	107	1462	14.7%	0.90 [0.67 , 1.21]
Total (95% CI)		**3278**		**3745**	**100.0%**	**0.95 [0.83 , 1.07]**
Total events:	476		533			

Heterogeneity: Tau² = 0.00; Chi² = 11.10, df = 10 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 7: All-cause mortality, SA Mantel-Haenszel fixed-effect

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	6.5%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.3%	0.33 [0.07 , 1.61]
MRC 1968	28	199	31	194	1.8%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	3.8%	0.74 [0.54 , 1.02]
Rose corn oil 1965	5	28	0	13	0.0%	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	0.2%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	1.6%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	10.3%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	70.4%	0.98 [0.90 , 1.05]
WINS 2006	64	975	107	1462	5.0%	0.90 [0.67 , 1.21]
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.97 [0.91 , 1.03]**
Total events:	1465		2053			

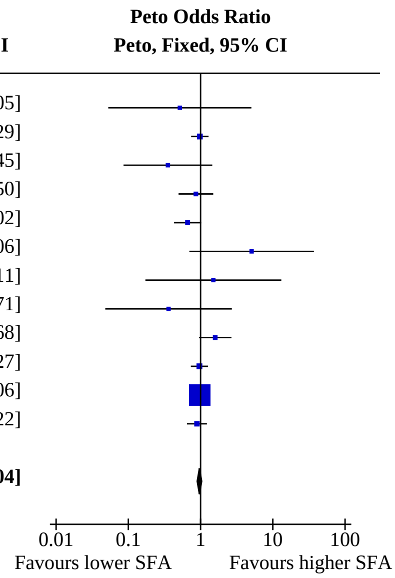


Heterogeneity: Chi² = 11.25, df = 11 (P = 0.42); I² = 2%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

Footnotes
(1) All-cause death during study, Prentice 2017

Analysis 1.8. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 8: All-cause mortality, SA Peto fixed-effect

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Black 1994	1	66	2	67	0.1%	0.52 [0.05 , 5.05]
DART 1989	111	1018	113	1015	6.5%	0.98 [0.74 , 1.29]
Ley 2004	2	88	6	88	0.3%	0.35 [0.09 , 1.45]
MRC 1968	28	199	31	194	1.6%	0.86 [0.50 , 1.50]
Oslo Diet-Heart 1966	48	206	65	206	2.7%	0.66 [0.43 , 1.02]
Rose corn oil 1965	5	28	0	13	0.1%	5.09 [0.70 , 37.06]
Rose olive 1965	3	26	1	13	0.1%	1.50 [0.17 , 13.11]
STARS 1992	1	27	3	28	0.1%	0.36 [0.05 , 2.71]
Sydney Diet-Heart 1978	39	221	28	237	1.9%	1.59 [0.95 , 2.68]
Veterans Admin 1969	174	424	177	422	6.7%	0.96 [0.73 , 1.27]
WHI 2006 (1)	989	19541	1520	29294	74.8%	0.97 [0.90 , 1.06]
WINS 2006	64	975	107	1462	5.0%	0.89 [0.65 , 1.22]
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.04]**
Total events:	1465		2053			



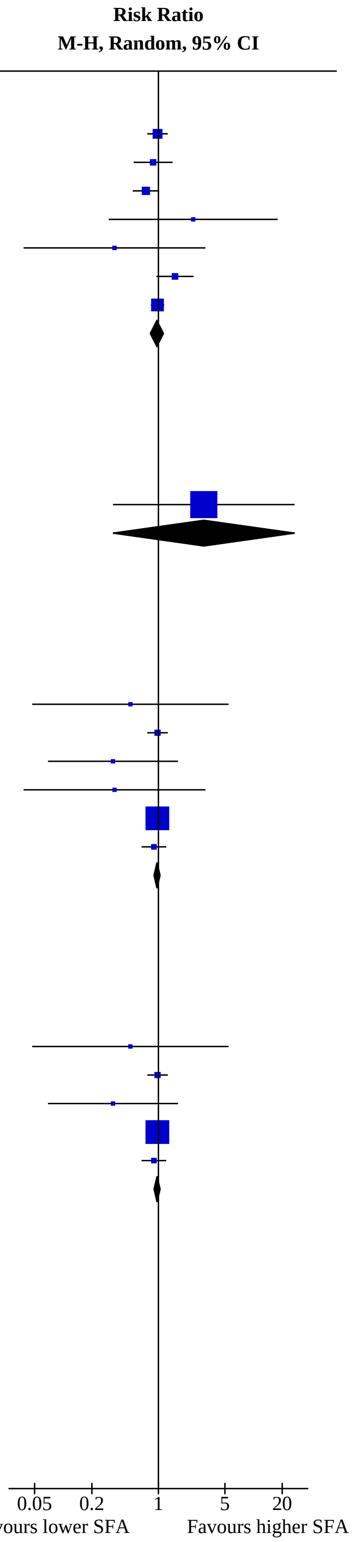
Heterogeneity: Chi² = 13.01, df = 11 (P = 0.29); I² = 15%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable

Footnotes
(1) All-cause death during study, Prentice 2017

Analysis 1.9. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 9: All-cause mortality, subgroup by any substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 replaced by PUFA						
DART 1989	111	1018	113	1015	24.4%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	9.5%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	17.5%	0.74 [0.54 , 1.02]
Rose corn oil 1965	5	28	1	13	0.6%	2.32 [0.30 , 17.92]
STARS 1992	1	27	3	28	0.5%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	10.3%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	37.2%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**2123**		**2115**	**100.0%**	**0.96 [0.82 , 1.13]**
Total events:	406		418			
Heterogeneity: Tau² = 0.01; Chi² = 8.06, df = 6 (P = 0.23); I² = 26%						
Test for overall effect: Z = 0.46 (P = 0.64)						
1.9.2 replaced by MUFA						
Rose olive 1965	3	26	1	26	100.0%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.33 , 26.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.9.3 replaced by CHO						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	8.5%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
WHI 2006 (1)	989	19541	1520	29294	85.3%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.8%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**21715**		**31954**	**100.0%**	**0.97 [0.90 , 1.04]**
Total events:	1168		1751			
Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 5 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.9.4 replaced by protein						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	8.5%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
WHI 2006 (1)	989	19541	1520	29294	85.4%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.8%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**21688**		**31926**	**100.0%**	**0.97 [0.90 , 1.04]**
Total events:	1167		1748			
Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 4 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.9.5 replacement unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 1.02, df = 3 (P = 0.80), I² = 0%



Footnotes

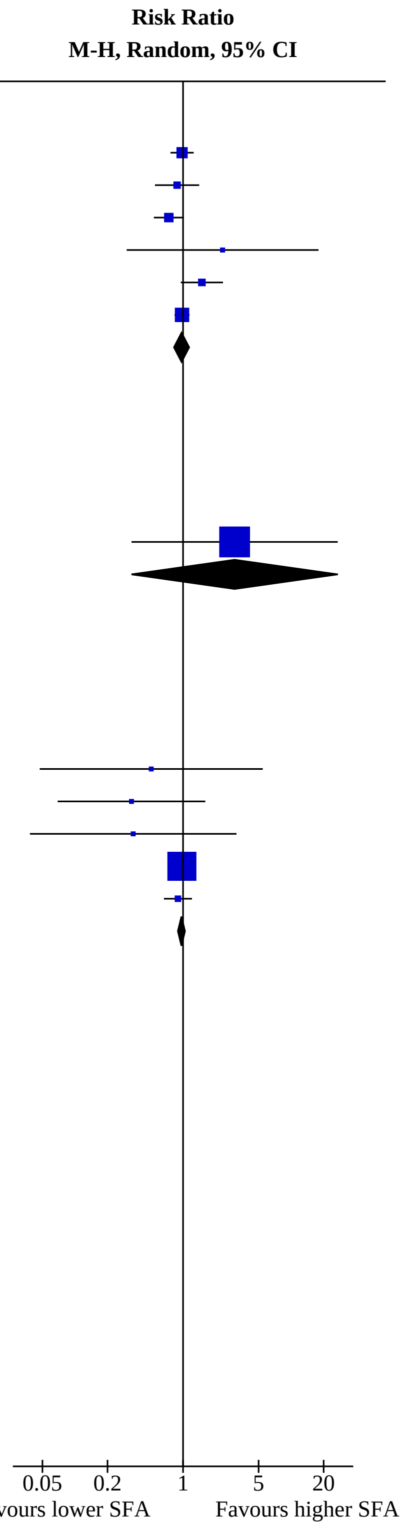
(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.10. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 10: All-cause mortality, subgroup by main substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 replaced by PUFA						
DART 1989	111	1018	113	1015	24.5%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	9.8%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	17.7%	0.74 [0.54 , 1.02]
Rose corn oil 1965	5	28	1	13	0.6%	2.32 [0.30 , 17.92]
Sydney Diet-Heart 1978	39	221	28	237	10.6%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	36.8%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**2096**		**2087**	**100.0%**	**0.97 [0.82 , 1.14]**
Total events:	405		415			
Heterogeneity: Tau² = 0.01; Chi² = 7.23, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 0.39 (P = 0.70)						
1.10.2 replaced by MUFA						
Rose olive 1965	3	26	1	26	100.0%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.33 , 26.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.10.3 replaced by CHO						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
WHI 2006 (1)	989	19541	1520	29294	93.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	6.3%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**20697**		**30939**	**100.0%**	**0.97 [0.90 , 1.04]**
Total events:	1057		1638			
Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.10.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.10.5 replacement unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 1.02, df = 2 (P = 0.60), I² = 0%



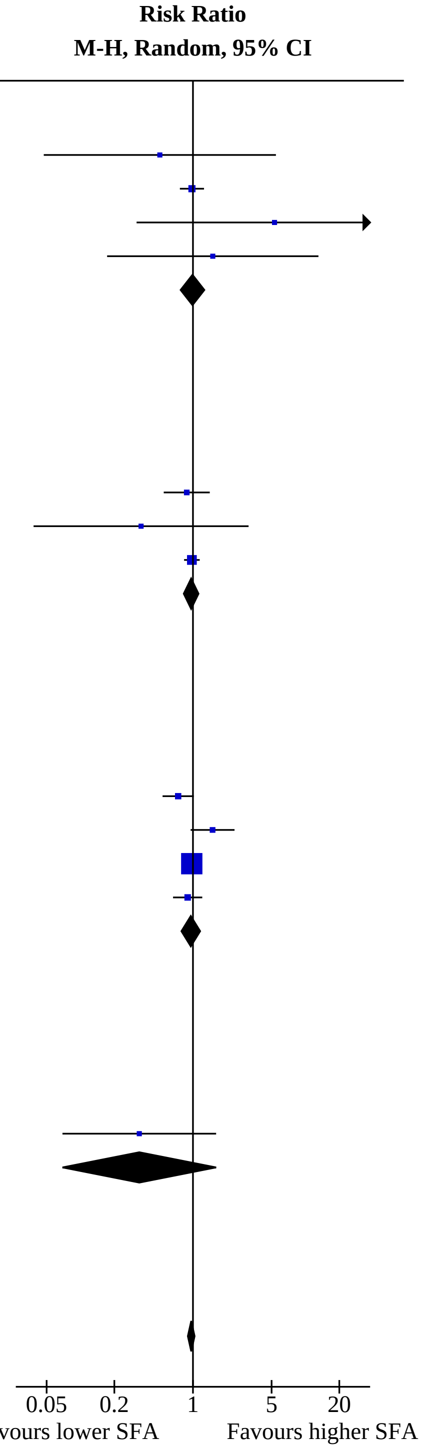
Footnotes

(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.11. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 11: All-cause mortality, subgroup by duration

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 up to 24mo						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	7.6%	0.98 [0.76 , 1.25]
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]
Subtotal (95% CI)		**1138**		**1108**	**7.8%**	**0.99 [0.78 , 1.26]**
Total events:	120		116			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.82, df = 3 (P = 0.61); I^2 = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
1.11.2 >24 to 48mo						
MRC 1968	28	199	31	194	2.1%	0.88 [0.55 , 1.41]
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**650**		**644**	**19.6%**	**0.96 [0.83 , 1.12]**
Total events:	203		211			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.02, df = 2 (P = 0.60); I^2 = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						
1.11.3 >48mo						
Oslo Diet-Heart 1966	48	206	65	206	4.6%	0.74 [0.54 , 1.02]
Sydney Diet-Heart 1978	39	221	28	237	2.3%	1.49 [0.95 , 2.34]
WHI 2006 (1)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**20943**		**31199**	**72.4%**	**0.96 [0.79 , 1.16]**
Total events:	1140		1720			
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.63, df = 3 (P = 0.08); I^2 = 55%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.11.4 unclear duration						
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
Subtotal (95% CI)		**88**		**88**	**0.2%**	**0.33 [0.07 , 1.61]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 11.25, df = 11 (P = 0.42); I^2 = 2%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi^2 = 1.80, df = 3 (P = 0.61), I^2 = 0%						



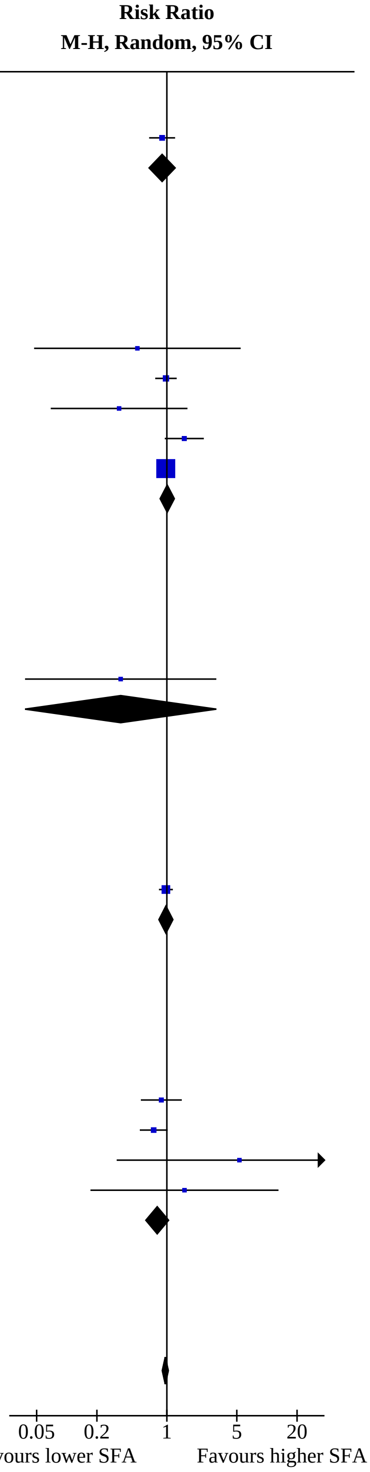
Footnotes

(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.12. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 12: All-cause mortality, subgroup by baseline SFA

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 up to 12%E SFA baseline						
WINS 2006 (1)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**975**		**1462**	**5.2%**	**0.90 [0.67 , 1.21]**
Total events:	64		107			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.12.2 >12 to 15%E SFA baseline						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	7.6%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
Sydney Diet-Heart 1978	39	221	28	237	2.3%	1.49 [0.95 , 2.34]
WHI 2006 (2)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
Subtotal (95% CI)		**20934**		**30701**	**70.4%**	**1.01 [0.86 , 1.19]**
Total events:	1142		1669			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.48$, df = 4 (P = 0.24); $I^2 = 27\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
1.12.3 >15 to 18%E SFA baseline						
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
Subtotal (95% CI)		**27**		**28**	**0.1%**	**0.35 [0.04 , 3.12]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.12.4 >18%E SFA baseline						
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**424**		**422**	**17.4%**	**0.98 [0.83 , 1.15]**
Total events:	174		177			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.12.5 unclear						
MRC 1968	28	199	31	194	2.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	4.6%	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]
Subtotal (95% CI)		**459**		**426**	**6.9%**	**0.80 [0.62 , 1.04]**
Total events:	84		97			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.50$, df = 3 (P = 0.47); $I^2 = 0\%$						
Test for overall effect: Z = 1.67 (P = 0.10)						
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.25$, df = 11 (P = 0.42); $I^2 = 2\%$						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: $Chi^2 = 3.25$, df = 4 (P = 0.52), $I^2 = 0\%$						



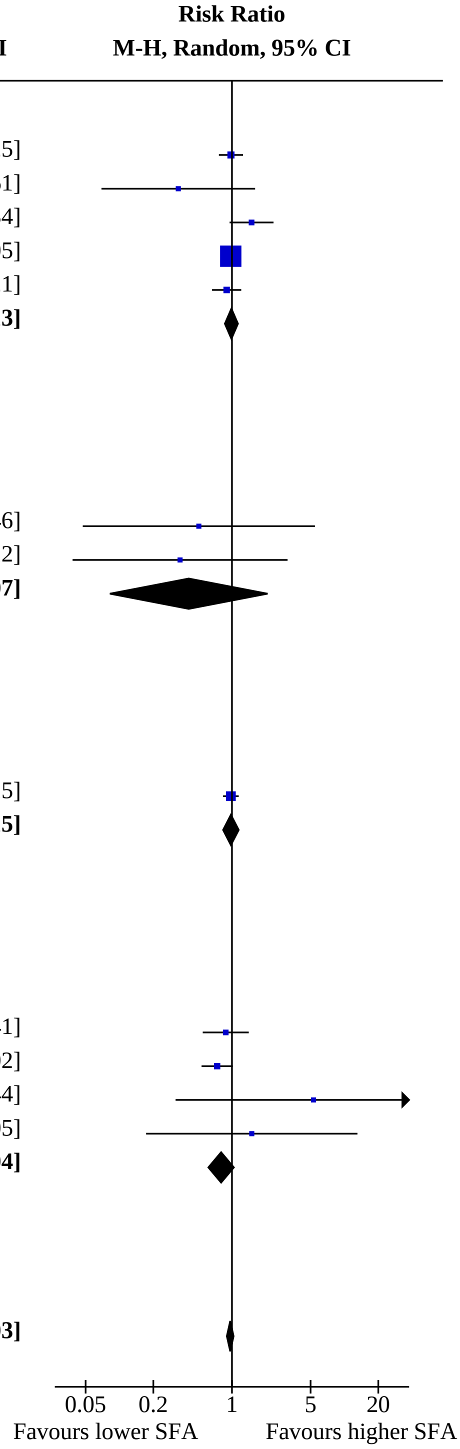
Footnotes

(1) All-cause mortality during trial, Chlebowski 2015

(2) All-cause death during study, Prentice 2017

Analysis 1.13. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 13: All-cause mortality, subgroup by SFA change

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 up to 4%E difference						
DART 1989	111	1018	113	1015	7.6%	0.98 [0.76 , 1.25]
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
Sydney Diet-Heart 1978	39	221	28	237	2.3%	1.49 [0.95 , 2.34]
WHI 2006 (1)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**21843**		**32096**	**75.5%**	**0.99 [0.86 , 1.13]**
Total events:	1205		1774			
Heterogeneity: Tau² = 0.01; Chi² = 5.53, df = 4 (P = 0.24); I² = 28%						
Test for overall effect: Z = 0.17 (P = 0.87)						
1.13.2 >4 to 8%E difference						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
Subtotal (95% CI)		**93**		**95**	**0.2%**	**0.41 [0.08 , 2.07]**
Total events:	2		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
1.13.3 >8%E difference						
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**424**		**422**	**17.4%**	**0.98 [0.83 , 1.15]**
Total events:	174		177			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.13.4 unclear						
MRC 1968	28	199	31	194	2.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	4.6%	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]
Subtotal (95% CI)		**459**		**426**	**6.9%**	**0.80 [0.62 , 1.04]**
Total events:	84		97			
Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			
Heterogeneity: Tau² = 0.00; Chi² = 11.25, df = 11 (P = 0.42); I² = 2%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 3.13, df = 3 (P = 0.37), I² = 4.0%						



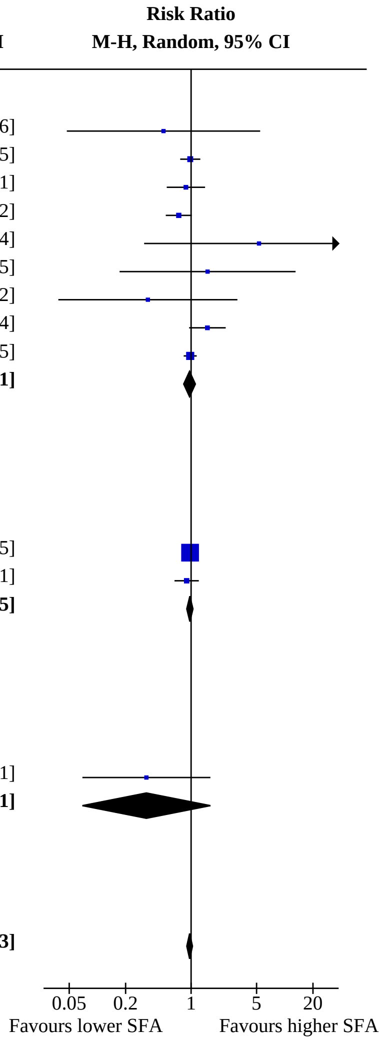
Footnotes

(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.14. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 14: All-cause mortality, subgroup by sex

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Men						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
DART 1989	111	1018	113	1015	7.6%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	2.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	4.6%	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	2.3%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**2215**		**2195**	**34.4%**	**0.96 [0.83 , 1.11]**
Total events:	410		420			
Heterogeneity: Tau² = 0.01; Chi² = 9.20, df = 8 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.53 (P = 0.60)						
1.14.2 Women						
WHI 2006 (1)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**20516**		**30756**	**65.4%**	**0.97 [0.90 , 1.05]**
Total events:	1053		1627			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.14.3 Mixed, men and women						
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
Subtotal (95% CI)		**88**		**88**	**0.2%**	**0.33 [0.07 , 1.61]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			
Heterogeneity: Tau² = 0.00; Chi² = 11.25, df = 11 (P = 0.42); I² = 2%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 1.77, df = 2 (P = 0.41), I² = 0%						



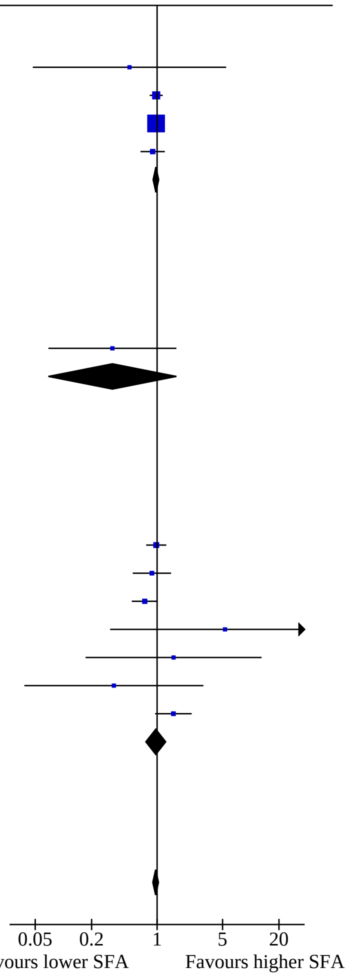
Footnotes

(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.15. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 15: All-cause mortality, subgroup by CVD risk

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Low CVD risk						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
WHI 2006 (1)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**21006**		**31245**	**82.9%**	**0.97 [0.91 , 1.04]**
Total events:	1228		1806			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 3 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.15.2 Moderate CVD risk						
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
Subtotal (95% CI)		**88**		**88**	**0.2%**	**0.33 [0.07 , 1.61]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.15.3 Existing CVD disease						
DART 1989	111	1018	113	1015	7.6%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	2.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	4.6%	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	2.3%	1.49 [0.95 , 2.34]
Subtotal (95% CI)		**1725**		**1706**	**16.9%**	**0.97 [0.76 , 1.24]**
Total events:	235		241			
Heterogeneity: Tau² = 0.03; Chi² = 8.89, df = 6 (P = 0.18); I² = 33%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			
Heterogeneity: Tau² = 0.00; Chi² = 11.25, df = 11 (P = 0.42); I² = 2%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 1.77, df = 2 (P = 0.41), I² = 0%						



Footnotes

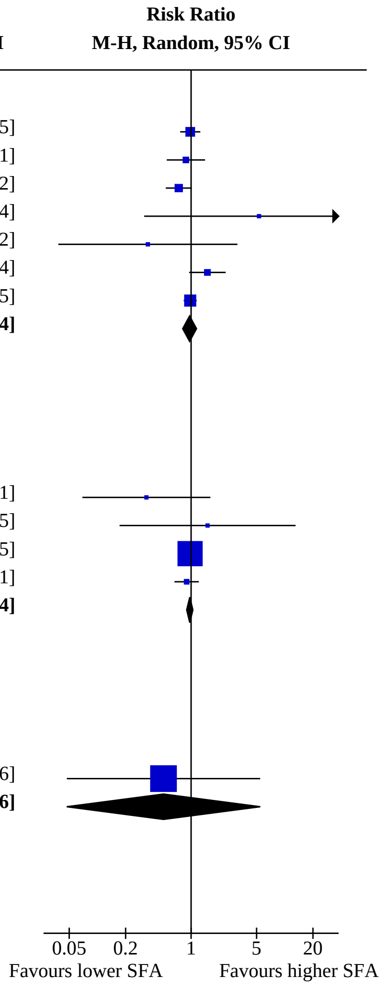
(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.16. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 16: All-cause mortality, subgroup by TC reduction

	lower SFA		higher SFA			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
1.16.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	111	1018	113	1015	24.5%	0.98 [0.76 , 1.25]
MRC 1968	28	199	31	194	10.3%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	18.1%	0.74 [0.54 , 1.02]
Rose corn oil 1965	5	28	0	13	0.4%	5.31 [0.32 , 89.44]
STARS 1992	1	27	3	28	0.6%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	39	221	28	237	11.1%	1.49 [0.95 , 2.34]
Veterans Admin 1969	174	424	177	422	35.1%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**2123**		**2115**	**100.0%**	**0.96 [0.81 , 1.14]**
Total events:	406		417			
Heterogeneity: Tau² = 0.01; Chi² = 8.76, df = 6 (P = 0.19); I² = 32%						
Test for overall effect: Z = 0.42 (P = 0.67)						
1.16.2 serum chol reduced by <0.2mmol/L						
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
Rose olive 1965	3	26	1	13	0.1%	1.50 [0.17 , 13.05]
WHI 2006 (1)	989	19541	1520	29294	93.3%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	6.4%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**20630**		**30857**	**100.0%**	**0.97 [0.90 , 1.04]**
Total events:	1058		1634			
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.16.3 serum chol reduction unclear						
Black 1994	1	66	2	67	100.0%	0.51 [0.05 , 5.46]
Subtotal (95% CI)		**66**		**67**	**100.0%**	**0.51 [0.05 , 5.46]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						

Test for subgroup differences: Chi² = 0.29, df = 2 (P = 0.87), I² = 0%



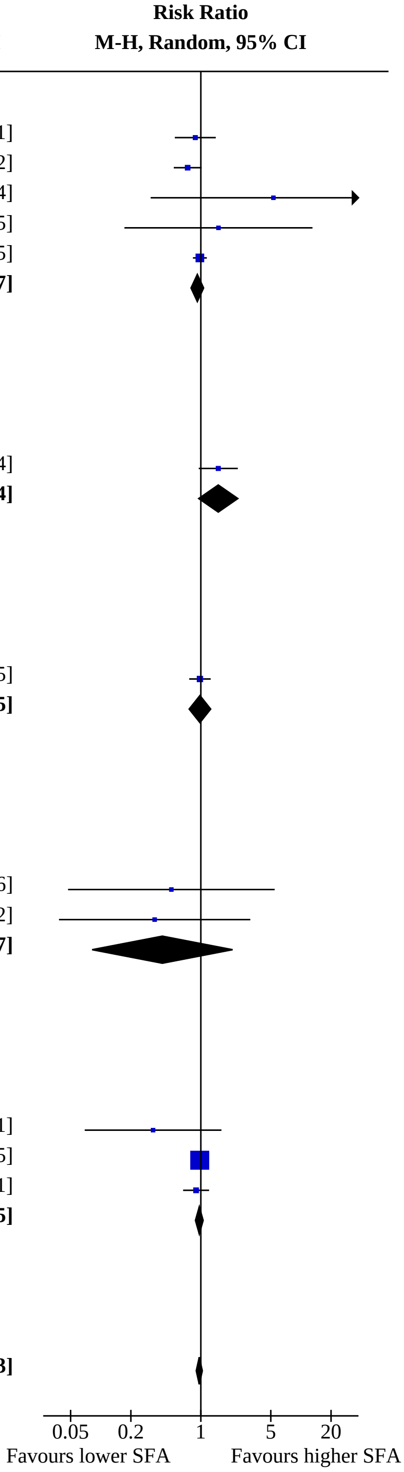
Footnotes

(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.17. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 17: All-cause mortality, subgroup decade of publication

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 1960s						
MRC 1968	28	199	31	194	2.1%	0.88 [0.55 , 1.41]
Oslo Diet-Heart 1966	48	206	65	206	4.6%	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]
Veterans Admin 1969	174	424	177	422	17.4%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**883**		**848**	**24.3%**	**0.92 [0.80 , 1.07]**
Total events:	258		274			
Heterogeneity: Tau² = 0.00; Chi² = 4.09, df = 4 (P = 0.39); I² = 2%						
Test for overall effect: Z = 1.09 (P = 0.27)						
1.17.2 1970s						
Sydney Diet-Heart 1978	39	221	28	237	2.3%	1.49 [0.95 , 2.34]
Subtotal (95% CI)		**221**		**237**	**2.3%**	**1.49 [0.95 , 2.34]**
Total events:	39		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.17.3 1980s						
DART 1989	111	1018	113	1015	7.6%	0.98 [0.76 , 1.25]
Subtotal (95% CI)		**1018**		**1015**	**7.6%**	**0.98 [0.76 , 1.25]**
Total events:	111		113			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
1.17.4 1990s						
Black 1994	1	66	2	67	0.1%	0.51 [0.05 , 5.46]
STARS 1992	1	27	3	28	0.1%	0.35 [0.04 , 3.12]
Subtotal (95% CI)		**93**		**95**	**0.2%**	**0.41 [0.08 , 2.07]**
Total events:	2		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
1.17.5 2000s						
Ley 2004	2	88	6	88	0.2%	0.33 [0.07 , 1.61]
WHI 2006 (1)	989	19541	1520	29294	60.2%	0.98 [0.90 , 1.05]
WINS 2006 (2)	64	975	107	1462	5.2%	0.90 [0.67 , 1.21]
Subtotal (95% CI)		**20604**		**30844**	**65.6%**	**0.97 [0.88 , 1.05]**
Total events:	1055		1633			
Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 2 (P = 0.36); I² = 3%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**22819**		**33039**	**100.0%**	**0.96 [0.90 , 1.03]**
Total events:	1465		2053			
Heterogeneity: Tau² = 0.00; Chi² = 11.25, df = 11 (P = 0.42); I² = 2%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 5.08, df = 4 (P = 0.28), I² = 21.2%						



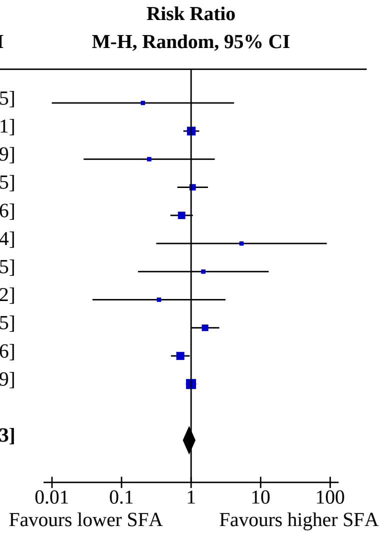
Footnotes

(1) All-cause death during study, Prentice 2017

(2) All-cause mortality during trial, Chlebowski 2015

Analysis 1.18. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 18: CARDIOVASCULAR MORTALITY

	lower SFA		higher SFA			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	19.9%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	0.7%	0.25 [0.03 , 2.19]
MRC 1968	27	199	25	194	9.5%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.2%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	0	13	0.4%	5.31 [0.32 , 89.44]
Rose olive 1965	3	26	1	13	0.7%	1.50 [0.17 , 13.05]
STARS 1992	1	27	3	28	0.7%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	10.5%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	17.2%	0.70 [0.51 , 0.96]
WHI 2006 (1)	213	19541	320	29294	25.7%	1.00 [0.84 , 1.19]
Total (95% CI)		**21844**		**31577**	**100.0%**	**0.94 [0.78 , 1.13]**
Total events:	483		613			

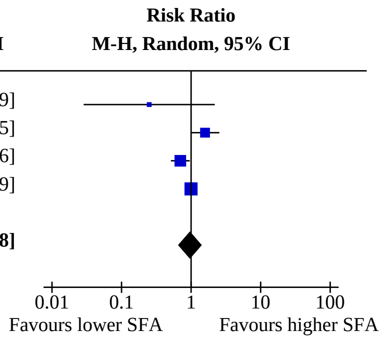


Heterogeneity: Tau² = 0.03; Chi² = 15.67, df = 10 (P = 0.11); I² = 36%
Test for overall effect: Z = 0.68 (P = 0.49)
Test for subgroup differences: Not applicable

Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.19. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 19: CVD mortality, SA low summary risk of bias

	lower SFA		higher SFA			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Ley 2004	1	88	4	88	2.6%	0.25 [0.03 , 2.19]
Sydney Diet-Heart 1978	37	221	25	237	25.0%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	32.9%	0.70 [0.51 , 0.96]
WHI 2006 (1)	213	19541	320	29294	39.5%	1.00 [0.84 , 1.19]
Total (95% CI)		**20274**		**30041**	**100.0%**	**0.96 [0.67 , 1.38]**
Total events:	308		430			

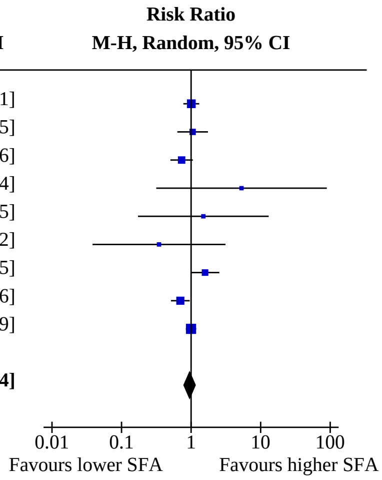


Heterogeneity: Tau² = 0.08; Chi² = 9.96, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable

Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.20. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 20: CVD mortality, SA aim to reduce SFA

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	101	1018	100	1015	20.2%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	9.5%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.3%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	0	13	0.4%	5.31 [0.32 , 89.44]
Rose olive 1965	3	26	1	13	0.7%	1.50 [0.17 , 13.05]
STARS 1992	1	27	3	28	0.7%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	10.4%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	17.3%	0.70 [0.51 , 0.96]
WHI 2006 (1)	213	19541	320	29294	26.5%	1.00 [0.84 , 1.19]
Total (95% CI)		**21690**		**31422**	**100.0%**	**0.95 [0.79 , 1.14]**
Total events:	482		607			

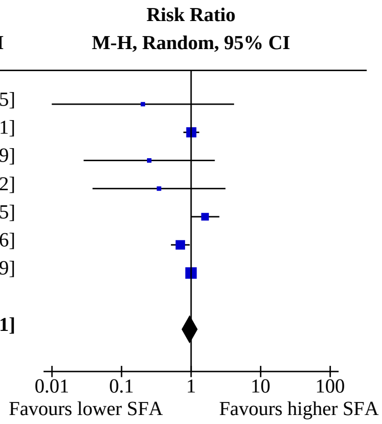


Heterogeneity: Tau² = 0.03; Chi² = 13.22, df = 8 (P = 0.10); I² = 39%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.21. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 21: CVD mortality, SA statistically significant SFA reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	0	66	2	67	0.6%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	26.3%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	1.2%	0.25 [0.03 , 2.19]
STARS 1992	1	27	3	28	1.1%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	15.3%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	23.3%	0.70 [0.51 , 0.96]
WHI 2006 (1)	213	19541	320	29294	32.2%	1.00 [0.84 , 1.19]
Total (95% CI)		**21385**		**31151**	**100.0%**	**0.95 [0.75 , 1.21]**
Total events:	410		535			



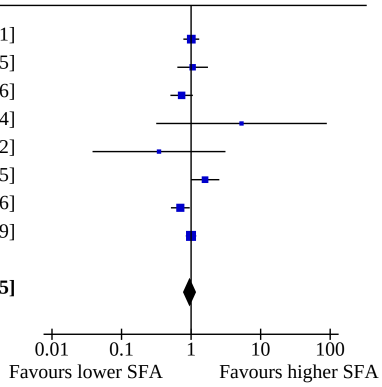
Heterogeneity: Tau² = 0.04; Chi² = 11.92, df = 6 (P = 0.06); I² = 50%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.22. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 22: CVD mortality, SA TC reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	101	1018	100	1015	20.2%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	9.9%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.6%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	0	13	0.5%	5.31 [0.32 , 89.44]
STARS 1992	1	27	3	28	0.7%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	10.9%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	17.5%	0.70 [0.51 , 0.96]
WHI 2006 (1)	213	19541	320	29294	25.7%	1.00 [0.84 , 1.19]
Total (95% CI)		**21664**		**31409**	**100.0%**	**0.95 [0.78 , 1.15]**
Total events:	479		606			

Heterogeneity: Tau² = 0.03; Chi² = 13.05, df = 7 (P = 0.07); I² = 46%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

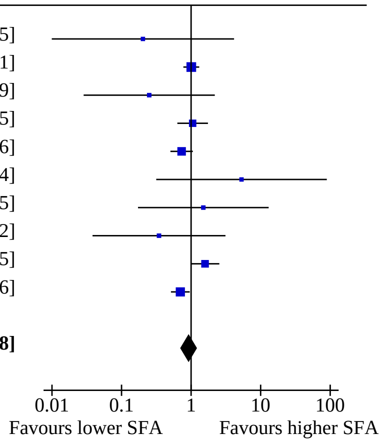


Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.23. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 23: CVD mortality, SA excluding WHI

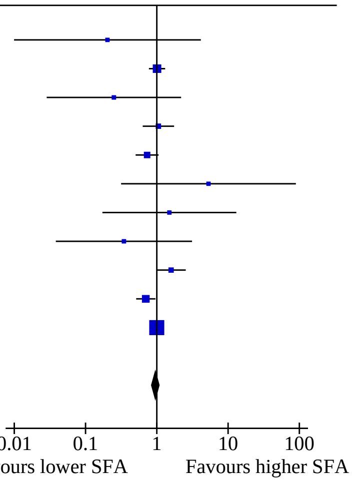
Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	0	66	2	67	0.7%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	24.3%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	1.3%	0.25 [0.03 , 2.19]
MRC 1968	27	199	25	194	14.1%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	19.2%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	0	13	0.8%	5.31 [0.32 , 89.44]
Rose olive 1965	3	26	1	13	1.3%	1.50 [0.17 , 13.05]
STARS 1992	1	27	3	28	1.3%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	15.2%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	21.9%	0.70 [0.51 , 0.96]
Total (95% CI)		**2303**		**2283**	**100.0%**	**0.92 [0.72 , 1.18]**
Total events:	270		293			

Heterogeneity: Tau² = 0.05; Chi² = 15.03, df = 9 (P = 0.09); I² = 40%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 24: CVD mortality, SA Mantel-Haenszel fixed-effect

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Black 1994	0	66	2	67	0.5%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	18.2%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	0.7%	0.25 [0.03 , 2.19]
MRC 1968	27	199	25	194	4.6%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	9.4%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	0	13	0.1%	5.31 [0.32 , 89.44]
Rose olive 1965	3	26	1	13	0.2%	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	4.4%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	14.8%	0.70 [0.51 , 0.96]
WHI 2006 (1)	213	19541	320	29294	46.5%	1.00 [0.84 , 1.19]
Total (95% CI)		**21844**		**31577**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	483		613			

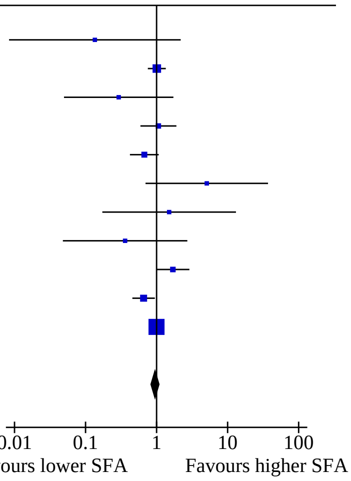


Heterogeneity: Chi² = 15.67, df = 10 (P = 0.11); I² = 36%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.25. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 25: CVD mortality, SA Peto fixed-effect

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Black 1994	0	66	2	67	0.2%	0.14 [0.01 , 2.19]
DART 1989	101	1018	100	1015	18.3%	1.01 [0.75 , 1.35]
Ley 2004	1	88	4	88	0.5%	0.29 [0.05 , 1.73]
MRC 1968	27	199	25	194	4.6%	1.06 [0.59 , 1.90]
Oslo Diet-Heart 1966	38	206	52	206	7.1%	0.67 [0.42 , 1.07]
Rose corn oil 1965	5	28	0	13	0.4%	5.09 [0.70 , 37.06]
Rose olive 1965	3	26	1	13	0.3%	1.50 [0.17 , 13.11]
STARS 1992	1	27	3	28	0.4%	0.36 [0.05 , 2.71]
Sydney Diet-Heart 1978	37	221	25	237	5.4%	1.70 [0.99 , 2.90]
Veterans Admin 1969	57	424	81	422	11.7%	0.66 [0.46 , 0.95]
WHI 2006 (1)	213	19541	320	29294	51.1%	1.00 [0.84 , 1.19]
Total (95% CI)		**21844**		**31577**	**100.0%**	**0.95 [0.84 , 1.08]**
Total events:	483		613			



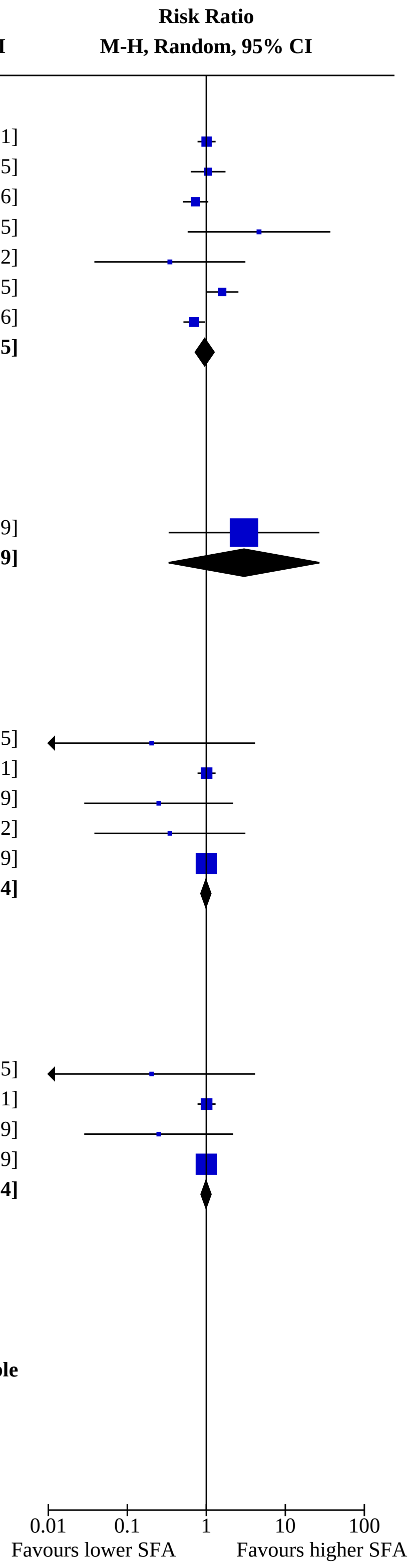
Heterogeneity: Chi² = 18.54, df = 10 (P = 0.05); I² = 46%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable

Footnotes
(1) In participants with and without CVD at baseline

Analysis 1.26. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 26: CVD mortality, subgroup by any substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.26.1 replaced by PUFA						
DART 1989	101	1018	100	1015	24.1%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	15.0%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	19.7%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	1.6%	4.64 [0.58 , 37.15]
STARS 1992	1	27	3	28	1.5%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	16.0%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	22.1%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**2123**		**2128**	**100.0%**	**0.95 [0.73 , 1.25]**
Total events:	266		287			
Heterogeneity: Tau² = 0.06; Chi² = 13.37, df = 6 (P = 0.04); I² = 55%						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.26.2 replaced by MUFA						
Rose olive 1965	3	26	1	26	100.0%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.33 , 26.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.26.3 replace by CHO						
Black 1994	0	66	2	67	0.2%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	29.8%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	0.4%	0.25 [0.03 , 2.19]
STARS 1992	1	27	3	28	0.4%	0.35 [0.04 , 3.12]
WHI 2006 (1)	213	19541	320	29294	69.1%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**20740**		**30492**	**100.0%**	**0.99 [0.85 , 1.14]**
Total events:	316		429			
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 4 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.26.4 replaced by protein						
Black 1994	0	66	2	67	0.2%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	29.9%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	0.4%	0.25 [0.03 , 2.19]
WHI 2006 (1)	213	19541	320	29294	69.4%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**20713**		**30464**	**100.0%**	**0.99 [0.86 , 1.14]**
Total events:	315		426			
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
1.26.5 replacement unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 1.05, df = 3 (P = 0.79), I² = 0%



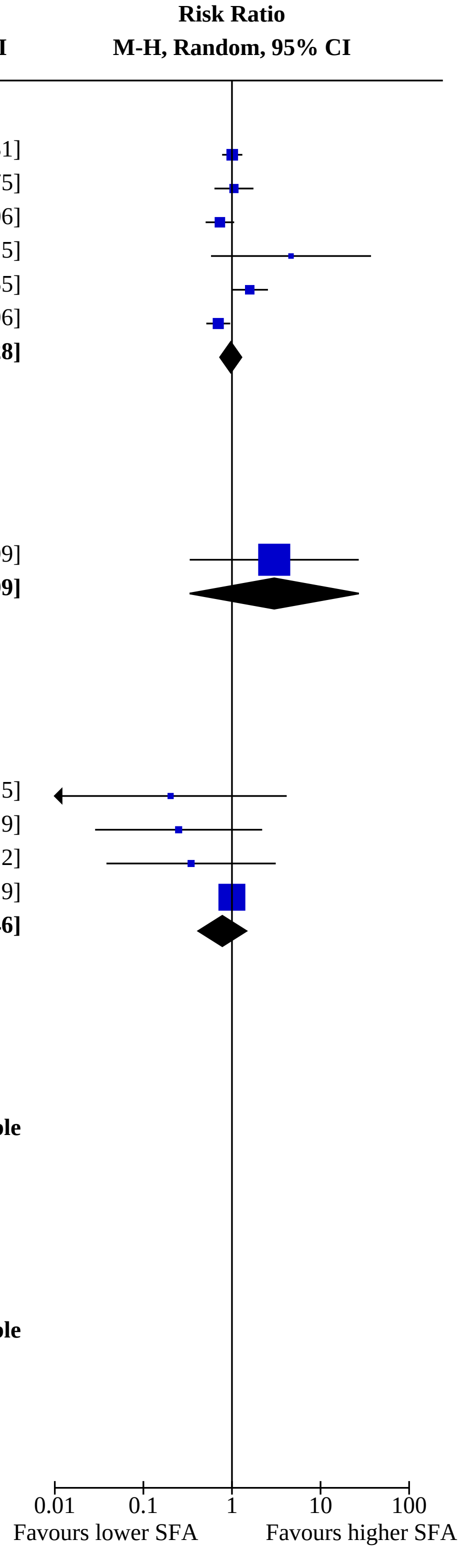
Footnotes

(1) Women with and without CVD at baseline

Analysis 1.27. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 27: CVD mortality, subgroup by main substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 replaced by PUFA						
DART 1989	101	1018	100	1015	24.3%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	15.3%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	20.0%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	1.7%	4.64 [0.58 , 37.15]
Sydney Diet-Heart 1978	37	221	25	237	16.3%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	22.4%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**2096**		**2100**	**100.0%**	**0.97 [0.73 , 1.28]**
Total events:	265		284			
Heterogeneity: Tau² = 0.06; Chi² = 12.62, df = 5 (P = 0.03); I² = 60%						
Test for overall effect: Z = 0.22 (P = 0.82)						
1.27.2 replaced by MUFA						
Rose olive 1965	3	26	1	26	100.0%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.33 , 26.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.27.3 replace by CHO						
Black 1994	0	66	2	67	4.1%	0.20 [0.01 , 4.15]
Ley 2004	1	88	4	88	7.6%	0.25 [0.03 , 2.19]
STARS 1992	1	27	3	28	7.4%	0.35 [0.04 , 3.12]
WHI 2006 (1)	213	19541	320	29294	81.0%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**19722**		**29477**	**100.0%**	**0.78 [0.42 , 1.46]**
Total events:	215		329			
Heterogeneity: Tau² = 0.12; Chi² = 3.47, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.78 (P = 0.43)						
1.27.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.27.5 replacement unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 1.46, df = 2 (P = 0.48), I² = 0%



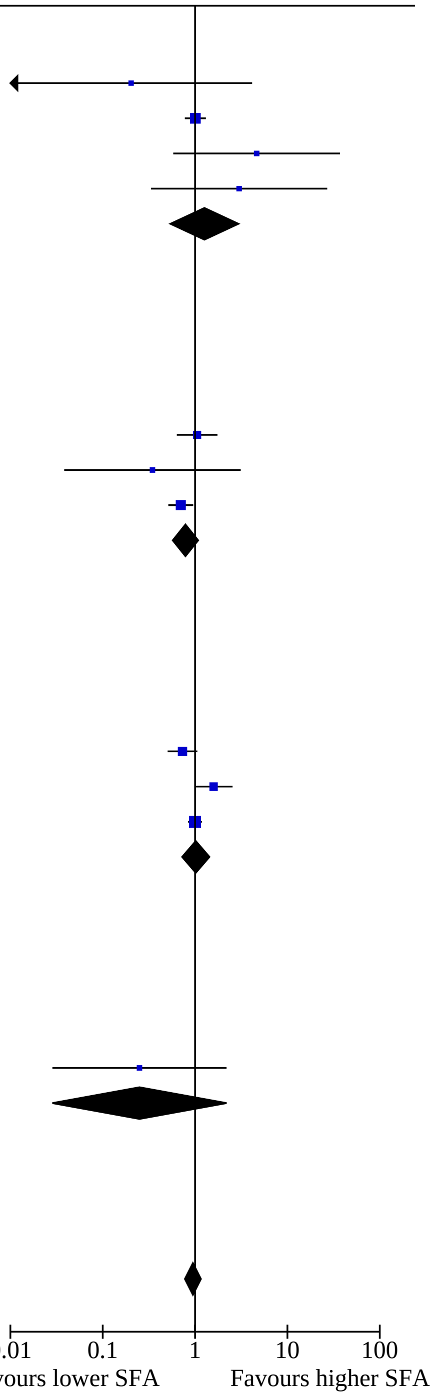
Footnotes

(1) Women with and without CVD at baseline

Analysis 1.28. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 28: CVD mortality, subgroup by duration

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.28.1 up to 24mo						
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	19.4%	1.01 [0.77 , 1.31]
Rose corn oil 1965	5	28	1	26	0.9%	4.64 [0.58 , 37.15]
Rose olive 1965	3	26	1	26	0.8%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**1138**		**1134**	**21.5%**	**1.26 [0.54 , 2.94]**
Total events:	109		104			
Heterogeneity: Tau² = 0.26; Chi² = 4.07, df = 3 (P = 0.25); I² = 26%						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.28.2 >24 to 48mo						
MRC 1968	27	199	25	194	10.1%	1.05 [0.63 , 1.75]
STARS 1992	1	27	3	28	0.8%	0.35 [0.04 , 3.12]
Veterans Admin 1969	57	424	81	422	17.1%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**650**		**644**	**28.0%**	**0.79 [0.57 , 1.08]**
Total events:	85		109			
Heterogeneity: Tau² = 0.01; Chi² = 2.33, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.28.3 >48 mo						
Oslo Diet-Heart 1966	38	206	52	206	14.5%	0.73 [0.50 , 1.06]
Sydney Diet-Heart 1978	37	221	25	237	11.0%	1.59 [0.99 , 2.55]
WHI 2006 (1)	213	19541	320	29294	24.1%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**19968**		**29737**	**49.6%**	**1.02 [0.73 , 1.43]**
Total events:	288		397			
Heterogeneity: Tau² = 0.06; Chi² = 6.40, df = 2 (P = 0.04); I² = 69%						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.28.4 unclear duration						
Ley 2004	1	88	4	88	0.8%	0.25 [0.03 , 2.19]
Subtotal (95% CI)		**88**		**88**	**0.8%**	**0.25 [0.03 , 2.19]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**21844**		**31603**	**100.0%**	**0.95 [0.78 , 1.16]**
Total events:	483		614			
Heterogeneity: Tau² = 0.04; Chi² = 17.36, df = 10 (P = 0.07); I² = 42%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 3.15, df = 3 (P = 0.37), I² = 4.9%						

Risk Ratio
M-H, Random, 95% CI

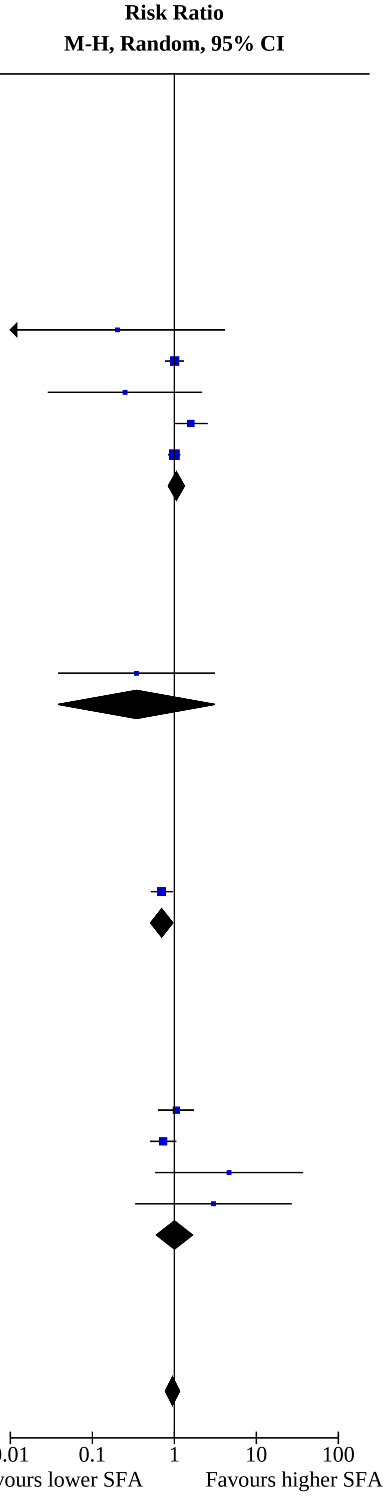


Footnotes

(1) Women with and without CVD at baseline

Analysis 1.29. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 29: CVD mortality, subgroup by baseline SFA

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.29.2 >12 to 15%E SFA baseline						
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	19.4%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	0.8%	0.25 [0.03 , 2.19]
Sydney Diet-Heart 1978	37	221	25	237	11.0%	1.59 [0.99 , 2.55]
WHI 2006 (1)	213	19541	320	29294	24.1%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**20934**		**30701**	**55.8%**	**1.06 [0.84 , 1.32]**
Total events:	352		451			
Heterogeneity: Tau² = 0.02; Chi² = 6.12, df = 4 (P = 0.19); I² = 35%						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.29.3 >15 to 18%E SFA baseline						
STARS 1992	1	27	3	28	0.8%	0.35 [0.04 , 3.12]
Subtotal (95% CI)		**27**		**28**	**0.8%**	**0.35 [0.04 , 3.12]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.29.4 >18%E SFA baseline						
Veterans Admin 1969	57	424	81	422	17.1%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**424**		**422**	**17.1%**	**0.70 [0.51 , 0.96]**
Total events:	57		81			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.29.5 unclear						
MRC 1968	27	199	25	194	10.1%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.5%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	0.9%	4.64 [0.58 , 37.15]
Rose olive 1965	3	26	1	26	0.8%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**459**		**452**	**26.3%**	**1.00 [0.61 , 1.66]**
Total events:	73		79			
Heterogeneity: Tau² = 0.10; Chi² = 5.16, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**21844**		**31603**	**100.0%**	**0.95 [0.78 , 1.16]**
Total events:	483		614			
Heterogeneity: Tau² = 0.04; Chi² = 17.36, df = 10 (P = 0.07); I² = 42%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 5.29, df = 3 (P = 0.15), I² = 43.3%						

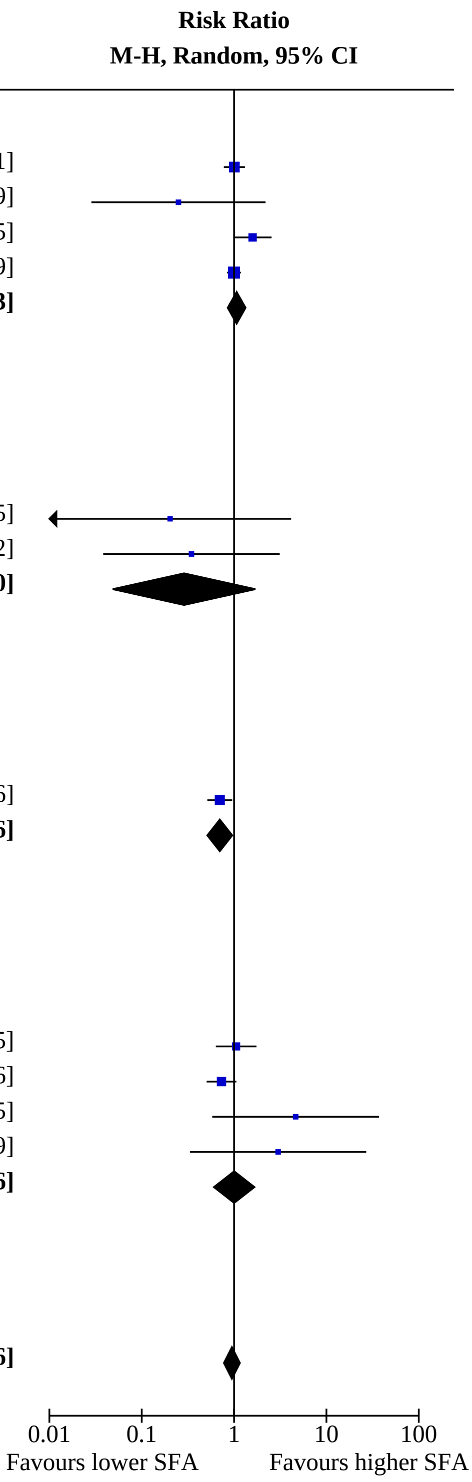


Footnotes

(1) Women with and without CVD at baseline

Analysis 1.30. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 30: CVD mortality, subgroup by SFA change

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.30.1 up to 4%E difference						
DART 1989	101	1018	100	1015	19.4%	1.01 [0.77 , 1.31]
Ley 2004	1	88	4	88	0.8%	0.25 [0.03 , 2.19]
Sydney Diet-Heart 1978	37	221	25	237	11.0%	1.59 [0.99 , 2.55]
WHI 2006 (1)	213	19541	320	29294	24.1%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**20868**		**30634**	**55.4%**	**1.07 [0.85 , 1.33]**
Total events:	352		449			
Heterogeneity: Tau² = 0.02; Chi² = 5.00, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 0.56 (P = 0.57)						
1.30.2 >4 to 8%E difference						
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
STARS 1992	1	27	3	28	0.8%	0.35 [0.04 , 3.12]
Subtotal (95% CI)		**93**		**95**	**1.2%**	**0.29 [0.05 , 1.70]**
Total events:	1		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.30.3 >8%E difference						
Veterans Admin 1969	57	424	81	422	17.1%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**424**		**422**	**17.1%**	**0.70 [0.51 , 0.96]**
Total events:	57		81			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.30.4 unclear						
MRC 1968	27	199	25	194	10.1%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.5%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	0.9%	4.64 [0.58 , 37.15]
Rose olive 1965	3	26	1	26	0.8%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**459**		**452**	**26.3%**	**1.00 [0.61 , 1.66]**
Total events:	73		79			
Heterogeneity: Tau² = 0.10; Chi² = 5.16, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**21844**		**31603**	**100.0%**	**0.95 [0.78 , 1.16]**
Total events:	483		614			
Heterogeneity: Tau² = 0.04; Chi² = 17.36, df = 10 (P = 0.07); I² = 42%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 6.39, df = 3 (P = 0.09), I² = 53.1%						

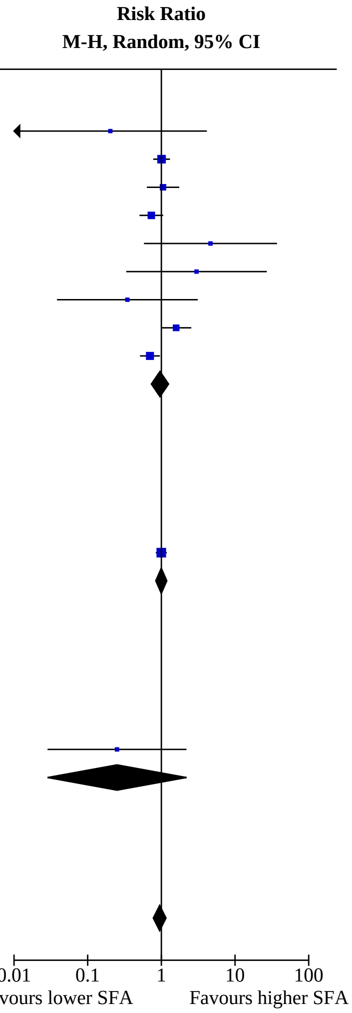


Footnotes

(1) Women with and without CVD at baseline

Analysis 1.31. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 31: CVD mortality, subgroup by sex

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.31.1 Men						
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
DART 1989	101	1018	100	1015	19.4%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	10.1%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.5%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	0.9%	4.64 [0.58 , 37.15]
Rose olive 1965	3	26	1	26	0.8%	3.00 [0.33 , 26.99]
STARS 1992	1	27	3	28	0.8%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	11.0%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	17.1%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**2215**		**2221**	**75.1%**	**0.96 [0.73 , 1.25]**
Total events:	269		290			
Heterogeneity: Tau² = 0.06; Chi² = 15.45, df = 8 (P = 0.05); I² = 48%						
Test for overall effect: Z = 0.32 (P = 0.75)						
1.31.2 Women						
WHI 2006 (1)	213	19541	320	29294	24.1%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**19541**		**29294**	**24.1%**	**1.00 [0.84 , 1.19]**
Total events:	213		320			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.31.3 Mixed, men and women						
Ley 2004	1	88	4	88	0.8%	0.25 [0.03 , 2.19]
Subtotal (95% CI)		**88**		**88**	**0.8%**	**0.25 [0.03 , 2.19]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**21844**		**31603**	**100.0%**	**0.95 [0.78 , 1.16]**
Total events:	483		614			
Heterogeneity: Tau² = 0.04; Chi² = 17.36, df = 10 (P = 0.07); I² = 42%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 1.59, df = 2 (P = 0.45), I² = 0%						

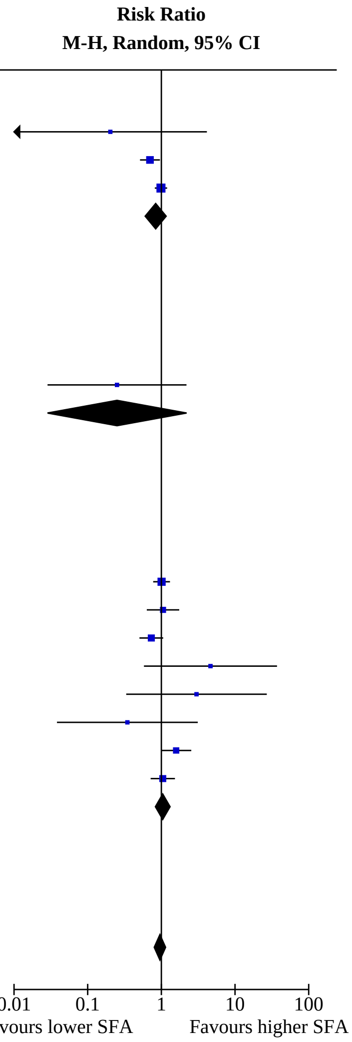


Footnotes

(1) Women with and without CVD at baseline

Analysis 1.32. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 32: CVD mortality, subgroup by CVD risk

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.32.1 Low CVD risk						
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
Veterans Admin 1969	57	424	81	422	15.2%	0.70 [0.51 , 0.96]
WHI 2006 (1)	170	18633	258	27925	21.4%	0.99 [0.81 , 1.20]
Subtotal (95% CI)		**19123**		**28414**	**36.9%**	**0.84 [0.60 , 1.16]**
Total events:	227		341			
Heterogeneity: Tau² = 0.04; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.32.2 Moderate CVD risk						
Ley 2004	1	88	4	88	0.6%	0.25 [0.03 , 2.19]
Subtotal (95% CI)		**88**		**88**	**0.6%**	**0.25 [0.03 , 2.19]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
1.32.3 Existing CVD disease						
DART 1989	101	1018	100	1015	17.6%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	8.5%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	12.7%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	0.7%	4.64 [0.58 , 37.15]
Rose olive 1965	3	26	1	26	0.6%	3.00 [0.33 , 26.99]
STARS 1992	1	27	3	28	0.6%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	9.4%	1.59 [0.99 , 2.55]
WHI 2006 (2)	43	908	62	1369	12.3%	1.05 [0.72 , 1.53]
Subtotal (95% CI)		**2633**		**3101**	**62.4%**	**1.04 [0.83 , 1.31]**
Total events:	255		269			
Heterogeneity: Tau² = 0.03; Chi² = 10.41, df = 7 (P = 0.17); I² = 33%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**21844**		**31603**	**100.0%**	**0.96 [0.80 , 1.14]**
Total events:	483		614			
Heterogeneity: Tau² = 0.03; Chi² = 17.45, df = 11 (P = 0.10); I² = 37%						
Test for overall effect: Z = 0.50 (P = 0.61)						
Test for subgroup differences: Chi² = 2.66, df = 2 (P = 0.26), I² = 24.9%						



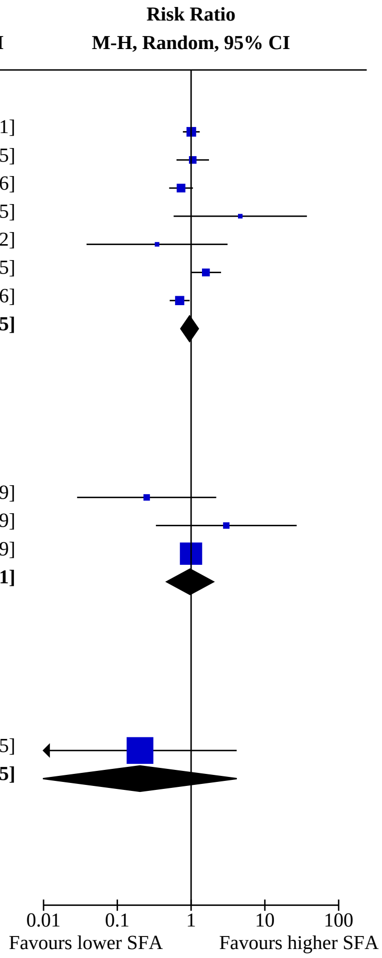
Footnotes

(1) Women without CVD at baseline

(2) Women with CVD at baseline

Analysis 1.33. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 33: CVD mortality, subgroup by TC reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.33.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	101	1018	100	1015	24.1%	1.01 [0.77 , 1.31]
MRC 1968	27	199	25	194	15.0%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	19.7%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	1	26	1.6%	4.64 [0.58 , 37.15]
STARS 1992	1	27	3	28	1.5%	0.35 [0.04 , 3.12]
Sydney Diet-Heart 1978	37	221	25	237	16.0%	1.59 [0.99 , 2.55]
Veterans Admin 1969	57	424	81	422	22.1%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**2123**		**2128**	**100.0%**	**0.95 [0.73 , 1.25]**
Total events:	266		287			
Heterogeneity: Tau² = 0.06; Chi² = 13.37, df = 6 (P = 0.04); I² = 55%						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.33.2 serum chol reduced by <0.2mmol/L						
Ley 2004	1	88	4	88	9.9%	0.25 [0.03 , 2.19]
Rose olive 1965	3	26	1	26	9.7%	3.00 [0.33 , 26.99]
WHI 2006 (1)	213	19541	320	29294	80.3%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**19655**		**29408**	**100.0%**	**0.97 [0.47 , 2.01]**
Total events:	217		325			
Heterogeneity: Tau² = 0.16; Chi² = 2.53, df = 2 (P = 0.28); I² = 21%						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.33.3 serum chol reduction unclear						
Black 1994	0	66	2	67	100.0%	0.20 [0.01 , 4.15]
Subtotal (95% CI)		**66**		**67**	**100.0%**	**0.20 [0.01 , 4.15]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Test for subgroup differences: Chi² = 1.01, df = 2 (P = 0.60), I² = 0%						

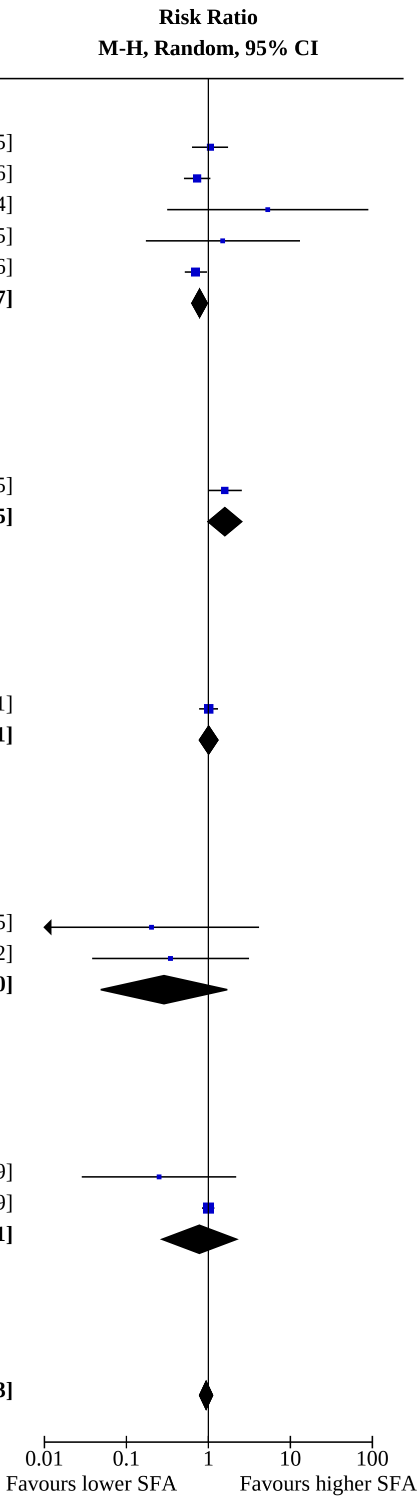


Footnotes

(1) Women with and without CVD at baseline

Analysis 1.34. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 34: CVD mortality, subgroup decade of publication

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.34.1 1960s						
MRC 1968	27	199	25	194	9.5%	1.05 [0.63 , 1.75]
Oslo Diet-Heart 1966	38	206	52	206	14.2%	0.73 [0.50 , 1.06]
Rose corn oil 1965	5	28	0	13	0.4%	5.31 [0.32 , 89.44]
Rose olive 1965	3	26	1	13	0.7%	1.50 [0.17 , 13.05]
Veterans Admin 1969	57	424	81	422	17.2%	0.70 [0.51 , 0.96]
Subtotal (95% CI)		**883**		**848**	**42.1%**	**0.78 [0.63 , 0.97]**
Total events:	130		159			
Heterogeneity: Tau² = 0.00; Chi² = 4.07, df = 4 (P = 0.40); I² = 2%						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.34.2 1970s						
Sydney Diet-Heart 1978	37	221	25	237	10.5%	1.59 [0.99 , 2.55]
Subtotal (95% CI)		**221**		**237**	**10.5%**	**1.59 [0.99 , 2.55]**
Total events:	37		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.34.3 1980s						
DART 1989	101	1018	100	1015	19.9%	1.01 [0.77 , 1.31]
Subtotal (95% CI)		**1018**		**1015**	**19.9%**	**1.01 [0.77 , 1.31]**
Total events:	101		100			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.34.4 1990s						
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
STARS 1992	1	27	3	28	0.7%	0.35 [0.04 , 3.12]
Subtotal (95% CI)		**93**		**95**	**1.1%**	**0.29 [0.05 , 1.70]**
Total events:	1		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.34.5 2000s						
Ley 2004	1	88	4	88	0.7%	0.25 [0.03 , 2.19]
WHI 2006 (1)	213	19541	320	29294	25.7%	1.00 [0.84 , 1.19]
Subtotal (95% CI)		**19629**		**29382**	**26.5%**	**0.78 [0.27 , 2.21]**
Total events:	214		324			
Heterogeneity: Tau² = 0.34; Chi² = 1.55, df = 1 (P = 0.21); I² = 36%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**21844**		**31577**	**100.0%**	**0.94 [0.78 , 1.13]**
Total events:	483		613			
Heterogeneity: Tau² = 0.03; Chi² = 15.67, df = 10 (P = 0.11); I² = 36%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Test for subgroup differences: Chi² = 9.48, df = 4 (P = 0.05), I² = 57.8%						

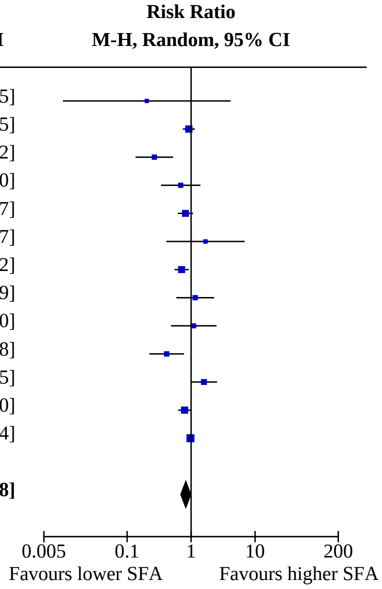


Footnotes

(1) Women with and without CVD at baseline

Analysis 1.35. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 35: COMBINED CARDIOVASCULAR EVENTS

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	13.6%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	4.7%	0.27 [0.14 , 0.52]
Ley 2004	11	88	16	88	4.4%	0.69 [0.34 , 1.40]
MRC 1968	62	199	74	194	12.0%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	1.4%	1.68 [0.41 , 6.87]
Oslo Diet-Heart 1966	64	206	90	206	12.5%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	4.7%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.5%	1.10 [0.48 , 2.50]
STARS 1992	8	27	20	28	5.3%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	7.5%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	13.2%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1399	19541	2145	29294	16.8%	0.98 [0.92 , 1.04]
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	1853		2685			

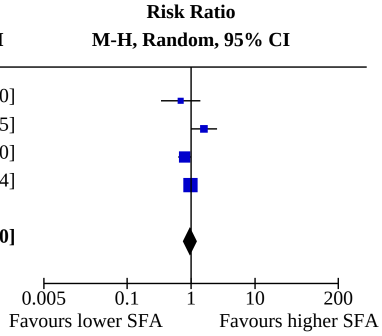


Heterogeneity: Tau² = 0.04; Chi² = 36.65, df = 12 (P = 0.0003); I² = 67%
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable

Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.36. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 36: CVD events, SA low summary risk of bias

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	11	88	16	88	8.4%	0.69 [0.34 , 1.40]
Sydney Diet-Heart 1978	37	221	25	237	15.3%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	31.4%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1399	19541	2145	29294	44.9%	0.98 [0.92 , 1.04]
Total (95% CI)		**20274**		**30041**	**100.0%**	**0.96 [0.76 , 1.20]**
Total events:	1544		2308			

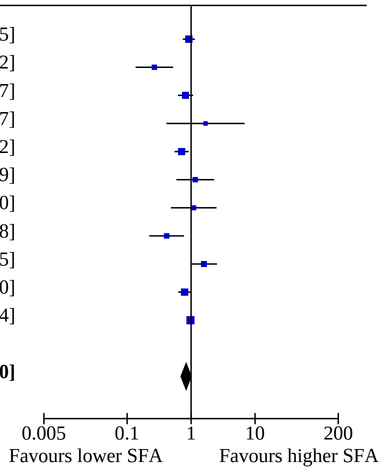


Heterogeneity: Tau² = 0.03; Chi² = 8.14, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.37. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 37: CVD events, SA aim to reduce SFA

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	136	1018	147	1015	14.2%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	5.0%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	12.6%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	1.5%	1.68 [0.41 , 6.87]
Oslo Diet-Heart 1966	64	206	90	206	13.1%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	5.0%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.8%	1.10 [0.48 , 2.50]
STARS 1992	8	27	20	28	5.6%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	7.9%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	13.8%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1399	19541	2145	29294	17.5%	0.98 [0.92 , 1.04]
Total (95% CI)		**21858**		**31591**	**100.0%**	**0.84 [0.70 , 1.00]**
Total events:	1842		2667			

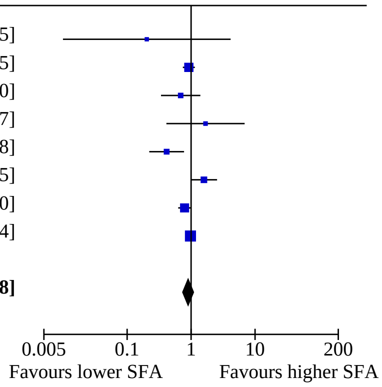


Heterogeneity: Tau² = 0.05; Chi² = 34.96, df = 10 (P = 0.0001); I² = 71%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable

Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.38. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 38: CVD events, SA statistically significant SFA reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	0	66	2	67	0.4%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	22.4%	0.92 [0.74 , 1.15]
Ley 2004	11	88	16	88	5.8%	0.69 [0.34 , 1.40]
Moy 2001	5	117	3	118	1.7%	1.68 [0.41 , 6.87]
STARS 1992	8	27	20	28	7.0%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	10.6%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	21.5%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1399	19541	2145	29294	30.6%	0.98 [0.92 , 1.04]
Total (95% CI)		**21502**		**31269**	**100.0%**	**0.90 [0.74 , 1.08]**
Total events:	1693		2480			



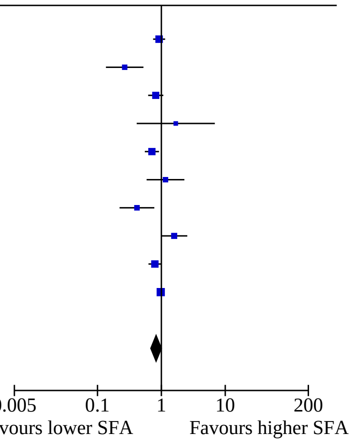
Heterogeneity: Tau² = 0.03; Chi² = 16.87, df = 7 (P = 0.02); I² = 58%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable

Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.39. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 39: CVD events, SA TC reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	136	1018	147	1015	14.7%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	5.3%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	13.1%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	1.6%	1.68 [0.41 , 6.87]
Oslo Diet-Heart 1966	64	206	90	206	13.6%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	5.3%	1.16 [0.59 , 2.29]
STARS 1992	8	27	20	28	5.9%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	8.4%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	14.3%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1399	19541	2145	29294	17.9%	0.98 [0.92 , 1.04]
Total (95% CI)		**21832**		**31578**	**100.0%**	**0.83 [0.69 , 1.00]**
Total events:	1831		2662			

Heterogeneity: Tau² = 0.05; Chi² = 34.81, df = 9 (P < 0.0001); I² = 74%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable

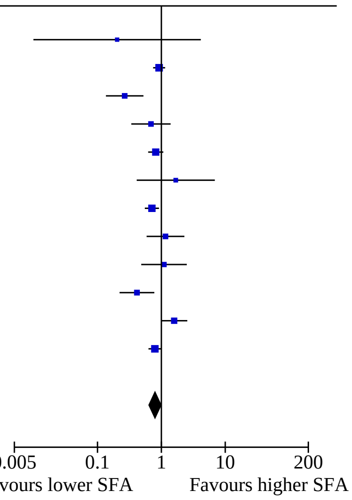


Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.40. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 40: CVD events, SA excluding WHI

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	0	66	2	67	0.5%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	15.0%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	6.3%	0.27 [0.14 , 0.52]
Ley 2004	11	88	16	88	6.0%	0.69 [0.34 , 1.40]
MRC 1968	62	199	74	194	13.7%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	2.0%	1.68 [0.41 , 6.87]
Oslo Diet-Heart 1966	64	206	90	206	14.1%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	6.3%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	4.9%	1.10 [0.48 , 2.50]
STARS 1992	8	27	20	28	7.0%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	9.4%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	14.7%	0.79 [0.63 , 1.00]
Total (95% CI)		**2471**		**2452**	**100.0%**	**0.79 [0.64 , 0.98]**
Total events:	454		540			

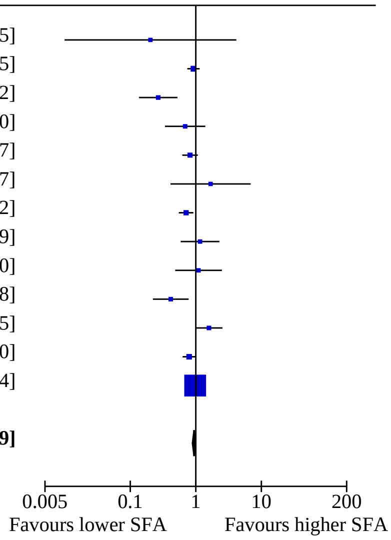
Heterogeneity: Tau² = 0.07; Chi² = 28.58, df = 11 (P = 0.003); I² = 62%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.41. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 41: CVD events, SA Mantel-Haenszel fixed-effect

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Black 1994	0	66	2	67	0.1%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	6.5%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	1.3%	0.27 [0.14 , 0.52]
Ley 2004	11	88	16	88	0.7%	0.69 [0.34 , 1.40]
MRC 1968	62	199	74	194	3.3%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	0.1%	1.68 [0.41 , 6.87]
Oslo Diet-Heart 1966	64	206	90	206	4.0%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	0.4%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	0.3%	1.10 [0.48 , 2.50]
STARS 1992	8	27	20	28	0.9%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	1.1%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	5.4%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1399	19541	2145	29294	75.9%	0.98 [0.92 , 1.04]
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.94 [0.89 , 0.99]**
Total events:	1853		2685			

Heterogeneity: Chi² = 36.65, df = 12 (P = 0.0003); I² = 67%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable

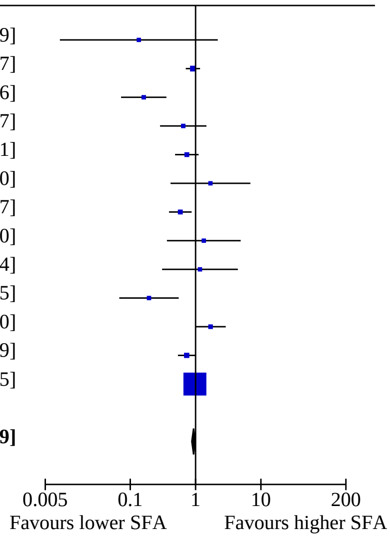


Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.42. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 42: CVD events, SA Peto fixed-effect

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Black 1994	0	66	2	67	0.1%	0.14 [0.01 , 2.19]
DART 1989	136	1018	147	1015	6.3%	0.91 [0.71 , 1.17]
Houtsmuller 1979	8	51	30	51	0.6%	0.16 [0.07 , 0.36]
Ley 2004	11	88	16	88	0.6%	0.65 [0.29 , 1.47]
MRC 1968	62	199	74	194	2.3%	0.73 [0.49 , 1.11]
Moy 2001	5	117	3	118	0.2%	1.69 [0.41 , 6.90]
Oslo Diet-Heart 1966	64	206	90	206	2.5%	0.58 [0.39 , 0.87]
Rose corn oil 1965	15	28	6	13	0.2%	1.34 [0.36 , 4.90]
Rose olive 1965	11	26	5	13	0.2%	1.17 [0.31 , 4.44]
STARS 1992	8	27	20	28	0.4%	0.19 [0.07 , 0.55]
Sydney Diet-Heart 1978	37	221	25	237	1.4%	1.70 [0.99 , 2.90]
Veterans Admin 1969	97	424	122	422	4.2%	0.73 [0.54 , 0.99]
WHI 2006 (1)	1399	19541	2145	29294	81.1%	0.98 [0.91 , 1.05]
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.93 [0.88 , 0.99]**
Total events:	1853		2685			

Heterogeneity: Chi² = 46.40, df = 12 (P < 0.00001); I² = 74%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable

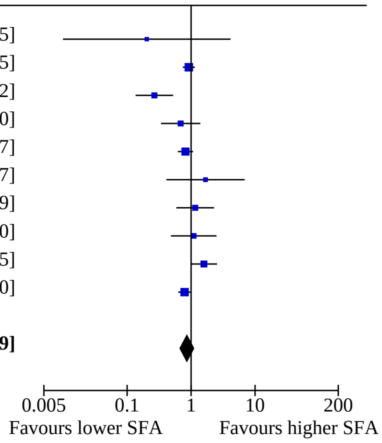


Footnotes
(1) Total CVD during study period, Prentice 2017

Analysis 1.43. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 43: CVD events, SA excluding trials with additional interventions

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Black 1994	0	66	2	67	0.6%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	18.9%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	8.1%	0.27 [0.14 , 0.52]
Ley 2004	11	88	16	88	7.6%	0.69 [0.34 , 1.40]
MRC 1968	62	199	74	194	17.4%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	2.6%	1.68 [0.41 , 6.87]
Rose corn oil 1965	15	28	6	13	8.0%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	6.2%	1.10 [0.48 , 2.50]
Sydney Diet-Heart 1978	37	221	25	237	12.0%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	18.6%	0.79 [0.63 , 1.00]
Total (95% CI)		**2238**		**2218**	**100.0%**	**0.86 [0.67 , 1.09]**
Total events:	382		430			

Risk Ratio M-H, Random, 95% CI

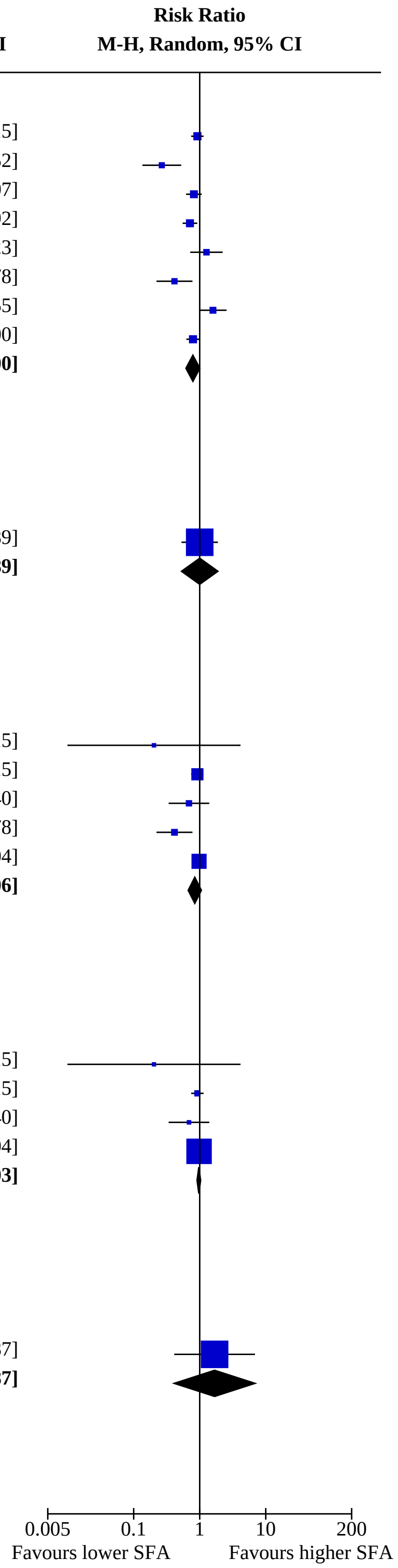


Heterogeneity: Tau² = 0.07; Chi² = 22.22, df = 9 (P = 0.008); I² = 59%
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable

Analysis 1.44. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 44: CVD events, subgroup by any substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.44.1 replaced by PUFA						
DART 1989	136	1018	147	1015	16.5%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	7.7%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	15.3%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	15.7%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	11	26	9.3%	1.27 [0.72 , 2.23]
STARS 1992	8	27	20	28	8.4%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	11.0%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	16.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**2174**		**2179**	**100.0%**	**0.79 [0.62 , 1.00]**
Total events:	427		519			
Heterogeneity: Tau² = 0.08; Chi² = 27.31, df = 7 (P = 0.0003); I² = 74%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.44.2 replaced by MUFA						
Rose olive 1965	11	26	11	26	100.0%	1.00 [0.53 , 1.89]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.00 [0.53 , 1.89]**
Total events:	11		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.44.3 replace by CHO						
Black 1994	0	66	2	67	0.6%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	33.8%	0.92 [0.74 , 1.15]
Ley 2004	11	88	16	88	8.6%	0.69 [0.34 , 1.40]
STARS 1992	8	27	20	28	10.5%	0.41 [0.22 , 0.78]
WHI 2006 (1)	1399	19541	2145	29294	46.5%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**20740**		**30492**	**100.0%**	**0.84 [0.67 , 1.06]**
Total events:	1554		2330			
Heterogeneity: Tau² = 0.03; Chi² = 9.20, df = 4 (P = 0.06); I² = 57%						
Test for overall effect: Z = 1.46 (P = 0.14)						
1.44.4 replaced by protein						
Black 1994	0	66	2	67	0.0%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	8.2%	0.92 [0.74 , 1.15]
Ley 2004	11	88	16	88	0.8%	0.69 [0.34 , 1.40]
WHI 2006 (1)	1399	19541	2145	29294	91.0%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**20713**		**30464**	**100.0%**	**0.97 [0.91 , 1.03]**
Total events:	1546		2310			
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.44.5 replacement unclear						
Moy 2001	5	117	3	118	100.0%	1.68 [0.41 , 6.87]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**1.68 [0.41 , 6.87]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						

Test for subgroup differences: Chi² = 4.40, df = 4 (P = 0.35), I² = 9.2%



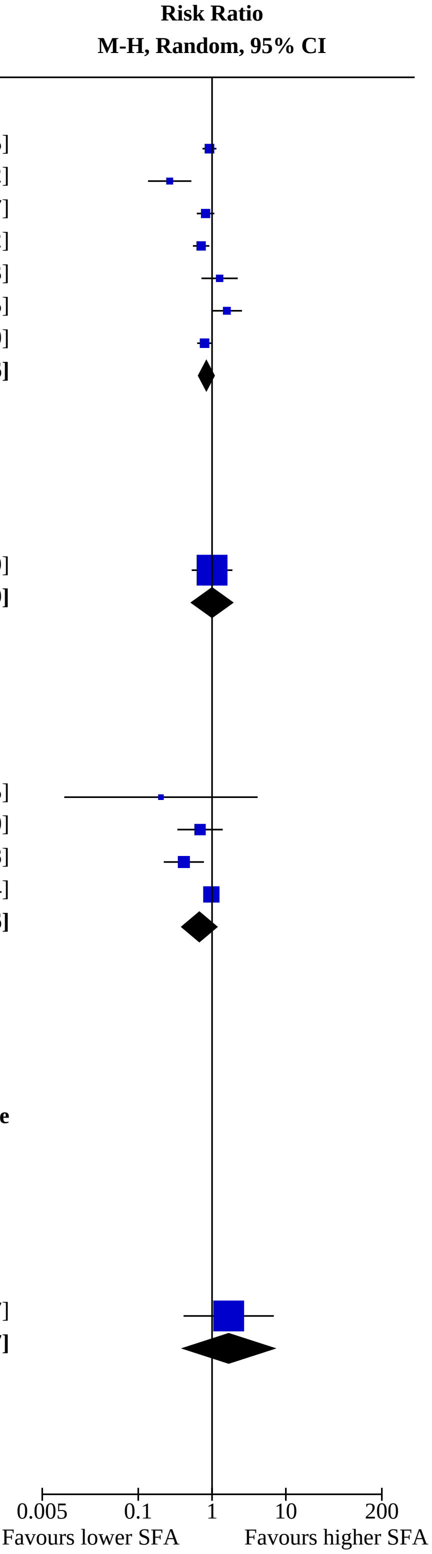
Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.45. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 45: CVD events, subgroup by main substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.45.1 replaced by PUFA						
DART 1989	136	1018	147	1015	18.4%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	7.9%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	16.9%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	17.3%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	11	26	9.8%	1.27 [0.72 , 2.23]
Sydney Diet-Heart 1978	37	221	25	237	11.7%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	18.0%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**2147**		**2151**	**100.0%**	**0.84 [0.66 , 1.06]**
Total events:	419		499			
Heterogeneity: Tau² = 0.07; Chi² = 22.66, df = 6 (P = 0.0009); I² = 74%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.45.2 replaced by MUFA						
Rose olive 1965	11	26	11	26	100.0%	1.00 [0.53 , 1.89]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.00 [0.53 , 1.89]**
Total events:	11		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.45.3 replace by CHO						
Black 1994	0	66	2	67	3.0%	0.20 [0.01 , 4.15]
Ley 2004	11	88	16	88	25.2%	0.69 [0.34 , 1.40]
STARS 1992	8	27	20	28	27.8%	0.41 [0.22 , 0.78]
WHI 2006 (1)	1399	19541	2145	29294	44.1%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**19722**		**29477**	**100.0%**	**0.67 [0.39 , 1.16]**
Total events:	1418		2183			
Heterogeneity: Tau² = 0.17; Chi² = 9.04, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.45.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.45.5 replacement unclear						
Moy 2001	5	117	3	118	100.0%	1.68 [0.41 , 6.87]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**1.68 [0.41 , 6.87]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						

Test for subgroup differences: Chi² = 1.87, df = 3 (P = 0.60), I² = 0%

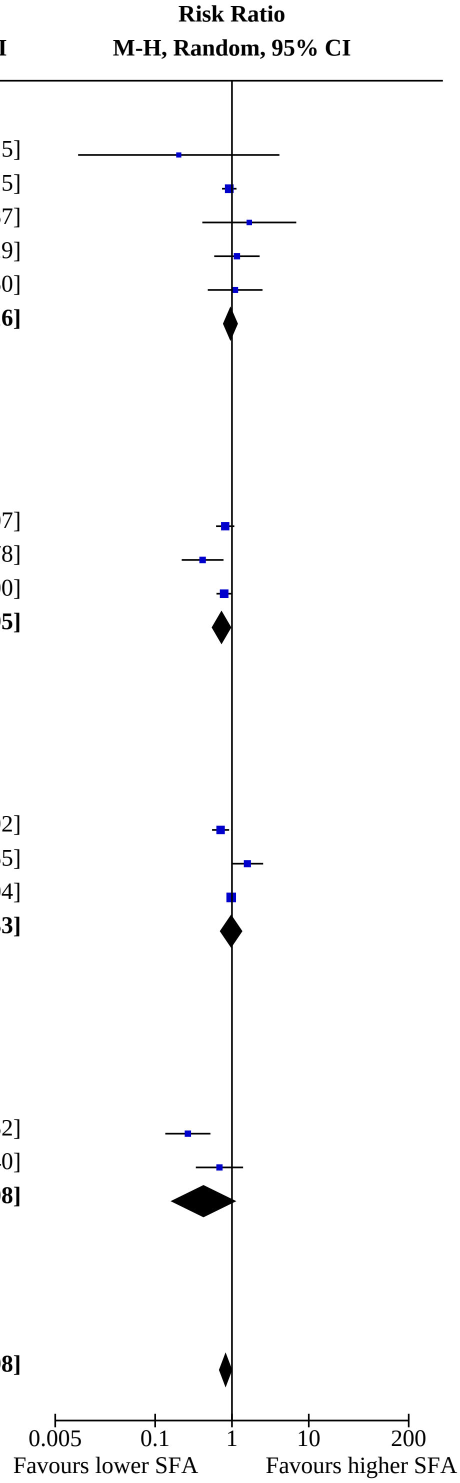


Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.46. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 46: CVD events, subgroup by duration

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.46.1 up to 24mo						
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	13.6%	0.92 [0.74 , 1.15]
Moy 2001	5	117	3	118	1.4%	1.68 [0.41 , 6.87]
Rose corn oil 1965	15	28	6	13	4.7%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.5%	1.10 [0.48 , 2.50]
Subtotal (95% CI)		**1255**		**1226**	**23.5%**	**0.96 [0.78 , 1.16]**
Total events:	167		163			
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 4 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.46.2 >24 to 48mo						
MRC 1968	62	199	74	194	12.0%	0.82 [0.62 , 1.07]
STARS 1992	8	27	20	28	5.3%	0.41 [0.22 , 0.78]
Veterans Admin 1969	97	424	122	422	13.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**650**		**644**	**30.5%**	**0.73 [0.56 , 0.95]**
Total events:	167		216			
Heterogeneity: Tau² = 0.03; Chi² = 3.97, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 2.31 (P = 0.02)						
1.46.3 >48mo						
Oslo Diet-Heart 1966	64	206	90	206	12.5%	0.71 [0.55 , 0.92]
Sydney Diet-Heart 1978	37	221	25	237	7.5%	1.59 [0.99 , 2.55]
WHI 2006 (1)	1399	19541	2145	29294	16.8%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**19968**		**29737**	**36.9%**	**0.97 [0.72 , 1.33]**
Total events:	1500		2260			
Heterogeneity: Tau² = 0.06; Chi² = 9.90, df = 2 (P = 0.007); I² = 80%						
Test for overall effect: Z = 0.16 (P = 0.87)						
1.46.4 unclear duration						
Houtsmuller 1979	8	51	30	51	4.7%	0.27 [0.14 , 0.52]
Ley 2004	11	88	16	88	4.4%	0.69 [0.34 , 1.40]
Subtotal (95% CI)		**139**		**139**	**9.1%**	**0.43 [0.17 , 1.08]**
Total events:	19		46			
Heterogeneity: Tau² = 0.32; Chi² = 3.59, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	1853		2685			
Heterogeneity: Tau² = 0.04; Chi² = 36.65, df = 12 (P = 0.0003); I² = 67%						
Test for overall effect: Z = 2.17 (P = 0.03)						
Test for subgroup differences: Chi² = 5.30, df = 3 (P = 0.15), I² = 43.4%						

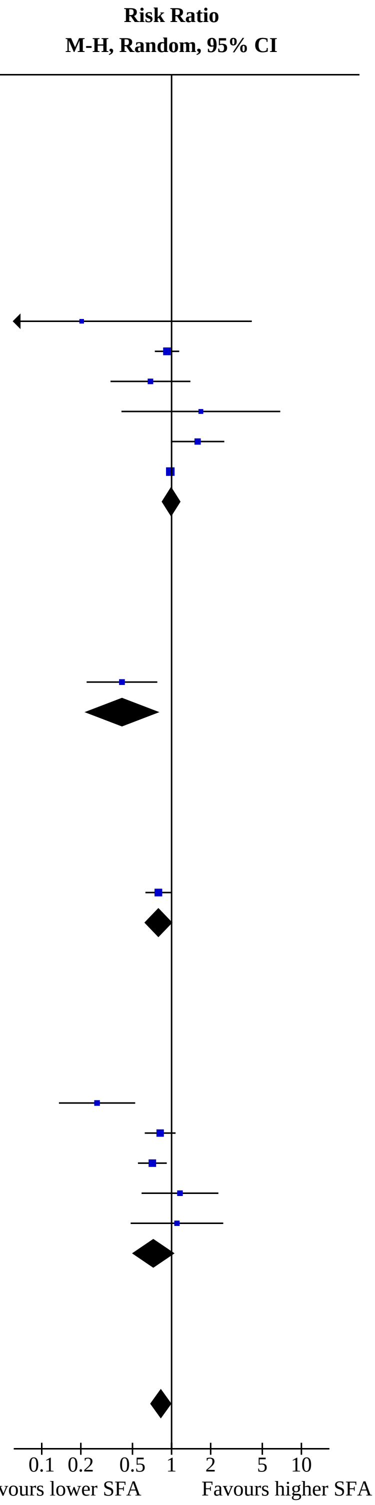


Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.47. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 47: CVD events, subgroup by baseline SFA

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.47.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.47.2 >12 to 15%E SFA baseline						
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	13.6%	0.92 [0.74 , 1.15]
Ley 2004	11	88	16	88	4.4%	0.69 [0.34 , 1.40]
Moy 2001	5	117	3	118	1.4%	1.68 [0.41 , 6.87]
Sydney Diet-Heart 1978	37	221	25	237	7.5%	1.59 [0.99 , 2.55]
WHI 2006 (1)	1399	19541	2145	29294	16.8%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**21051**		**30819**	**44.0%**	**0.99 [0.85 , 1.15]**
Total events:	1588		2338			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.86$, df = 5 (P = 0.23); $I^2 = 27\%$						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.47.3 >15 to 18%E SFA baseline						
STARS 1992	8	27	20	28	5.3%	0.41 [0.22 , 0.78]
Subtotal (95% CI)		**27**		**28**	**5.3%**	**0.41 [0.22 , 0.78]**
Total events:	8		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.75 (P = 0.006)						
1.47.4 >18%E SFA baseline						
Veterans Admin 1969	97	424	122	422	13.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**424**		**422**	**13.2%**	**0.79 [0.63 , 1.00]**
Total events:	97		122			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.47.5 unclear						
Houtsmuller 1979	8	51	30	51	4.7%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	12.0%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	12.5%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	4.7%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.5%	1.10 [0.48 , 2.50]
Subtotal (95% CI)		**510**		**477**	**37.5%**	**0.72 [0.51 , 1.03]**
Total events:	160		205			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 12.08$, df = 4 (P = 0.02); $I^2 = 67\%$						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	1853		2685			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 36.65$, df = 12 (P = 0.0003); $I^2 = 67\%$						
Test for overall effect: Z = 2.17 (P = 0.03)						
Test for subgroup differences: $Chi^2 = 9.90$, df = 3 (P = 0.02), $I^2 = 69.7\%$						

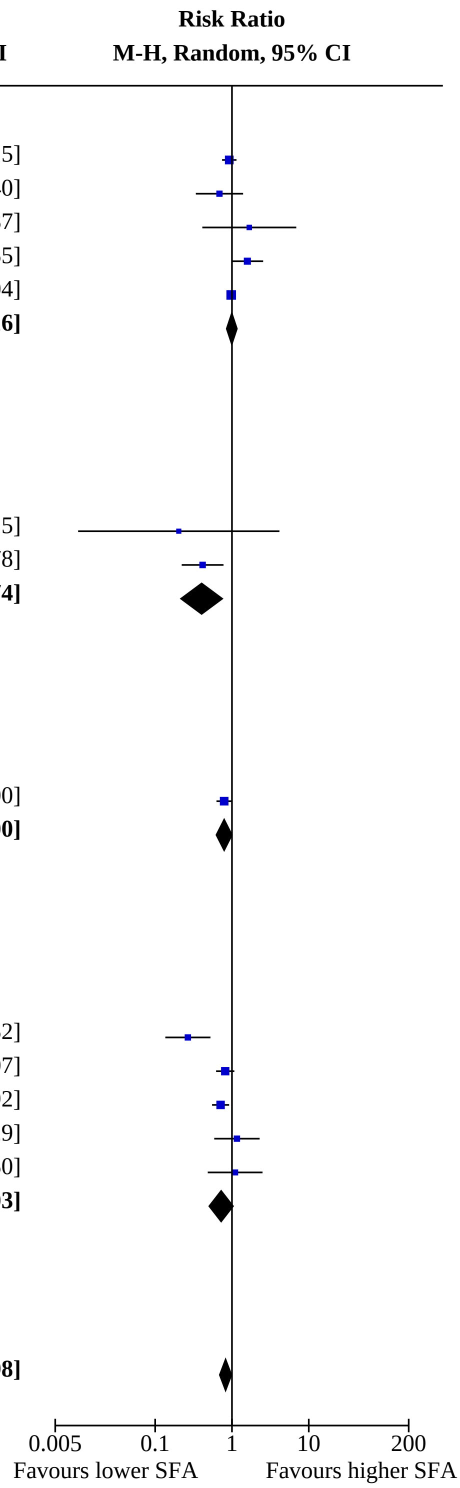


Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.48. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 48: CVD events, subgroup by SFA change

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.48.1 up to 4%E difference						
DART 1989	136	1018	147	1015	13.6%	0.92 [0.74 , 1.15]
Ley 2004	11	88	16	88	4.4%	0.69 [0.34 , 1.40]
Moy 2001	5	117	3	118	1.4%	1.68 [0.41 , 6.87]
Sydney Diet-Heart 1978	37	221	25	237	7.5%	1.59 [0.99 , 2.55]
WHI 2006 (1)	1399	19541	2145	29294	16.8%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**20985**		**30752**	**43.7%**	**1.00 [0.86 , 1.16]**
Total events:	1588		2336			
Heterogeneity: Tau² = 0.01; Chi² = 5.82, df = 4 (P = 0.21); I² = 31%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.48.2 >4 to 8%E difference						
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
STARS 1992	8	27	20	28	5.3%	0.41 [0.22 , 0.78]
Subtotal (95% CI)		**93**		**95**	**5.6%**	**0.40 [0.22 , 0.74]**
Total events:	8		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.90 (P = 0.004)						
1.48.3 >8%E difference						
Veterans Admin 1969	97	424	122	422	13.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**424**		**422**	**13.2%**	**0.79 [0.63 , 1.00]**
Total events:	97		122			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.48.4 unclear						
Houtsmuller 1979	8	51	30	51	4.7%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	12.0%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	12.5%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	4.7%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.5%	1.10 [0.48 , 2.50]
Subtotal (95% CI)		**510**		**477**	**37.5%**	**0.72 [0.51 , 1.03]**
Total events:	160		205			
Heterogeneity: Tau² = 0.09; Chi² = 12.08, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	1853		2685			
Heterogeneity: Tau² = 0.04; Chi² = 36.65, df = 12 (P = 0.0003); I² = 67%						
Test for overall effect: Z = 2.17 (P = 0.03)						
Test for subgroup differences: Chi² = 10.78, df = 3 (P = 0.01), I² = 72.2%						

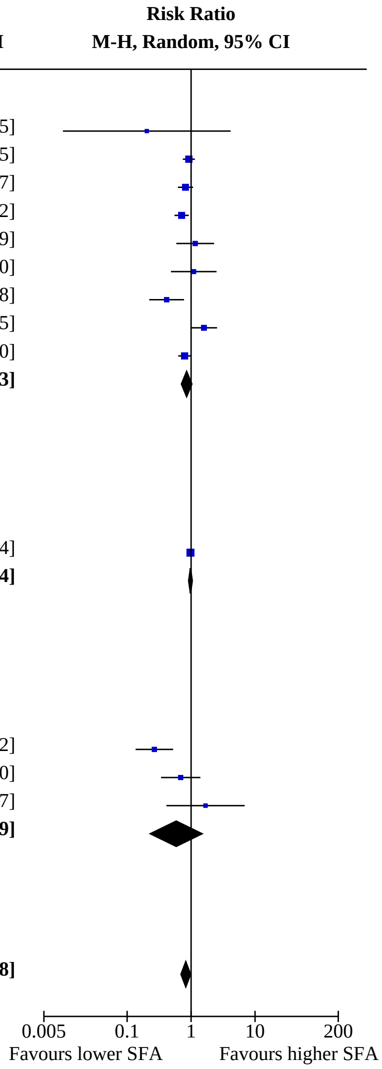


Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.49. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 49: CVD events, subgroup by sex

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.49.1 Men						
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
DART 1989	136	1018	147	1015	13.6%	0.92 [0.74 , 1.15]
MRC 1968	62	199	74	194	12.0%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	12.5%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	4.7%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.5%	1.10 [0.48 , 2.50]
STARS 1992	8	27	20	28	5.3%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	7.5%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	13.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**2215**		**2195**	**72.6%**	**0.85 [0.71 , 1.03]**
Total events:	430		491			
Heterogeneity: Tau² = 0.04; Chi² = 16.65, df = 8 (P = 0.03); I² = 52%						
Test for overall effect: Z = 1.67 (P = 0.09)						
1.49.2 Women						
WHI 2006 (1)	1399	19541	2145	29294	16.8%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**19541**		**29294**	**16.8%**	**0.98 [0.92 , 1.04]**
Total events:	1399		2145			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.49.3 Mixed, men and women						
Houtsmuller 1979	8	51	30	51	4.7%	0.27 [0.14 , 0.52]
Ley 2004	11	88	16	88	4.4%	0.69 [0.34 , 1.40]
Moy 2001	5	117	3	118	1.4%	1.68 [0.41 , 6.87]
Subtotal (95% CI)		**256**		**257**	**10.5%**	**0.59 [0.23 , 1.49]**
Total events:	24		49			
Heterogeneity: Tau² = 0.46; Chi² = 6.93, df = 2 (P = 0.03); I² = 71%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	1853		2685			
Heterogeneity: Tau² = 0.04; Chi² = 36.65, df = 12 (P = 0.0003); I² = 67%						
Test for overall effect: Z = 2.17 (P = 0.03)						
Test for subgroup differences: Chi² = 2.94, df = 2 (P = 0.23), I² = 32.0%						

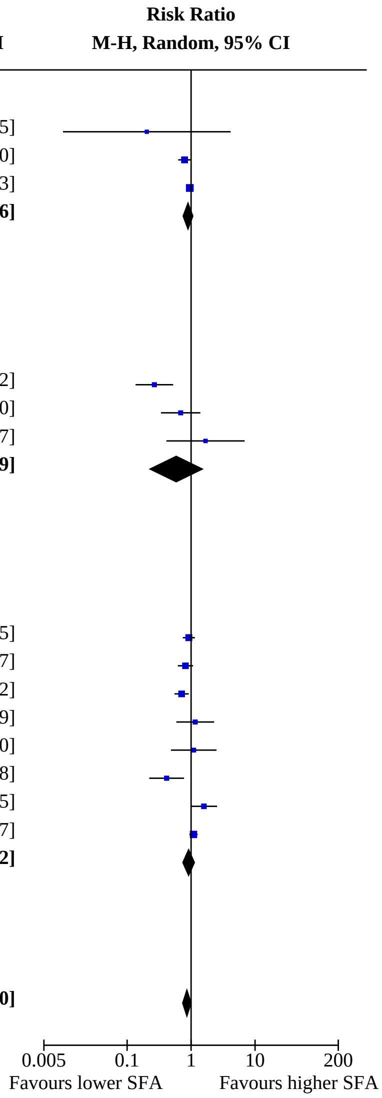


Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.50. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 50: CVD events, subgroup by CVD risk

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.50.1 Low CVD risk						
Black 1994	0	66	2	67	0.2%	0.20 [0.01 , 4.15]
Veterans Admin 1969	97	424	122	422	11.7%	0.79 [0.63 , 1.00]
WHI 2006 (1)	1132	18633	1777	27925	15.7%	0.95 [0.89 , 1.03]
Subtotal (95% CI)		**19123**		**28414**	**27.7%**	**0.89 [0.75 , 1.06]**
Total events:	1229		1901			
Heterogeneity: Tau² = 0.01; Chi² = 3.32, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 1.28 (P = 0.20)						
1.50.2 Moderate CVD risk						
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]
Subtotal (95% CI)		**256**		**257**	**8.2%**	**0.59 [0.23 , 1.49]**
Total events:	24		49			
Heterogeneity: Tau² = 0.46; Chi² = 6.93, df = 2 (P = 0.03); I² = 71%						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.50.3 Existing CVD disease						
DART 1989	136	1018	147	1015	12.1%	0.92 [0.74 , 1.15]
MRC 1968	62	199	74	194	10.5%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	11.0%	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	4.1%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	6.1%	1.59 [0.99 , 2.55]
WHI 2006 (2)	225	908	311	1369	14.0%	1.09 [0.94 , 1.27]
Subtotal (95% CI)		**2633**		**3075**	**64.2%**	**0.91 [0.75 , 1.12]**
Total events:	558		678			
Heterogeneity: Tau² = 0.05; Chi² = 21.20, df = 7 (P = 0.003); I² = 67%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.86 [0.74 , 1.00]**
Total events:	1811		2628			
Heterogeneity: Tau² = 0.03; Chi² = 39.17, df = 13 (P = 0.0002); I² = 67%						
Test for overall effect: Z = 2.01 (P = 0.04)						
Test for subgroup differences: Chi² = 0.84, df = 2 (P = 0.66), I² = 0%						



Footnotes

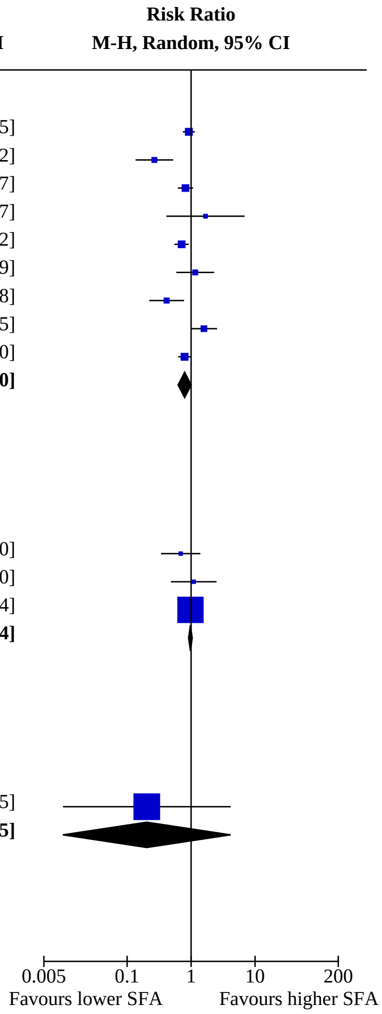
(1) Women without CVD at baseline

(2) Women with CVD at baseline

Analysis 1.51. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 51: CVD events, subgroup by TC reduction

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.51.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	136	1018	147	1015	16.5%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	7.5%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	15.3%	0.82 [0.62 , 1.07]
Moy 2001	5	117	3	118	2.5%	1.68 [0.41 , 6.87]
Oslo Diet-Heart 1966	64	206	90	206	15.7%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	7.4%	1.16 [0.59 , 2.29]
STARS 1992	8	27	20	28	8.2%	0.41 [0.22 , 0.78]
Sydney Diet-Heart 1978	37	221	25	237	10.8%	1.59 [0.99 , 2.55]
Veterans Admin 1969	97	424	122	422	16.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**2291**		**2284**	**100.0%**	**0.79 [0.63 , 1.00]**
Total events:	432		517			
Heterogeneity: Tau² = 0.08; Chi² = 27.05, df = 8 (P = 0.0007); I² = 70%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.51.2 serum chol reduced by <0.2mmol/L						
Ley 2004	11	88	16	88	0.8%	0.69 [0.34 , 1.40]
Rose olive 1965	11	26	5	13	0.6%	1.10 [0.48 , 2.50]
WHI 2006 (1)	1399	19541	2145	29294	98.6%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**19655**		**29395**	**100.0%**	**0.98 [0.91 , 1.04]**
Total events:	1421		2166			
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.45)						
1.51.3 serum chol reduction unclear						
Black 1994	0	66	2	67	100.0%	0.20 [0.01 , 4.15]
Subtotal (95% CI)		**66**		**67**	**100.0%**	**0.20 [0.01 , 4.15]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						

Test for subgroup differences: Chi² = 3.77, df = 2 (P = 0.15), I² = 47.0%

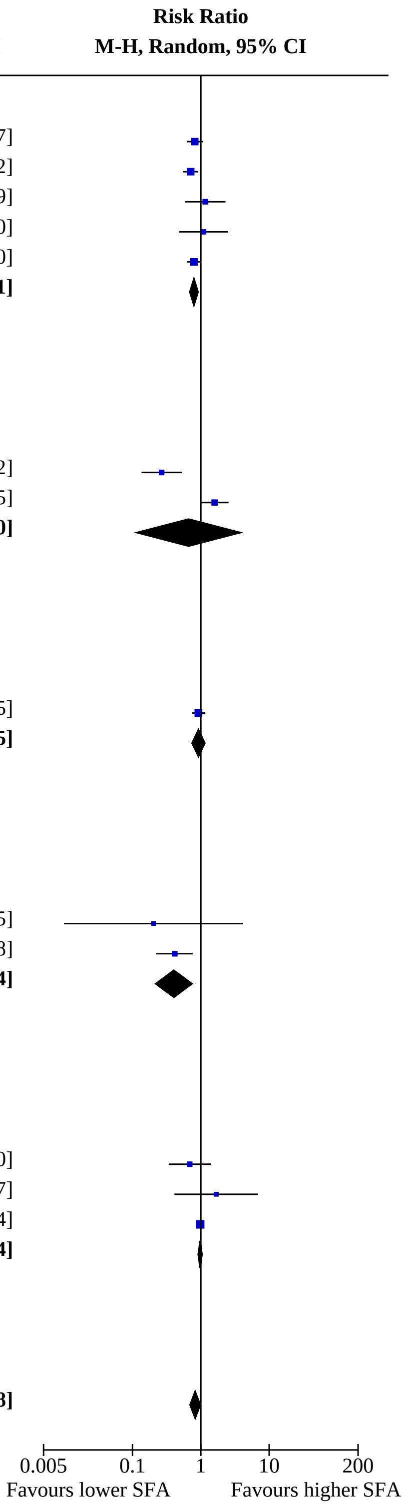


Footnotes

(1) Total CVD during study period, Prentice 2017

Analysis 1.52. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 52: CVD events, subgroup decade of publication

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.52.1 1960s						
MRC 1968	62	199	74	194	12.0%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	12.5%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	6	13	4.7%	1.16 [0.59 , 2.29]
Rose olive 1965	11	26	5	13	3.5%	1.10 [0.48 , 2.50]
Veterans Admin 1969	97	424	122	422	13.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**883**		**848**	**46.0%**	**0.79 [0.69 , 0.91]**
Total events:	249		297			
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 3.25 (P = 0.001)						
1.52.2 1970s						
Houtsmuller 1979	8	51	30	51	4.7%	0.27 [0.14 , 0.52]
Sydney Diet-Heart 1978	37	221	25	237	7.5%	1.59 [0.99 , 2.55]
Subtotal (95% CI)		**272**		**288**	**12.2%**	**0.66 [0.12 , 3.80]**
Total events:	45		55			
Heterogeneity: Tau² = 1.50; Chi² = 17.96, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 0.46 (P = 0.64)						
1.52.3 1980s						
DART 1989	136	1018	147	1015	13.6%	0.92 [0.74 , 1.15]
Subtotal (95% CI)		**1018**		**1015**	**13.6%**	**0.92 [0.74 , 1.15]**
Total events:	136		147			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
1.52.4 1990s						
Black 1994	0	66	2	67	0.3%	0.20 [0.01 , 4.15]
STARS 1992	8	27	20	28	5.3%	0.41 [0.22 , 0.78]
Subtotal (95% CI)		**93**		**95**	**5.6%**	**0.40 [0.22 , 0.74]**
Total events:	8		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.90 (P = 0.004)						
1.52.5 2000s						
Ley 2004	11	88	16	88	4.4%	0.69 [0.34 , 1.40]
Moy 2001	5	117	3	118	1.4%	1.68 [0.41 , 6.87]
WHI 2006 (1)	1399	19541	2145	29294	16.8%	0.98 [0.92 , 1.04]
Subtotal (95% CI)		**19746**		**29500**	**22.6%**	**0.98 [0.91 , 1.04]**
Total events:	1415		2164			
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**22012**		**31746**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	1853		2685			
Heterogeneity: Tau² = 0.04; Chi² = 36.65, df = 12 (P = 0.0003); I² = 67%						
Test for overall effect: Z = 2.17 (P = 0.03)						
Test for subgroup differences: Chi² = 14.43, df = 4 (P = 0.006), I² = 72.3%						



Footnotes

(1) Total CVD during study period, Prentice 2017

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 MYOCARDIAL INFARCTION	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.2 MI, SA by low summary risk of bias	3	49857	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.08]
2.3 MI, SA aim to reduce SFA	10	52991	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.02]
2.4 MI, SA statistically significant SFA reduction	6	52180	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
2.5 MI, SA by TC reduction	9	52952	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.01]
2.6 MI, SA excluding WHI	10	4332	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 0.98]
2.7 MI, SA Mantel-Haenszel fixed-effect	11	53167	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.84, 1.01]
2.8 MI, SA Peto fixed-effect	11	53167	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.83, 1.01]
2.9 MI, subgroup by any substitution	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.9.1 replaced by PUFA	7	3895	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.67, 1.02]
2.9.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.51, 3.85]
2.9.3 replace by CHO	4	51099	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.06]
2.9.4 replaced by protein	3	51044	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.07]
2.9.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.19, 21.94]
2.10 MI, subgroup by main substitution	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.10.1 replaced by PUFA	6	3840	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.67, 1.04]
2.10.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.51, 3.85]
2.10.3 replace by CHO	3	49066	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
2.10.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.10.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.19, 21.94]
2.11 MI, subgroup by duration	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.11.1 up to 24mo	4	2348	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.77, 1.17]
2.11.2 >24 to 48mo	3	1294	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.64, 1.06]
2.11.3 >48mo	2	49247	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.54, 1.24]
2.11.4 unclear	2	278	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.02, 7.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.12 MI, subgroup by baseline SFA	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.12.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.12.2 >12 to 15%E SFA baseline	4	51279	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.07]
2.12.3 >15 to 18%E SFA baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.39]
2.12.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.55, 1.05]
2.12.5 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.30]
2.13 MI, subgroup by SFA change	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.13.1 up to 4%E difference	4	51279	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.07]
2.13.2 >4 to 8%E difference	1	55	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.39]
2.13.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.55, 1.05]
2.13.4 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.30]
2.14 MI, subgroup by sex	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.14.1 Men	7	3819	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 0.98]
2.14.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
2.14.3 Mixed, men and women	3	513	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.13, 4.47]
2.15 MI, subgroup by CVD risk	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.15.1 Low CVD risk	2	49681	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.13]
2.15.2 Moderate CVD risk	3	513	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.13, 4.47]
2.15.3 Existing CVD disease	6	2973	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.03]
2.16 MI, subgroup by TC reduction	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.16.1 serum chol reduced by at least 0.2mmol/L	8	4117	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
2.16.2 serum chol reduced by <0.2mmol/L	3	49050	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.87, 1.10]
2.16.3 serum chol reduction unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.17 MI, subgroup decade of publication	11	53167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
2.17.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.00]
2.17.2 1970s	1	102	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.17.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.14]
2.17.4 1990s	1	55	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.39]
2.17.5 2000s	3	49246	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.87, 1.10]
2.18 NON-FATAL MYOCARDIAL INFARCTION	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.19 Non-fatal MI, SA by low summary risk of bias	2	49681	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.35]
2.20 Non-fatal MI, SA aim to reduce SFA	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.21 Non-fatal MI, SA statistically significant SFA reduction	4	51949	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.14]
2.22 Non-fatal MI, SA by TC reduction	7	52795	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.23 Non-fatal MI, SA excluding WHI	7	3999	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.04]
2.24 Non-fatal MI, SA Mantel-Haenszel fixed-effect	8	52834	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.08]
2.25 Non-fatal MI, SA Peto fixed-effect	8	52834	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.87, 1.08]
2.26 Non-fatal MI, subgroup by any substitution	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.26.1 replaced by PUFA	5	3738	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.03]
2.26.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.42, 3.45]
2.26.3 replace by CHO	2	50868	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.72, 1.21]
2.26.4 replaced by protein	2	50868	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.72, 1.21]
2.26.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.19, 21.94]
2.27 Non-fatal MI, subgroup by main substitution	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.27.1 replaced by PUFA	5	3738	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.03]
2.27.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.42, 3.45]
2.27.3 replace by CHO	1	48835	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
2.27.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.27.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.19, 21.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.28 Non-fatal MI, subgroup by duration	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.28.1 up to 24mo	4	2348	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.22]
2.28.2 >24 to 48mo	2	1239	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.53, 1.27]
2.28.3 >48mo	2	49247	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.12]
2.28.4 unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.29 Non-fatal MI, subgroup by baseline SFA	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.29.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.29.2 >12 to 15%E SFA baseline	3	51103	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.13]
2.29.3 >15 to 18%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.29.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.31, 1.21]
2.29.5 unclear	4	885	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.65, 1.27]
2.30 Non-fatal MI, subgroup by SFA change	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.30.1 up to 4%E difference	3	51103	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.13]
2.30.2 >4 to 8%E difference	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.30.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.31, 1.21]
2.30.4 unclear	4	885	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.65, 1.27]
2.31 Non-fatal MI, subgroup by sex	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.31.1 Men	6	3764	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.03]
2.31.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
2.31.3 Mixed, men and women	1	235	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.19, 21.94]
2.32 Non-fatal MI, subgroup by CVD risk	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.13]
2.32.1 Low CVD risk	2	47404	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.68, 1.12]
2.32.2 Moderate CVD risk	1	235	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.19, 21.94]
2.32.3 Existing CVD disease	6	5195	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.76, 1.31]
2.33 Non-fatal MI, subgroup by TC reduction	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.33.1 serum chol reduced by at least 0.2mmol/L	6	3960	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.03]
2.33.2 serum chol reduced by <0.2mmol/L	2	48874	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
2.33.3 serum chol reduction unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.34 Non-fatal MI, subgroup decade of publication	8	52834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.34.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.62, 1.13]
2.34.2 1970s	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.34.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.48, 1.14]
2.34.4 1990s	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.34.5 2000s	2	49070	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
2.35 STROKE	7	50952	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.25]
2.36 Stroke, SA by low summary risk of bias	3	49857	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.42, 1.38]
2.37 Stroke, SA aim to reduce SFA	6	50776	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.14]
2.38 Stroke, SA statistically significant SFA reduction	5	50147	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.55, 1.25]
2.39 Stroke, SA by TC reduction	6	50776	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.14]
2.40 Stroke, SA excluding WHI	6	2117	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.35, 1.14]
2.41 Stroke, SA Mantel-Haenszel fixed-effect	7	50952	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.89, 1.13]
2.42 Stroke, SA Peto fixed-effect	7	50952	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.89, 1.14]
2.43 Stroke, subgroup by any substitution	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.43.1 replaced by PUFA	4	1706	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.37, 1.27]
2.43.2 replaced by MUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.43.3 replace by CHO	3	49066	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.29, 1.87]
2.43.4 replaced by protein	2	49011	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.75]
2.43.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.06, 15.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.44 Stroke, subgroup by main substitution	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.44.1 replaced by PUFA	3	1651	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.31, 2.69]
2.44.2 replaced by MUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.44.3 replace by CHO	3	49066	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.29, 1.87]
2.44.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.44.5 replacement unclear	1	235	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.06, 15.93]
2.45 Stroke, subgroup by duration	6	50559	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.23]
2.45.1 up to 24mo	1	235	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.06, 15.93]
2.45.2 >24 to 48mo	2	901	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.30, 1.11]
2.45.3 >48mo	2	49247	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]
2.45.4 unclear duration	1	176	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.02, 1.68]
2.46 Stroke, subgroup by baseline SFA	6	50559	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.23]
2.46.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.46.2 >12 to 15%E SFA baseline	3	49246	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.50, 1.66]
2.46.3 >15 to 18%E SFA baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.12]
2.46.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
2.46.5 unclear	1	412	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.18, 21.89]
2.47 Stroke, subgroup by SFA change	6	50559	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.23]
2.47.1 up to 4%E difference	3	49246	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.50, 1.66]
2.47.2 >4 to 8%E difference	1	55	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.12]
2.47.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
2.47.4 unclear	1	412	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.18, 21.89]
2.48 Stroke, subgroup by sex	6	50559	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.23]
2.48.1 Men	3	1313	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.33, 1.18]
2.48.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]
2.48.3 Mixed, men and women	2	411	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.07, 1.97]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.49 Stroke, subgroup by CVD risk	6	50559	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.11]
2.49.1 Low CVD risk	2	47404	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.52, 1.42]
2.49.2 Moderate CVD risk	2	411	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.07, 1.97]
2.49.3 Existing CVD disease	3	2744	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.86, 1.18]
2.50 Stroke, subgroup by TC reduction	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.50.1 serum chol reduced by at least 0.2mmol/L	5	1941	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.38, 1.28]
2.50.2 serum chol reduced by <0.2mmol/L	2	49011	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.75]
2.50.3 serum chol reduction unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.51 Stroke, subgroup decade of publi-cation	7	50952	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.25]
2.51.1 1960s	3	1651	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.31, 2.69]
2.51.2 1970s	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.51.3 1980s	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.51.4 1990s	1	55	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.12]
2.51.5 2000s	3	49246	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.50, 1.66]
2.52 CORONARY HEART DISEASE MOR-TALITY	9	53159	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.16]
2.53 CHD mortality, SA by low summary risk of bias	3	50139	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.43]
2.54 CHD mortality, SA aim to reduce SFA	9	53159	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.16]
2.55 CHD mortality, SA statistically sig-nificant SFA reduction	4	52172	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.84, 1.24]
2.56 CHD mortality, SA by TC reduction	8	53120	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.16]
2.57 CHD mortality, SA excluding WHI	8	4324	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.24]
2.58 CHD mortality, SA Mantel-Haenszel fixed-effect	9	53159	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.10]
2.59 CHD mortality, SA Peto fixed-effect	9	53159	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.85, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.60 CHD mortality, subgroup by any substitution	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.60.1 replaced by PUFA	7	4298	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.28]
2.60.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.99]
2.60.3 replaced by CHO	2	50868	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.16]
2.60.4 replaced by protein	2	50868	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.16]
2.60.5 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.61 CHD mortality, subgroup by main substitution	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.61.1 replaced by PUFA	7	4298	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.28]
2.61.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 26.99]
2.61.3 replaced by CHO	1	48835	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.20]
2.61.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.61.5 replacement unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.62 CHD mortality, subgroup by duration	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.62.1 up to 24mo	3	2113	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.78, 1.33]
2.62.2 >24 to 48months	2	1239	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.19]
2.62.3 >48 months	3	49705	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
2.62.4 unclear duration	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.60]
2.63 CHD mortality, subgroup by baseline SFA	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.63.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.63.2 >12% to 15%E SFA baseline	3	51326	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.34]
2.63.3 >15 to 18%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.63.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.55, 1.21]
2.63.5 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.56, 1.29]
2.64 CHD mortality, subgroup by SFA change	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.64.1 up to 4%E difference	3	51326	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.34]
2.64.2 >4 to 8%E difference	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.64.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.55, 1.21]
2.64.4 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.56, 1.29]
2.65 CHD mortality, subgroup by sex	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.65.1 Men	7	4222	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.79, 1.23]
2.65.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.20]
2.65.3 Mixed, men and women	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.60]
2.66 CHD mortality, subgroup by CVD risk	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.66.1 Low CVD risk	2	47404	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
2.66.2 Moderate CVD risk	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.60]
2.66.3 Existing CVD disease	7	5653	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.83, 1.27]
2.67 CHD mortality, subgroup by TC reduction	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.67.1 serum chol reduced by at least 0.2mmol/L	7	4285	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.24]
2.67.2 serum chol reduced by <0.2mmol/L	2	48874	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.20]
2.67.3 serum chol reduction unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.68 CHD mortality, subgroup decade of publication	9	53159	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.16]
2.68.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.06]
2.68.2 1970s	2	560	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.03, 9.26]
2.68.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.76, 1.30]
2.68.4 1990s	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.68.5 2000s	1	48835	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.20]
2.69 CORONARY HEART DISEASE EVENTS	11	53199	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.68, 1.01]

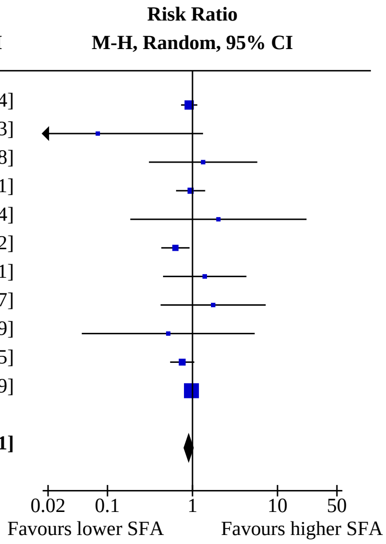
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.70 CHD events, SA by low summary risk of bias	3	49857	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.10]
2.71 CHD events, SA excluding WHI	10	4364	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.03]
2.72 CHD events, SA statistically significant SFA reduction	6	52212	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.06]
2.73 CHD events, SA by TC reduction	9	52984	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
2.74 CHD events, SA aim to reduce SFA	10	53023	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.00]
2.75 CHD events, SA Mantel-Haenszel fixed-effect	11	53199	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.84, 0.99]
2.76 CHD events, SA Peto fixed-effect	11	53199	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.83, 0.99]
2.77 CHD events, subgroup by any substitution	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.77.1 replaced by PUFA	7	3895	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 1.00]
2.77.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.62, 3.61]
2.77.3 replaced by CHO	4	51104	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.11]
2.77.4 replaced by protein	3	51044	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]
2.77.5 replacement unclear	1	267	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.31, 27.84]
2.78 CHD events, subgroup by main substitution	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.78.1 replaced by PUFA	6	3840	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.60, 1.04]
2.78.2 replaced by MUFA	1	52	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.62, 3.61]
2.78.3 replaced by CHO	3	49071	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.39, 1.72]
2.78.4 replaced by protein	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.78.5 replacement unclear	1	267	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.31, 27.84]
2.79 CHD events, subgroup by duration	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.79.1 up to 24 months	4	2380	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.35]
2.79.2 >24 to 48 months	3	1294	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.13]
2.79.3 >48 months	2	49247	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.63, 1.15]
2.79.4 unclear duration	2	278	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.10, 3.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.80 CHD events, subgroup by baseline SFA	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.80.1 up to 12%E SFA baseline	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.80.2 >12 to 15%E SFA baseline	4	51311	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.06]
2.80.3 >15 to 18%E SFA baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.10, 1.01]
2.80.4 >18%E SFA baseline	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
2.80.5 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.49, 1.26]
2.81 CHD events, subgroup by SFA change	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.81.1 up to 4%E difference	4	51311	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.06]
2.81.2 >4 to 8%E difference	1	55	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.10, 1.01]
2.81.3 >8%E difference	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
2.81.4 unclear	5	987	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.49, 1.26]
2.82 CHD events, subgroup by sex	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.82.1 Men	7	3819	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.02]
2.82.2 Women	1	48835	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.07]
2.82.3 Mixed, men and women	3	545	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.18, 4.36]
2.83 CHD events, subgroup by CVD risk	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.83.1 Low CVD risk	2	47404	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.05]
2.83.2 Moderate CVD risk	3	545	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.18, 4.36]
2.83.3 Existing CVD disease	7	5250	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.16]
2.84 CHD events, subgroup by TC reduction	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.84.1 serum chol reduced by at least 0.2mmol/L	8	4149	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 0.99]
2.84.2 serum chol reduced by <0.2mmol/L	3	49050	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.08]
2.84.3 serum chol reduction unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.85 CHD events, subgroup decade of publication	11	53201	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.68, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.85.1 1960s	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.68, 1.05]
2.85.2 1970s	1	102	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.52]
2.85.3 1980s	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.14]
2.85.4 1990s	1	57	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.10, 1.09]
2.85.5 2000s	3	49278	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.08]
2.86 DIABETES DIAGNOSES	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 1: MYOCARDIAL INFARCTION

	Lower SFA		Higher SFA			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	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]
MRC 1968	39	199	40	194	8.2%	0.95 [0.64 , 1.41]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
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 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		997			

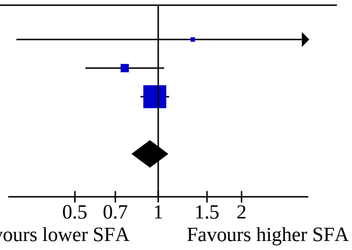


Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 2: MI, SA by low summary risk of bias

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	4	88	3	88	1.0%	1.33 [0.31 , 5.78]
Veterans Admin 1969	54	424	71	422	17.5%	0.76 [0.55 , 1.05]
WHI 2006	435	19541	671	29294	81.6%	0.97 [0.86 , 1.09]
Total (95% CI)		**20053**		**29804**	**100.0%**	**0.93 [0.81 , 1.08]**
Total events:	493		745			

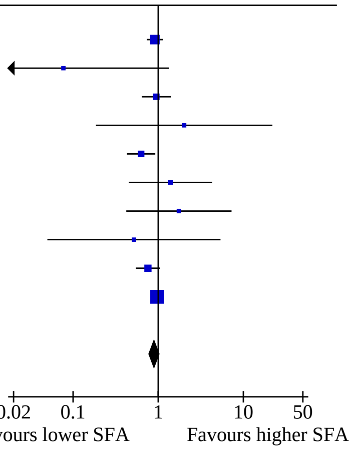
Heterogeneity: Tau² = 0.00; Chi² = 2.19, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 3: MI, SA aim to reduce SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	22.9%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.2%	0.08 [0.00 , 1.33]
MRC 1968	39	199	40	194	9.5%	0.95 [0.64 , 1.41]
Moy 2001	2	117	1	118	0.3%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	34	206	54	206	9.9%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	3	13	1.3%	1.39 [0.45 , 4.31]
Rose olive 1965	7	26	2	13	0.8%	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	12.9%	0.76 [0.55 , 1.05]
WHI 2006	435	19541	671	29294	41.8%	0.97 [0.86 , 1.09]
Total (95% CI)		**21637**		**31354**	**100.0%**	**0.89 [0.78 , 1.02]**
Total events:	713		994			

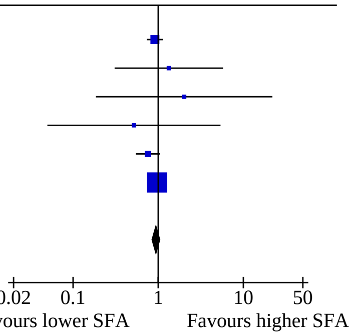
Heterogeneity: Tau² = 0.01; Chi² = 10.83, df = 9 (P = 0.29); I² = 17%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 4: MI, SA statistically significant SFA reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	20.5%	0.91 [0.73 , 1.14]
Ley 2004	4	88	3	88	0.5%	1.33 [0.31 , 5.78]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
STARS 1992	1	27	2	28	0.2%	0.52 [0.05 , 5.39]
Veterans Admin 1969	54	424	71	422	9.2%	0.76 [0.55 , 1.05]
WHI 2006	435	19541	671	29294	69.5%	0.97 [0.86 , 1.09]
Total (95% CI)		**21215**		**30965**	**100.0%**	**0.94 [0.85 , 1.04]**
Total events:	628		892			

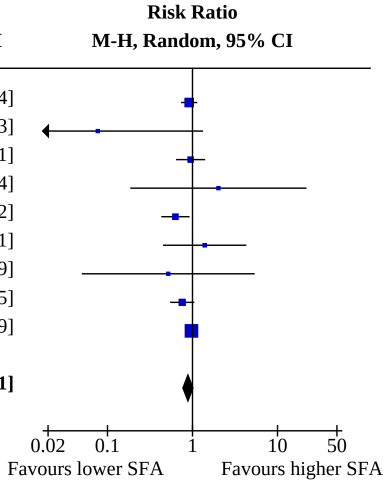
Heterogeneity: Tau² = 0.00; Chi² = 2.91, df = 5 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 5: MI, SA by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	23.3%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.2%	0.08 [0.00 , 1.33]
MRC 1968	39	199	40	194	9.9%	0.95 [0.64 , 1.41]
Moy 2001	2	117	1	118	0.3%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	34	206	54	206	10.3%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	3	13	1.4%	1.39 [0.45 , 4.31]
STARS 1992	1	27	2	28	0.3%	0.52 [0.05 , 5.39]
Veterans Admin 1969	54	424	71	422	13.3%	0.76 [0.55 , 1.05]
WHI 2006	435	19541	671	29294	40.9%	0.97 [0.86 , 1.09]
Total (95% CI)		**21611**		**31341**	**100.0%**	**0.88 [0.77 , 1.01]**
Total events:	706		992			

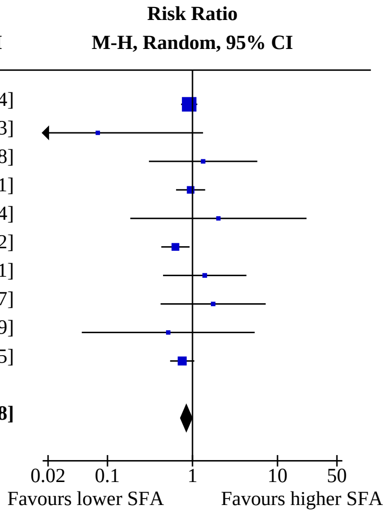
Heterogeneity: Tau² = 0.01; Chi² = 10.04, df = 8 (P = 0.26); I² = 20%
Test for overall effect: Z = 1.79 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 6: MI, SA excluding WHI

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	44.9%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.3%	0.08 [0.00 , 1.33]
Ley 2004	4	88	3	88	1.0%	1.33 [0.31 , 5.78]
MRC 1968	39	199	40	194	14.3%	0.95 [0.64 , 1.41]
Moy 2001	2	117	1	118	0.4%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	34	206	54	206	15.1%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	3	13	1.8%	1.39 [0.45 , 4.31]
Rose olive 1965	7	26	2	13	1.1%	1.75 [0.42 , 7.27]
STARS 1992	1	27	2	28	0.4%	0.52 [0.05 , 5.39]
Veterans Admin 1969	54	424	71	422	20.7%	0.76 [0.55 , 1.05]
Total (95% CI)		**2184**		**2148**	**100.0%**	**0.85 [0.73 , 0.98]**
Total events:	282		326			

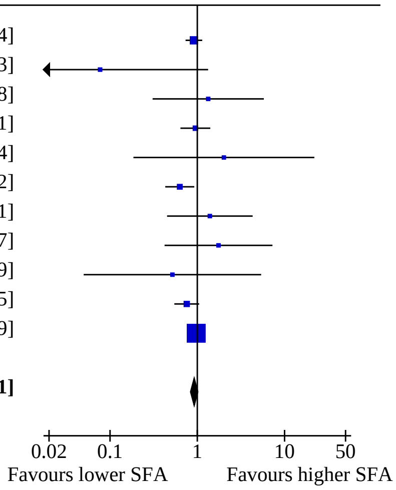
Heterogeneity: Tau² = 0.00; Chi² = 9.07, df = 9 (P = 0.43); I² = 1%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 7: MI, SA Mantel-Haenszel fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	132	1018	144	1015	16.7%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.8%	0.08 [0.00 , 1.33]
Ley 2004	4	88	3	88	0.3%	1.33 [0.31 , 5.78]
MRC 1968	39	199	40	194	4.7%	0.95 [0.64 , 1.41]
Moy 2001	2	117	1	118	0.1%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	34	206	54	206	6.2%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	3	13	0.5%	1.39 [0.45 , 4.31]
Rose olive 1965	7	26	2	13	0.3%	1.75 [0.42 , 7.27]
STARS 1992	1	27	2	28	0.2%	0.52 [0.05 , 5.39]
Veterans Admin 1969	54	424	71	422	8.2%	0.76 [0.55 , 1.05]
WHI 2006	435	19541	671	29294	62.0%	0.97 [0.86 , 1.09]
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.92 [0.84 , 1.01]**
Total events:	717		997			

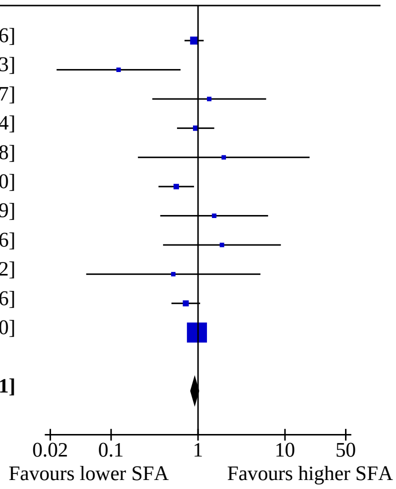
Heterogeneity: Chi² = 11.07, df = 10 (P = 0.35); I² = 10%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 8: MI, SA Peto fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
DART 1989	132	1018	144	1015	15.4%	0.90 [0.70 , 1.16]
Houtsmuller 1979	0	51	6	51	0.4%	0.12 [0.02 , 0.63]
Ley 2004	4	88	3	88	0.4%	1.34 [0.30 , 6.07]
MRC 1968	39	199	40	194	4.1%	0.94 [0.57 , 1.54]
Moy 2001	2	117	1	118	0.2%	1.98 [0.20 , 19.18]
Oslo Diet-Heart 1966	34	206	54	206	4.5%	0.56 [0.35 , 0.90]
Rose corn oil 1965	9	28	3	13	0.5%	1.53 [0.37 , 6.39]
Rose olive 1965	7	26	2	13	0.4%	1.88 [0.40 , 8.96]
STARS 1992	1	27	2	28	0.2%	0.52 [0.05 , 5.22]
Veterans Admin 1969	54	424	71	422	6.9%	0.72 [0.49 , 1.06]
WHI 2006	435	19541	671	29294	67.0%	0.97 [0.86 , 1.10]
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.92 [0.83 , 1.01]**
Total events:	717		997			

Heterogeneity: Chi² = 14.59, df = 10 (P = 0.15); I² = 31%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable

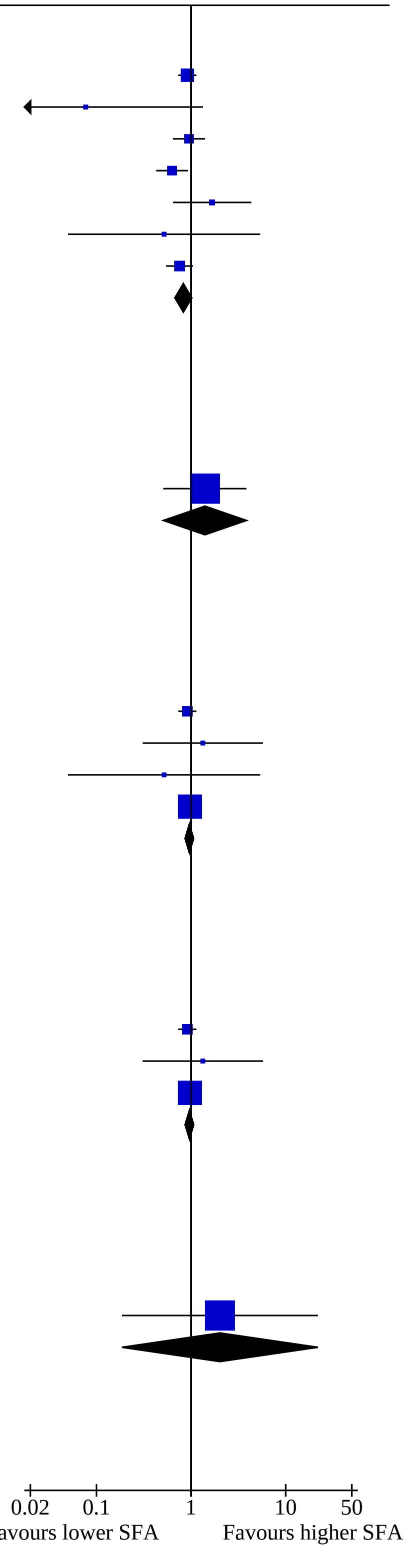


Analysis 2.9. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 9: MI, subgroup by any substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 replaced by PUFA						
DART 1989	132	1018	144	1015	34.0%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.5%	0.08 [0.00 , 1.33]
MRC 1968	39	199	40	194	18.3%	0.95 [0.64 , 1.41]
Oslo Diet-Heart 1966	34	206	54	206	19.0%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	5	26	4.3%	1.67 [0.64 , 4.34]
STARS 1992	1	27	2	28	0.8%	0.52 [0.05 , 5.39]
Veterans Admin 1969	54	424	71	422	23.1%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**1953**		**1942**	**100.0%**	**0.83 [0.67 , 1.02]**
Total events:	269		322			
Heterogeneity: Tau² = 0.02; Chi² = 8.40, df = 6 (P = 0.21); I² = 29%						
Test for overall effect: Z = 1.79 (P = 0.07)						
2.9.2 replaced by MUFA						
Rose olive 1965	7	26	5	26	100.0%	1.40 [0.51 , 3.85]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.40 [0.51 , 3.85]**
Total events:	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
2.9.3 replace by CHO						
DART 1989	132	1018	144	1015	22.6%	0.91 [0.73 , 1.14]
Ley 2004	4	88	3	88	0.5%	1.33 [0.31 , 5.78]
STARS 1992	1	27	2	28	0.2%	0.52 [0.05 , 5.39]
WHI 2006	435	19541	671	29294	76.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**20674**		**30425**	**100.0%**	**0.96 [0.86 , 1.06]**
Total events:	572		820			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
2.9.4 replaced by protein						
DART 1989	132	1018	144	1015	22.7%	0.91 [0.73 , 1.14]
Ley 2004	4	88	3	88	0.5%	1.33 [0.31 , 5.78]
WHI 2006	435	19541	671	29294	76.8%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**20647**		**30397**	**100.0%**	**0.96 [0.86 , 1.07]**
Total events:	571		818			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
2.9.5 replacement unclear						
Moy 2001	2	117	1	118	100.0%	2.02 [0.19 , 21.94]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**2.02 [0.19 , 21.94]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						

Test for subgroup differences: Chi² = 2.70, df = 4 (P = 0.61), I² = 0%

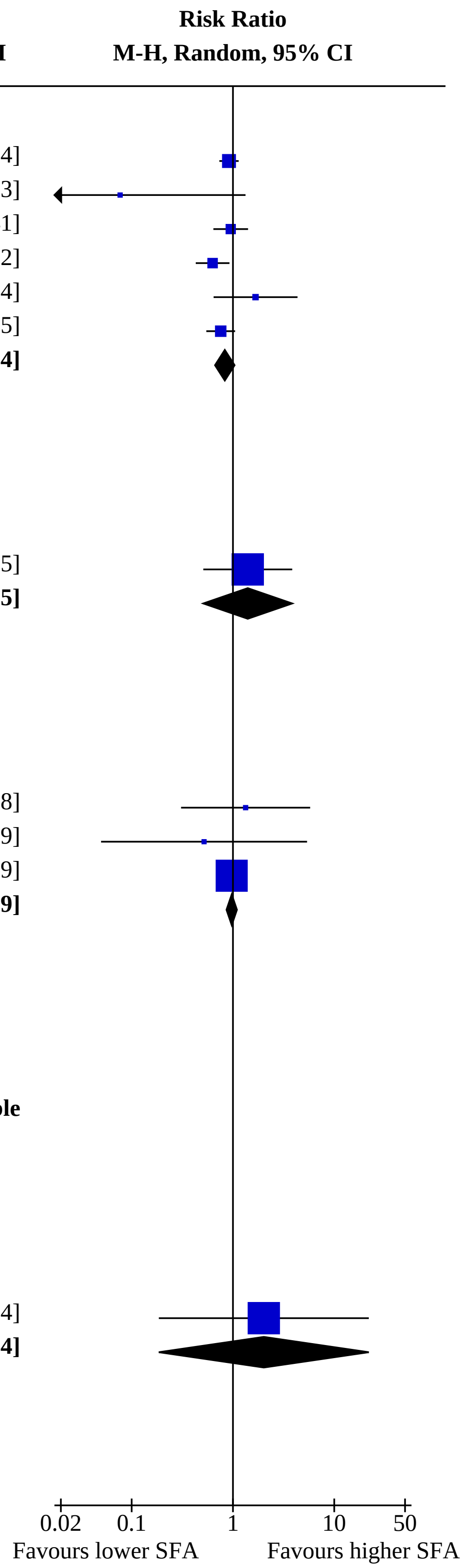
Risk Ratio
M-H, Random, 95% CI



Analysis 2.10. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 10: MI, subgroup by main substitution

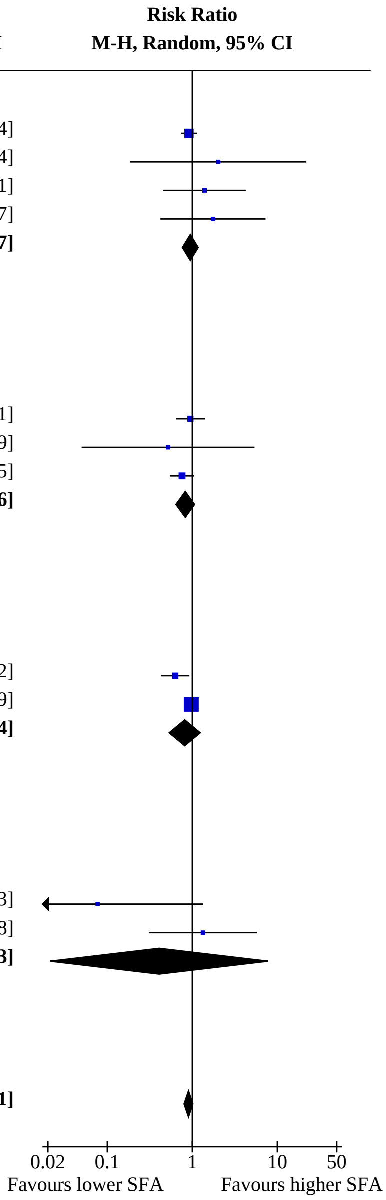
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 replaced by PUFA						
DART 1989	132	1018	144	1015	32.4%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.6%	0.08 [0.00 , 1.33]
MRC 1968	39	199	40	194	19.0%	0.95 [0.64 , 1.41]
Oslo Diet-Heart 1966	34	206	54	206	19.7%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	5	26	4.9%	1.67 [0.64 , 4.34]
Veterans Admin 1969	54	424	71	422	23.4%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**1926**		**1914**	**100.0%**	**0.83 [0.67 , 1.04]**
Total events:	268		320			
Heterogeneity: Tau² = 0.03; Chi² = 8.23, df = 5 (P = 0.14); I² = 39%						
Test for overall effect: Z = 1.63 (P = 0.10)						
2.10.2 replaced by MUFA						
Rose olive 1965	7	26	5	26	100.0%	1.40 [0.51 , 3.85]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.40 [0.51 , 3.85]**
Total events:	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
2.10.3 replace by CHO						
Ley 2004	4	88	3	88	0.7%	1.33 [0.31 , 5.78]
STARS 1992	1	27	2	28	0.3%	0.52 [0.05 , 5.39]
WHI 2006	435	19541	671	29294	99.1%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**19656**		**29410**	**100.0%**	**0.97 [0.86 , 1.09]**
Total events:	440		676			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
2.10.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.10.5 replacement unclear						
Moy 2001	2	117	1	118	100.0%	2.02 [0.19 , 21.94]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**2.02 [0.19 , 21.94]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						

Test for subgroup differences: Chi² = 2.48, df = 3 (P = 0.48), I² = 0%



Analysis 2.11. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 11: MI, subgroup by duration

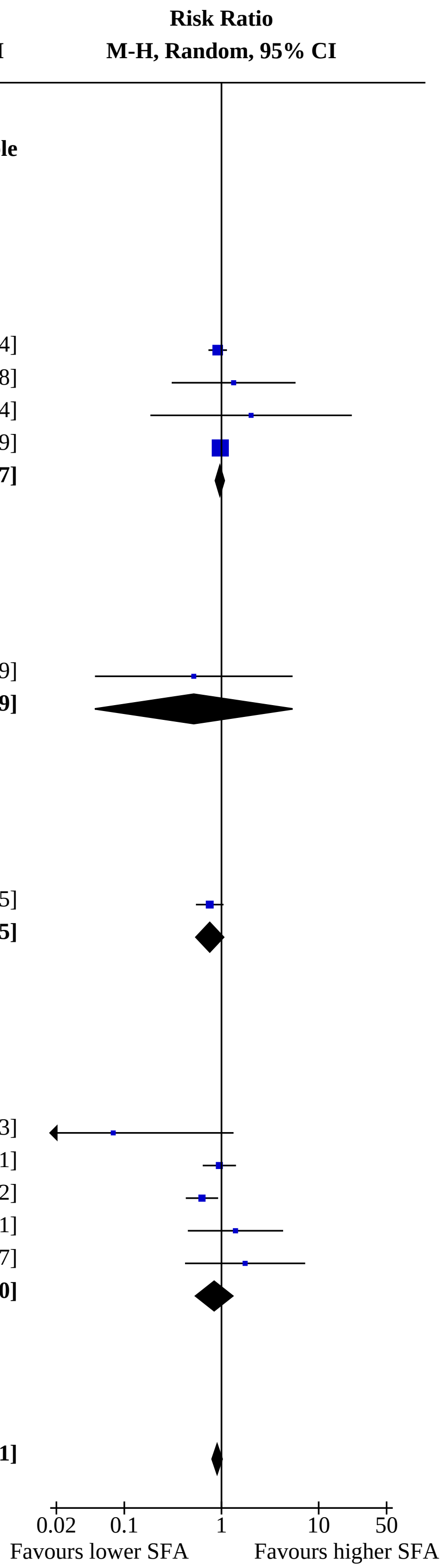
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 up to 24mo						
DART 1989	132	1018	144	1015	21.9%	0.91 [0.73 , 1.14]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
Rose corn oil 1965	9	28	3	13	1.1%	1.39 [0.45 , 4.31]
Rose olive 1965	7	26	2	13	0.7%	1.75 [0.42 , 7.27]
Subtotal (95% CI)		**1189**		**1159**	**23.9%**	**0.95 [0.77 , 1.17]**
Total events:	150		150			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
2.11.2 >24 to 48mo						
MRC 1968	39	199	40	194	8.2%	0.95 [0.64 , 1.41]
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]
Subtotal (95% CI)		**650**		**644**	**19.9%**	**0.83 [0.64 , 1.06]**
Total events:	94		113			
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 2 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.49 (P = 0.13)						
2.11.3 >48mo						
Oslo Diet-Heart 1966	34	206	54	206	8.6%	0.63 [0.43 , 0.92]
WHI 2006	435	19541	671	29294	46.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**19747**		**29500**	**55.4%**	**0.81 [0.54 , 1.24]**
Total events:	469		725			
Heterogeneity: Tau² = 0.07; Chi² = 4.50, df = 1 (P = 0.03); I² = 78%						
Test for overall effect: Z = 0.96 (P = 0.34)						
2.11.4 unclear						
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]
Subtotal (95% CI)		**139**		**139**	**0.8%**	**0.41 [0.02 , 7.73]**
Total events:	4		9			
Heterogeneity: Tau² = 3.31; Chi² = 3.47, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	717		997			
Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 1.10, df = 3 (P = 0.78), I² = 0%						



Analysis 2.12. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 12: MI, subgroup by baseline SFA

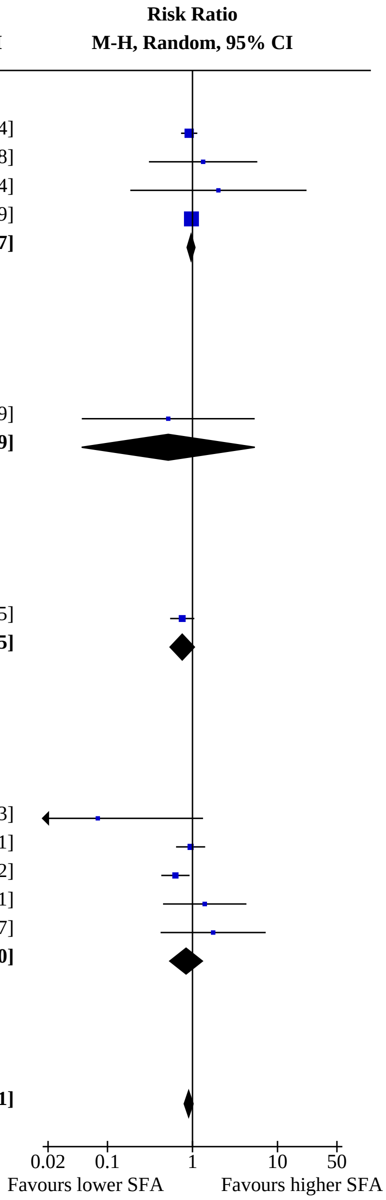
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.12.2 >12 to 15%E SFA baseline						
DART 1989	132	1018	144	1015	21.9%	0.91 [0.73 , 1.14]
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]
WHI 2006	435	19541	671	29294	46.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**20764**		**30515**	**69.5%**	**0.96 [0.87 , 1.07]**
Total events:	573		819			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.12.3 >15 to 18%E SFA baseline						
STARS 1992	1	27	2	28	0.3%	0.52 [0.05 , 5.39]
Subtotal (95% CI)		**27**		**28**	**0.3%**	**0.52 [0.05 , 5.39]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
2.12.4 >18%E SFA baseline						
Veterans Admin 1969	54	424	71	422	11.4%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**424**		**422**	**11.4%**	**0.76 [0.55 , 1.05]**
Total events:	54		71			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
2.12.5 unclear						
Houtsmuller 1979	0	51	6	51	0.2%	0.08 [0.00 , 1.33]
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]
Subtotal (95% CI)		**510**		**477**	**18.8%**	**0.84 [0.54 , 1.30]**
Total events:	89		105			
Heterogeneity: Tau² = 0.09; Chi² = 6.98, df = 4 (P = 0.14); I² = 43%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	717		997			

Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Chi² = 2.34, df = 3 (P = 0.50), I² = 0%



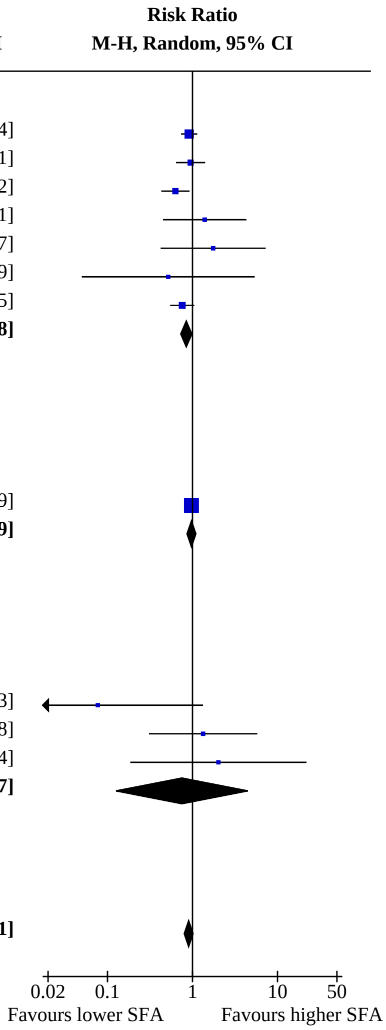
Analysis 2.13. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 13: MI, subgroup by SFA change

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 up to 4%E difference						
DART 1989	132	1018	144	1015	21.9%	0.91 [0.73 , 1.14]
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]
WHI 2006	435	19541	671	29294	46.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**20764**		**30515**	**69.5%**	**0.96 [0.87 , 1.07]**
Total events:	573		819			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.13.2 >4 to 8%E difference						
STARS 1992	1	27	2	28	0.3%	0.52 [0.05 , 5.39]
Subtotal (95% CI)		**27**		**28**	**0.3%**	**0.52 [0.05 , 5.39]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
2.13.3 >8%E difference						
Veterans Admin 1969	54	424	71	422	11.4%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**424**		**422**	**11.4%**	**0.76 [0.55 , 1.05]**
Total events:	54		71			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
2.13.4 unclear						
Houtsmuller 1979	0	51	6	51	0.2%	0.08 [0.00 , 1.33]
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]
Subtotal (95% CI)		**510**		**477**	**18.8%**	**0.84 [0.54 , 1.30]**
Total events:	89		105			
Heterogeneity: Tau² = 0.09; Chi² = 6.98, df = 4 (P = 0.14); I² = 43%						
Test for overall effect: Z = 0.78 (P = 0.44)						
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	717		997			
Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 2.34, df = 3 (P = 0.50), I² = 0%						



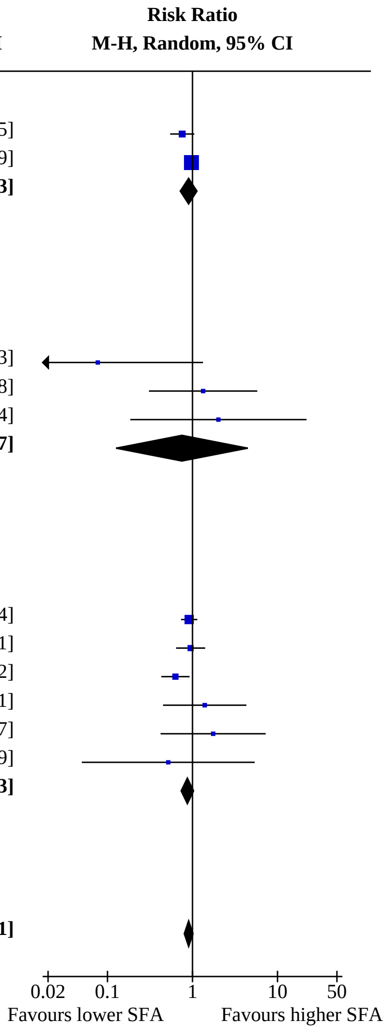
Analysis 2.14. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 14: MI, subgroup by sex

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 Men						
DART 1989	132	1018	144	1015	21.9%	0.91 [0.73 , 1.14]
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]
Subtotal (95% CI)		**1928**		**1891**	**52.2%**	**0.85 [0.73 , 0.98]**
Total events:	276		316			
Heterogeneity: Tau² = 0.00; Chi² = 5.46, df = 6 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
2.14.2 Women						
WHI 2006	435	19541	671	29294	46.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**19541**		**29294**	**46.7%**	**0.97 [0.86 , 1.09]**
Total events:	435		671			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
2.14.3 Mixed, men and women						
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]
Subtotal (95% CI)		**256**		**257**	**1.1%**	**0.75 [0.13 , 4.47]**
Total events:	6		10			
Heterogeneity: Tau² = 1.27; Chi² = 4.04, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	717		997			
Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 2.10, df = 2 (P = 0.35), I² = 4.6%						



Analysis 2.15. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 15: MI, subgroup by CVD risk

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 Low CVD risk						
Veterans Admin 1969	54	424	71	422	11.4%	0.76 [0.55 , 1.05]
WHI 2006	435	19541	671	29294	46.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**19965**		**29716**	**58.2%**	**0.90 [0.72 , 1.13]**
Total events:	489		742			
Heterogeneity: Tau² = 0.02; Chi² = 1.98, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 0.91 (P = 0.36)						
2.15.2 Moderate CVD risk						
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]
Subtotal (95% CI)		**256**		**257**	**1.1%**	**0.75 [0.13 , 4.47]**
Total events:	6		10			
Heterogeneity: Tau² = 1.27; Chi² = 4.04, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 0.31 (P = 0.75)						
2.15.3 Existing CVD disease						
DART 1989	132	1018	144	1015	21.9%	0.91 [0.73 , 1.14]
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]
Subtotal (95% CI)		**1504**		**1469**	**40.8%**	**0.87 [0.74 , 1.03]**
Total events:	222		245			
Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 5 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.10)						
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	717		997			
Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 0.09, df = 2 (P = 0.96), I² = 0%						

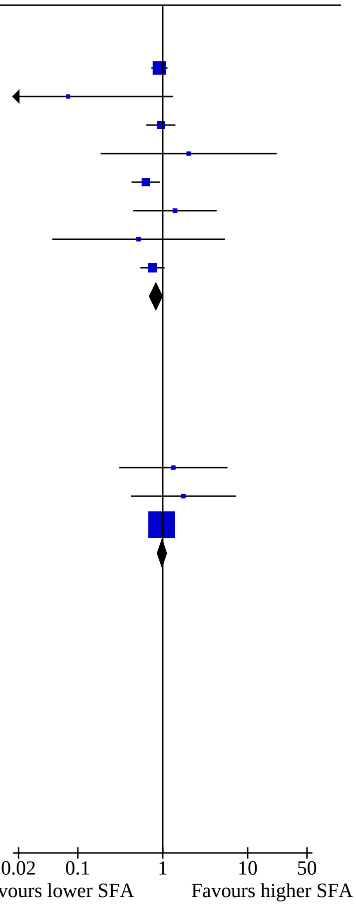


Analysis 2.16. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 16: MI, subgroup by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.16.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	132	1018	144	1015	41.0%	0.91 [0.73 , 1.14]
Houtsmuller 1979	0	51	6	51	0.4%	0.08 [0.00 , 1.33]
MRC 1968	39	199	40	194	16.2%	0.95 [0.64 , 1.41]
Moy 2001	2	117	1	118	0.5%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	34	206	54	206	17.0%	0.63 [0.43 , 0.92]
Rose corn oil 1965	9	28	3	13	2.2%	1.39 [0.45 , 4.31]
STARS 1992	1	27	2	28	0.5%	0.52 [0.05 , 5.39]
Veterans Admin 1969	54	424	71	422	22.3%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**2070**		**2047**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	271		321			
Heterogeneity: Tau² = 0.01; Chi² = 7.68, df = 7 (P = 0.36); I² = 9%						
Test for overall effect: Z = 2.17 (P = 0.03)						
2.16.2 serum chol reduced by <0.2mmol/L						
Ley 2004	4	88	3	88	0.7%	1.33 [0.31 , 5.78]
Rose olive 1965	7	26	2	13	0.7%	1.75 [0.42 , 7.27]
WHI 2006	435	19541	671	29294	98.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**19655**		**29395**	**100.0%**	**0.98 [0.87 , 1.10]**
Total events:	446		676			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
2.16.3 serum chol reduction unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

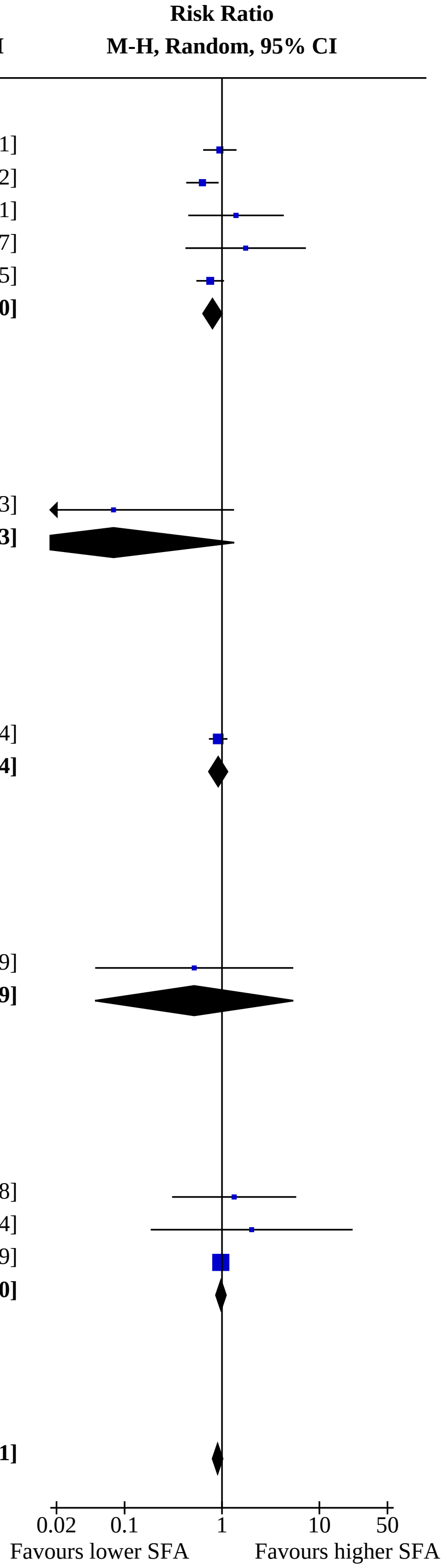
Test for subgroup differences: Chi² = 2.45, df = 1 (P = 0.12), I² = 59.1%

Risk Ratio M-H, Random, 95% CI



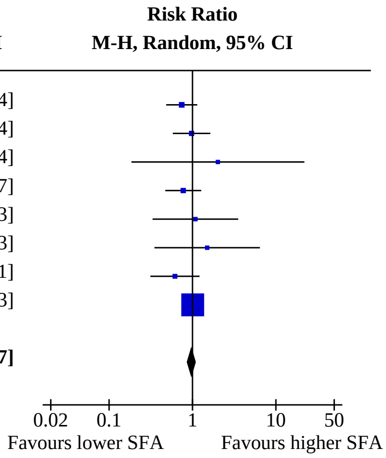
Analysis 2.17. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 17: MI, subgroup decade of publication

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.17.1 1960s						
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]
Veterans Admin 1969	54	424	71	422	11.4%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**883**		**848**	**30.0%**	**0.80 [0.64 , 1.00]**
Total events:	143		170			
Heterogeneity: Tau² = 0.01; Chi² = 4.43, df = 4 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.98 (P = 0.05)						
2.17.2 1970s						
Houtsmuller 1979	0	51	6	51	0.2%	0.08 [0.00 , 1.33]
Subtotal (95% CI)		**51**		**51**	**0.2%**	**0.08 [0.00 , 1.33]**
Total events:	0		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
2.17.3 1980s						
DART 1989	132	1018	144	1015	21.9%	0.91 [0.73 , 1.14]
Subtotal (95% CI)		**1018**		**1015**	**21.9%**	**0.91 [0.73 , 1.14]**
Total events:	132		144			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
2.17.4 1990s						
STARS 1992	1	27	2	28	0.3%	0.52 [0.05 , 5.39]
Subtotal (95% CI)		**27**		**28**	**0.3%**	**0.52 [0.05 , 5.39]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
2.17.5 2000s						
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]
WHI 2006	435	19541	671	29294	46.7%	0.97 [0.86 , 1.09]
Subtotal (95% CI)		**19746**		**29500**	**47.6%**	**0.98 [0.87 , 1.10]**
Total events:	441		675			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**21725**		**31442**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	717		997			
Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 10 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 5.62, df = 4 (P = 0.23), I² = 28.8%						



Analysis 2.18. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 18: NON-FATAL MYOCARDIAL INFARCTION

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			

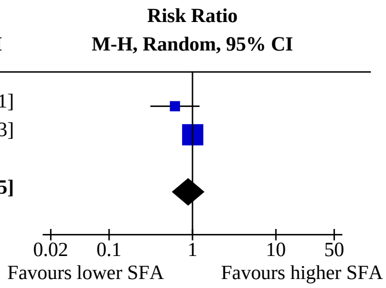


Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable

Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.19. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 19: Non-fatal MI, SA by low summary risk of bias

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Veterans Admin 1969	13	424	21	422	25.8%	0.62 [0.31 , 1.21]
WHI 2006 (1)	459	19541	684	29294	74.2%	1.01 [0.90 , 1.13]
Total (95% CI)		**19965**		**29716**	**100.0%**	**0.89 [0.58 , 1.35]**
Total events:	472		705			

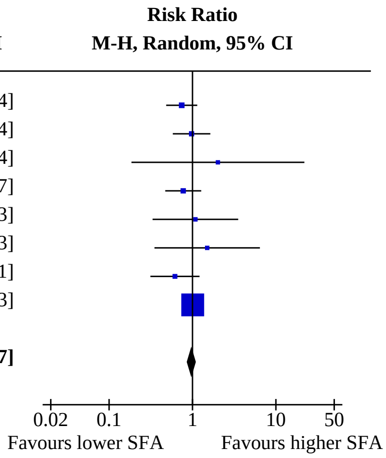


Heterogeneity: Tau² = 0.06; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable

Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.20. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 20: Non-fatal MI, SA aim to reduce SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			

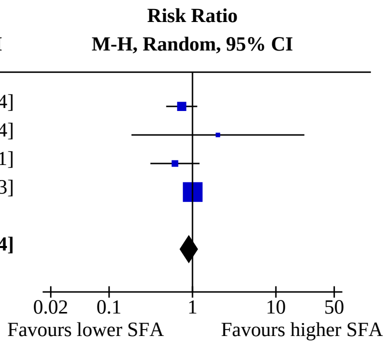


Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable

Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.21. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 21: Non-fatal MI, SA statistically significant SFA reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	35	1018	47	1015	21.4%	0.74 [0.48 , 1.14]
Moy 2001	2	117	1	118	0.9%	2.02 [0.19 , 21.94]
Veterans Admin 1969	13	424	21	422	10.1%	0.62 [0.31 , 1.21]
WHI 2006 (1)	459	19541	684	29294	67.5%	1.01 [0.90 , 1.13]
Total (95% CI)		**21100**		**30849**	**100.0%**	**0.90 [0.72 , 1.14]**
Total events:	509		753			



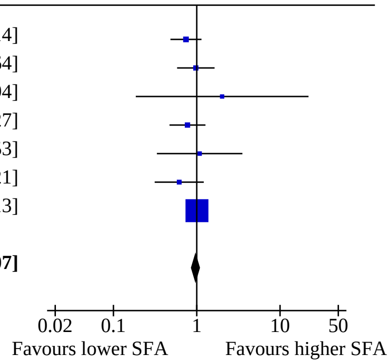
Heterogeneity: Tau² = 0.02; Chi² = 3.94, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable

Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.22. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 22: Non-fatal MI, SA by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	35	1018	47	1015	6.1%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	4.2%	0.97 [0.58 , 1.64]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
WHI 2006 (1)	459	19541	684	29294	81.8%	1.01 [0.90 , 1.13]
Total (95% CI)		**21533**		**31262**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	565		812			

Heterogeneity: Tau² = 0.00; Chi² = 4.76, df = 6 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable

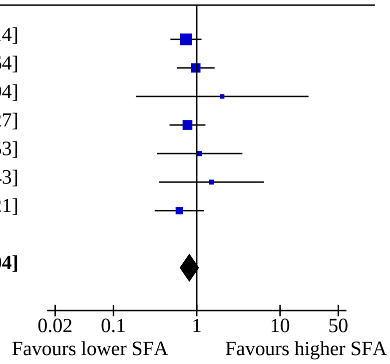


Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.23. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 23: Non-fatal MI, SA excluding WHI

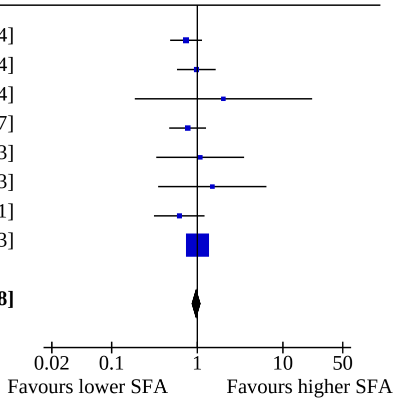
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	35	1018	47	1015	32.4%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	22.3%	0.97 [0.58 , 1.64]
Moy 2001	2	117	1	118	1.0%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	24	206	31	206	24.2%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	4.3%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	2.8%	1.50 [0.35 , 6.43]
Veterans Admin 1969	13	424	21	422	13.0%	0.62 [0.31 , 1.21]
Total (95% CI)		**2018**		**1981**	**100.0%**	**0.81 [0.64 , 1.04]**
Total events:	112		130			

Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 6 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 2.24. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 24: Non-fatal MI, SA Mantel-Haenszel fixed-effect

	Lower SFA		Higher SFA			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
DART 1989	35	1018	47	1015	6.9%	0.74 [0.48 , 1.14]	
MRC 1968	25	199	25	194	3.7%	0.97 [0.58 , 1.64]	
Moy 2001	2	117	1	118	0.1%	2.02 [0.19 , 21.94]	
Oslo Diet-Heart 1966	24	206	31	206	4.6%	0.77 [0.47 , 1.27]	
Rose corn oil 1965	7	28	3	13	0.6%	1.08 [0.33 , 3.53]	
Rose olive 1965	6	26	2	13	0.4%	1.50 [0.35 , 6.43]	
Veterans Admin 1969	13	424	21	422	3.1%	0.62 [0.31 , 1.21]	
WHI 2006 (1)	459	19541	684	29294	80.5%	1.01 [0.90 , 1.13]	
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.08]**	
Total events:	571		814				

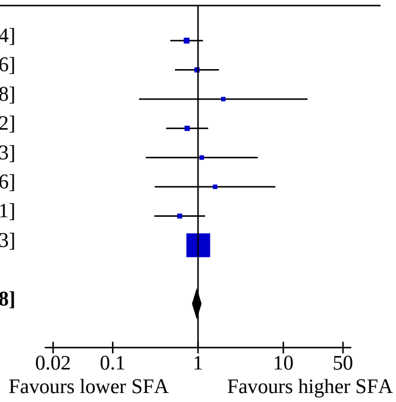


Heterogeneity: Chi² = 5.11, df = 7 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.25. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 25: Non-fatal MI, SA Peto fixed-effect

	Lower SFA		Higher SFA			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**Peto, Fixed, 95% CI**	**Peto, Fixed, 95% CI**
DART 1989	35	1018	47	1015	6.1%	0.73 [0.47 , 1.14]	
MRC 1968	25	199	25	194	3.4%	0.97 [0.54 , 1.76]	
Moy 2001	2	117	1	118	0.2%	1.98 [0.20 , 19.18]	
Oslo Diet-Heart 1966	24	206	31	206	3.7%	0.75 [0.42 , 1.32]	
Rose corn oil 1965	7	28	3	13	0.5%	1.11 [0.24 , 5.03]	
Rose olive 1965	6	26	2	13	0.4%	1.58 [0.31 , 8.06]	
Veterans Admin 1969	13	424	21	422	2.5%	0.61 [0.31 , 1.21]	
WHI 2006 (1)	459	19541	684	29294	83.1%	1.01 [0.89 , 1.13]	
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.08]**	
Total events:	571		814				



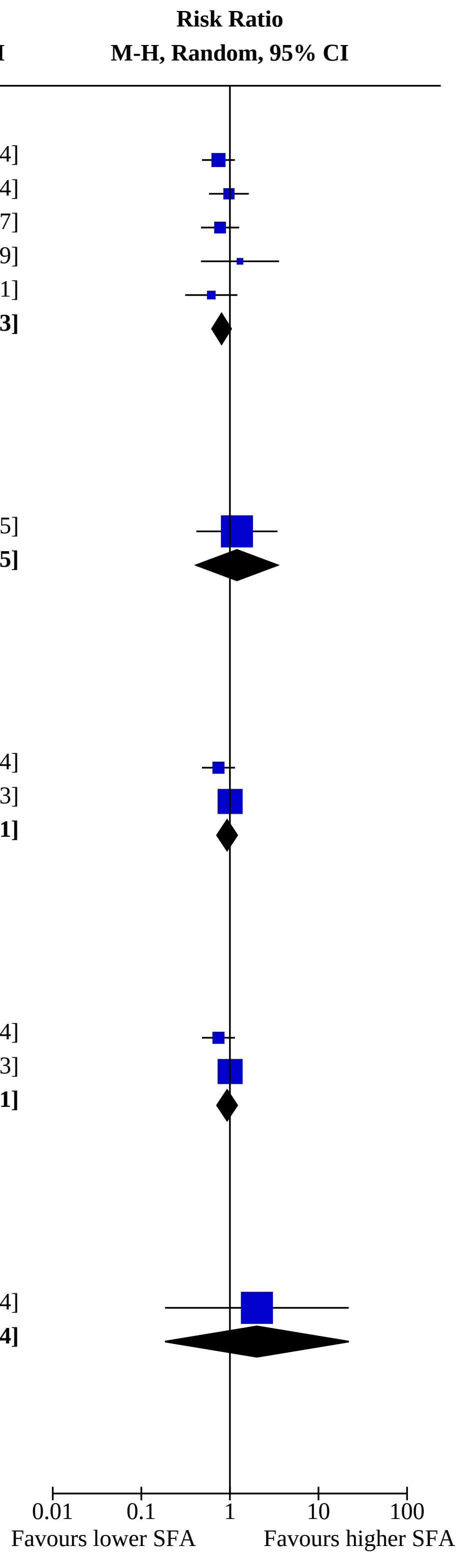
Heterogeneity: Chi² = 5.21, df = 7 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

Footnotes
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.26. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 26: Non-fatal MI, subgroup by any substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.26.1 replaced by PUFA						
DART 1989	35	1018	47	1015	33.2%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	22.8%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	24	206	31	206	24.8%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	5	26	5.9%	1.30 [0.47 , 3.59]
Veterans Admin 1969	13	424	21	422	13.3%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**1875**		**1863**	**100.0%**	**0.80 [0.63 , 1.03]**
Total events:	104		129			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
2.26.2 replaced by MUFA						
Rose olive 1965	6	26	5	26	100.0%	1.20 [0.42 , 3.45]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.20 [0.42 , 3.45]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
2.26.3 replace by CHO						
DART 1989	35	1018	47	1015	26.0%	0.74 [0.48 , 1.14]
WHI 2006 (1)	459	19541	684	29294	74.0%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**20559**		**30309**	**100.0%**	**0.93 [0.72 , 1.21]**
Total events:	494		731			
Heterogeneity: Tau² = 0.02; Chi² = 1.79, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 0.55 (P = 0.58)						
2.26.4 replaced by protein						
DART 1989	35	1018	47	1015	26.0%	0.74 [0.48 , 1.14]
WHI 2006 (1)	459	19541	684	29294	74.0%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**20559**		**30309**	**100.0%**	**0.93 [0.72 , 1.21]**
Total events:	494		731			
Heterogeneity: Tau² = 0.02; Chi² = 1.79, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 0.55 (P = 0.58)						
2.26.5 replacement unclear						
Moy 2001	2	117	1	118	100.0%	2.02 [0.19 , 21.94]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**2.02 [0.19 , 21.94]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						

Test for subgroup differences: Chi² = 1.61, df = 4 (P = 0.81), I² = 0%



Footnotes

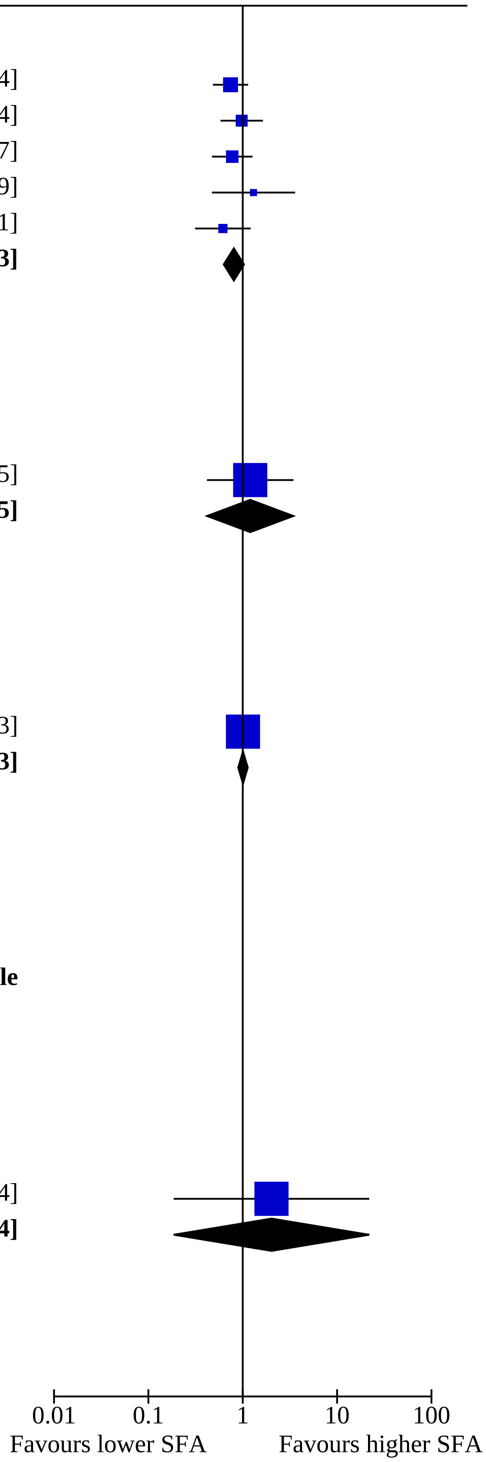
(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.27. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 27: Non-fatal MI, subgroup by main substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.27.1 replaced by PUFA						
DART 1989	35	1018	47	1015	33.2%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	22.8%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	24	206	31	206	24.8%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	5	26	5.9%	1.30 [0.47 , 3.59]
Veterans Admin 1969	13	424	21	422	13.3%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**1875**		**1863**	**100.0%**	**0.80 [0.63 , 1.03]**
Total events:	104		129			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
2.27.2 replaced by MUFA						
Rose olive 1965	6	26	5	26	100.0%	1.20 [0.42 , 3.45]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.20 [0.42 , 3.45]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
2.27.3 replace by CHO						
WHI 2006 (1)	459	19541	684	29294	100.0%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**19541**		**29294**	**100.0%**	**1.01 [0.90 , 1.13]**
Total events:	459		684			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
2.27.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.27.5 replacement unclear						
Moy 2001	2	117	1	118	100.0%	2.02 [0.19 , 21.94]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**2.02 [0.19 , 21.94]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						

Test for subgroup differences: Chi² = 3.08, df = 3 (P = 0.38), I² = 2.5%

Risk Ratio
M-H, Random, 95% CI

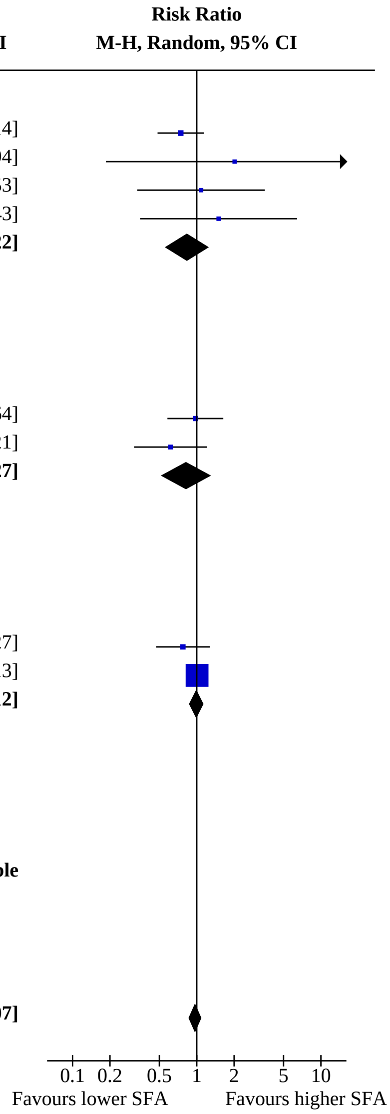


Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.28. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 28: Non-fatal MI, subgroup by duration

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.28.1 up to 24mo						
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Subtotal (95% CI)		**1189**		**1159**	**7.6%**	**0.83 [0.57 , 1.22]**
Total events:	50		53			
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
2.28.2 >24 to 48mo						
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**623**		**616**	**6.6%**	**0.82 [0.53 , 1.27]**
Total events:	38		46			
Heterogeneity: Tau² = 0.01; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.28.3 >48mo						
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**19747**		**29500**	**85.9%**	**0.99 [0.88 , 1.12]**
Total events:	483		715			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 0.15 (P = 0.88)						
2.28.4 unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			
Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 1.30, df = 2 (P = 0.52), I² = 0%						

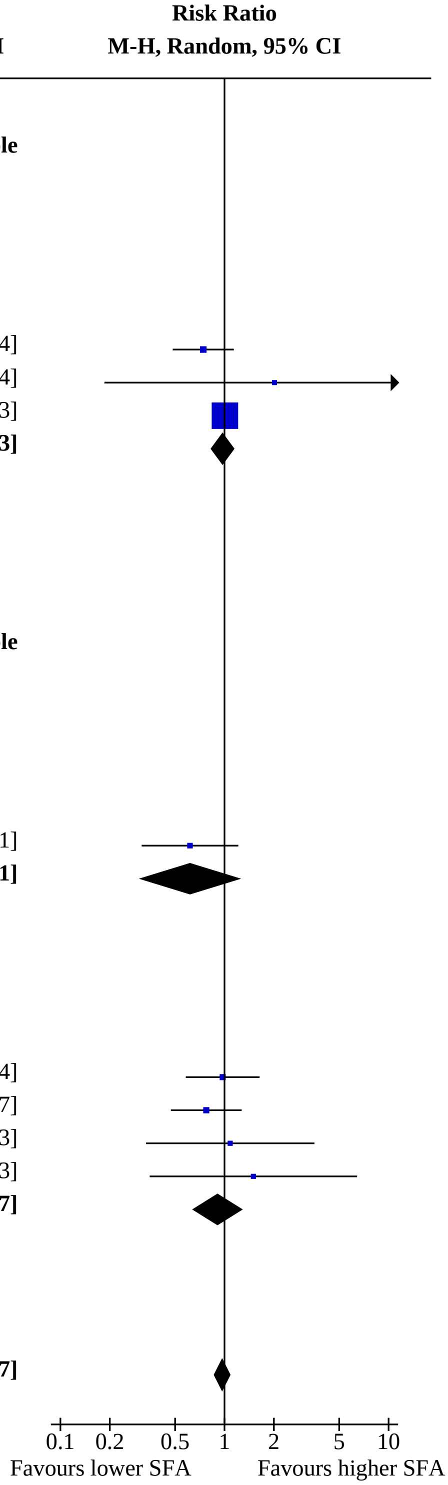


Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.29. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 29: Non-fatal MI, subgroup by baseline SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.29.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.29.2 >12 to 15%E SFA baseline						
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**20676**		**30427**	**87.6%**	**0.97 [0.83 , 1.13]**
Total events:	496		732			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 2 (P = 0.34); I² = 6%						
Test for overall effect: Z = 0.35 (P = 0.73)						
2.29.3 >15 to 18%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.29.4 >18%E SFA baseline						
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**424**		**422**	**2.4%**	**0.62 [0.31 , 1.21]**
Total events:	13		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
2.29.5 unclear						
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Subtotal (95% CI)		**459**		**426**	**10.0%**	**0.91 [0.65 , 1.27]**
Total events:	62		61			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			
Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 1.72, df = 2 (P = 0.42), I² = 0%						

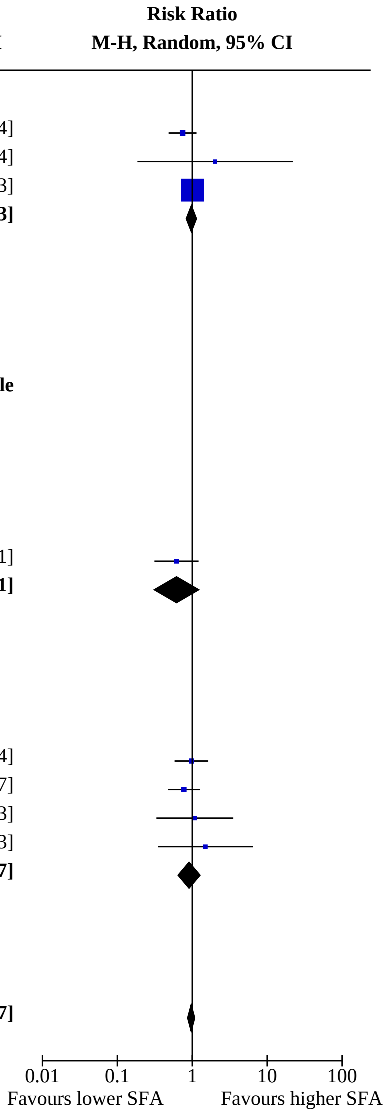


Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.30. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 30: Non-fatal MI, subgroup by SFA change

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.30.1 up to 4%E difference						
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**20676**		**30427**	**87.6%**	**0.97 [0.83 , 1.13]**
Total events:	496		732			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 2 (P = 0.34); I² = 6%						
Test for overall effect: Z = 0.35 (P = 0.73)						
2.30.2 >4 to 8%E difference						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.30.3 >8%E difference						
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**424**		**422**	**2.4%**	**0.62 [0.31 , 1.21]**
Total events:	13		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
2.30.4 unclear						
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Subtotal (95% CI)		**459**		**426**	**10.0%**	**0.91 [0.65 , 1.27]**
Total events:	62		61			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			
Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 1.72, df = 2 (P = 0.42), I² = 0%						



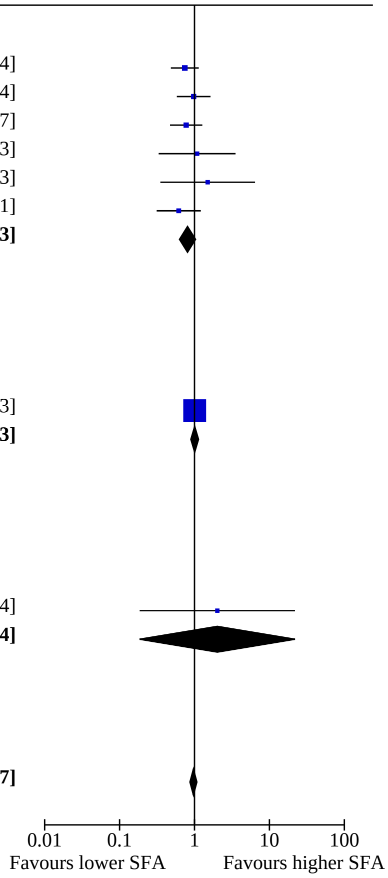
Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.31. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 31: Non-fatal MI, subgroup by sex

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.31.1 Men						
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**1901**		**1863**	**18.4%**	**0.81 [0.63 , 1.03]**
Total events:	110		129			
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 5 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
2.31.2 Women						
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**19541**		**29294**	**81.4%**	**1.01 [0.90 , 1.13]**
Total events:	459		684			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
2.31.3 Mixed, men and women						
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
Subtotal (95% CI)		**117**		**118**	**0.2%**	**2.02 [0.19 , 21.94]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			
Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 2.89, df = 2 (P = 0.24), I² = 30.7%						

Risk Ratio M-H, Random, 95% CI

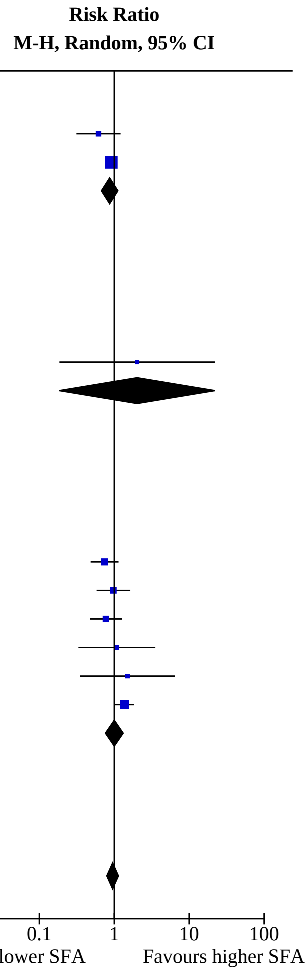


Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.32. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 32: Non-fatal MI, subgroup by CVD risk

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.32.1 Low CVD risk						
Veterans Admin 1969	13	424	21	422	5.9%	0.62 [0.31 , 1.21]
WHI 2006	353	18633	581	27925	37.3%	0.91 [0.80 , 1.04]
Subtotal (95% CI)		**19057**		**28347**	**43.3%**	**0.87 [0.68 , 1.12]**
Total events:	366		602			
Heterogeneity: Tau² = 0.01; Chi² = 1.23, df = 1 (P = 0.27); I² = 19%						
Test for overall effect: Z = 1.11 (P = 0.27)						
2.32.2 Moderate CVD risk						
Moy 2001	2	117	1	118	0.5%	2.02 [0.19 , 21.94]
Subtotal (95% CI)		**117**		**118**	**0.5%**	**2.02 [0.19 , 21.94]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.32.3 Existing CVD disease						
DART 1989	35	1018	47	1015	12.4%	0.74 [0.48 , 1.14]
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]
WHI 2006 (1)	82	908	90	1369	20.9%	1.37 [1.03 , 1.83]
Subtotal (95% CI)		**2385**		**2810**	**56.2%**	**1.00 [0.76 , 1.31]**
Total events:	179		198			
Heterogeneity: Tau² = 0.04; Chi² = 7.63, df = 5 (P = 0.18); I² = 34%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.95 [0.80 , 1.13]**
Total events:	547		801			
Heterogeneity: Tau² = 0.02; Chi² = 11.03, df = 8 (P = 0.20); I² = 27%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Chi² = 0.98, df = 2 (P = 0.61), I² = 0%						

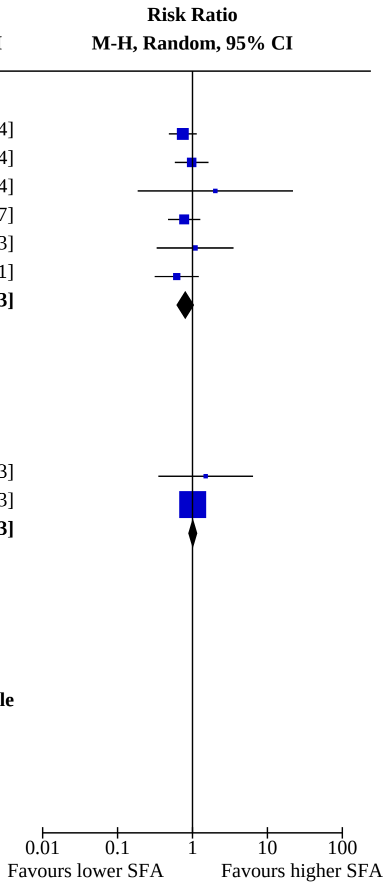


Footnotes
(1) Women with CVD at baseline

Analysis 2.33. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 33: Non-fatal MI, subgroup by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.33.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	35	1018	47	1015	33.4%	0.74 [0.48 , 1.14]
MRC 1968	25	199	25	194	22.9%	0.97 [0.58 , 1.64]
Moy 2001	2	117	1	118	1.1%	2.02 [0.19 , 21.94]
Oslo Diet-Heart 1966	24	206	31	206	24.9%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	4.4%	1.08 [0.33 , 3.53]
Veterans Admin 1969	13	424	21	422	13.3%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**1992**		**1968**	**100.0%**	**0.80 [0.62 , 1.03]**
Total events:	106		128			
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 5 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
2.33.2 serum chol reduced by <0.2mmol/L						
Rose olive 1965	6	26	2	13	0.6%	1.50 [0.35 , 6.43]
WHI 2006 (1)	459	19541	684	29294	99.4%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**19567**		**29307**	**100.0%**	**1.01 [0.90 , 1.13]**
Total events:	465		686			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
2.33.3 serum chol reduction unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 2.73, df = 1 (P = 0.10), I² = 63.4%



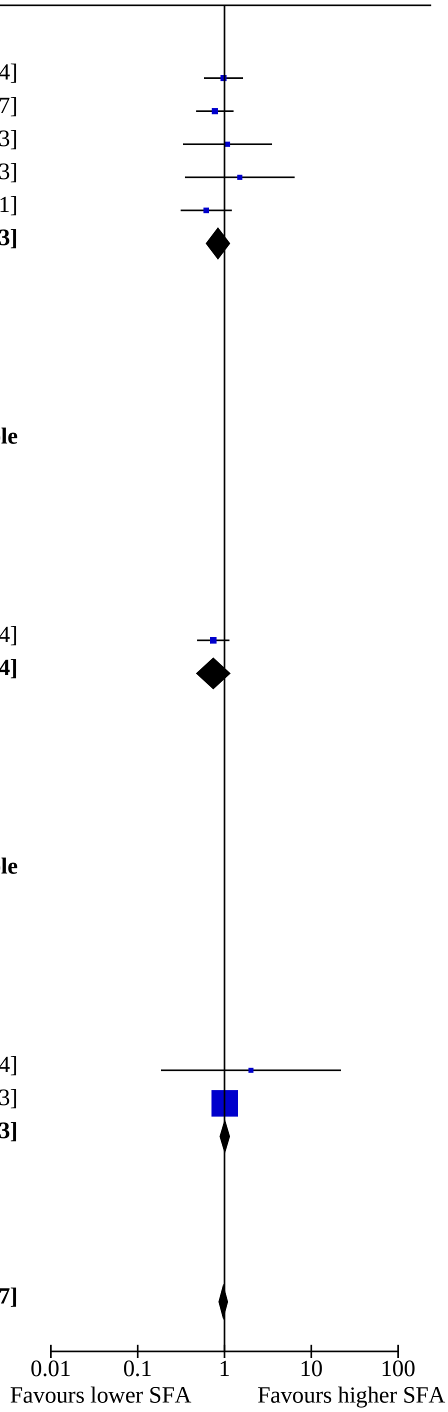
Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.34. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 34: Non-fatal MI, subgroup decade of publication

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.34.1 1960s						
MRC 1968	25	199	25	194	4.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	24	206	31	206	4.5%	0.77 [0.47 , 1.27]
Rose corn oil 1965	7	28	3	13	0.8%	1.08 [0.33 , 3.53]
Rose olive 1965	6	26	2	13	0.5%	1.50 [0.35 , 6.43]
Veterans Admin 1969	13	424	21	422	2.4%	0.62 [0.31 , 1.21]
Subtotal (95% CI)		**883**		**848**	**12.4%**	**0.84 [0.62 , 1.13]**
Total events:	75		82			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 4 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.26)						
2.34.2 1970s						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.34.3 1980s						
DART 1989	35	1018	47	1015	6.0%	0.74 [0.48 , 1.14]
Subtotal (95% CI)		**1018**		**1015**	**6.0%**	**0.74 [0.48 , 1.14]**
Total events:	35		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
2.34.4 1990s						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.34.5 2000s						
Moy 2001	2	117	1	118	0.2%	2.02 [0.19 , 21.94]
WHI 2006 (1)	459	19541	684	29294	81.4%	1.01 [0.90 , 1.13]
Subtotal (95% CI)		**19658**		**29412**	**81.6%**	**1.01 [0.90 , 1.13]**
Total events:	461		685			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**21559**		**31275**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	571		814			
Heterogeneity: Tau² = 0.00; Chi² = 5.11, df = 7 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 2.78, df = 2 (P = 0.25), I² = 28.0%						

Risk Ratio
M-H, Random, 95% CI



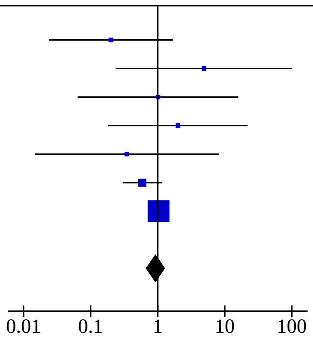
Footnotes

(1) Non-fatal MI during trial, Prentice 2017

Analysis 2.35. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 35: STROKE

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	1	88	5	88	2.0%	0.20 [0.02 , 1.68]
MRC 1968	2	199	0	194	1.0%	4.88 [0.24 , 100.89]
Moy 2001	1	117	1	118	1.2%	1.01 [0.06 , 15.93]
Oslo Diet-Heart 1966	2	206	1	206	1.6%	2.00 [0.18 , 21.89]
STARS 1992	0	27	1	28	0.9%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	16.4%	0.59 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	76.9%	1.03 [0.91 , 1.16]
Total (95% CI)		**20602**		**30350**	**100.0%**	**0.92 [0.68 , 1.25]**
Total events:	454		664			

Heterogeneity: Tau² = 0.03; Chi² = 6.59, df = 6 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable

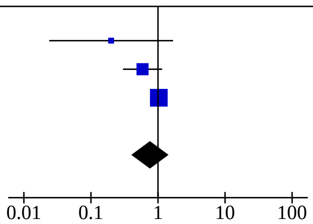


Footnotes
(1) During trial, Prentice 2017

Analysis 2.36. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 36: Stroke, SA by low summary risk of bias

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	1	88	5	88	7.0%	0.20 [0.02 , 1.68]
Veterans Admin 1969	13	424	22	422	34.2%	0.59 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	58.8%	1.03 [0.91 , 1.16]
Total (95% CI)		**20053**		**29804**	**100.0%**	**0.76 [0.42 , 1.38]**
Total events:	449		661			

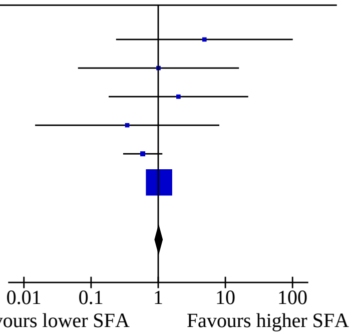
Heterogeneity: Tau² = 0.15; Chi² = 4.80, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



Footnotes
(1) During trial, Prentice 2017

Analysis 2.37. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 37: Stroke, SA aim to reduce SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
MRC 1968	2	199	0	194	0.2%	4.88 [0.24 , 100.89]
Moy 2001	1	117	1	118	0.2%	1.01 [0.06 , 15.93]
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	3.1%	0.59 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	96.2%	1.03 [0.91 , 1.16]
Total (95% CI)		**20514**		**30262**	**100.0%**	**1.01 [0.90 , 1.14]**
Total events:	453		659			

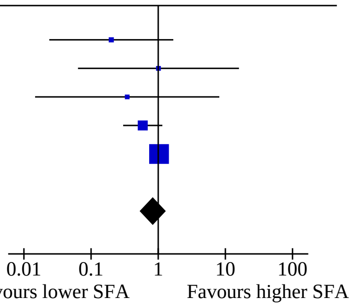


Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable

Footnotes
(1) During trial, Prentice 2017

Analysis 2.38. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 38: Stroke, SA statistically significant SFA reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	1	88	5	88	3.6%	0.20 [0.02 , 1.68]
Moy 2001	1	117	1	118	2.2%	1.01 [0.06 , 15.93]
STARS 1992	0	27	1	28	1.7%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	24.9%	0.59 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	67.6%	1.03 [0.91 , 1.16]
Total (95% CI)		**20197**		**29950**	**100.0%**	**0.83 [0.55 , 1.25]**
Total events:	450		663			



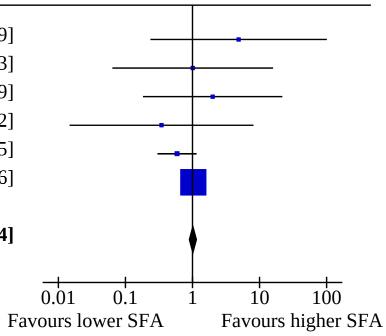
Heterogeneity: Tau² = 0.06; Chi² = 5.24, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

Footnotes
(1) During trial, Prentice 2017

Analysis 2.39. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 39: Stroke, SA by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
MRC 1968	2	199	0	194	0.2%	4.88 [0.24 , 100.89]
Moy 2001	1	117	1	118	0.2%	1.01 [0.06 , 15.93]
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	3.1%	0.59 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	96.2%	1.03 [0.91 , 1.16]
Total (95% CI)		**20514**		**30262**	**100.0%**	**1.01 [0.90 , 1.14]**
Total events:	453		659			

Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable

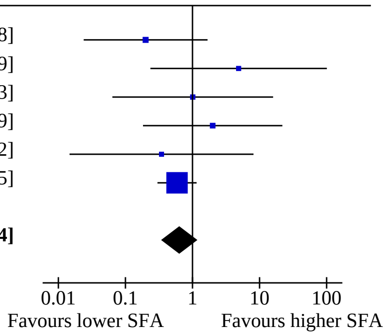


Footnotes
(1) During trial, Prentice 2017

Analysis 2.40. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 40: Stroke, SA excluding WHI

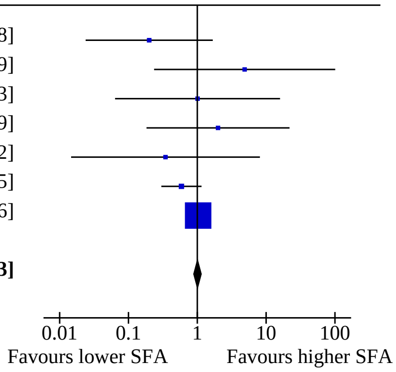
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	1	88	5	88	7.5%	0.20 [0.02 , 1.68]
MRC 1968	2	199	0	194	3.7%	4.88 [0.24 , 100.89]
Moy 2001	1	117	1	118	4.5%	1.01 [0.06 , 15.93]
Oslo Diet-Heart 1966	2	206	1	206	5.9%	2.00 [0.18 , 21.89]
STARS 1992	0	27	1	28	3.4%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	75.0%	0.59 [0.30 , 1.15]
Total (95% CI)		**1061**		**1056**	**100.0%**	**0.63 [0.35 , 1.14]**
Total events:	19		30			

Heterogeneity: Tau² = 0.00; Chi² = 4.06, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 2.41. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 41: Stroke, SA Mantel-Haenszel fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ley 2004	1	88	5	88	0.9%	0.20 [0.02 , 1.68]
MRC 1968	2	199	0	194	0.1%	4.88 [0.24 , 100.89]
Moy 2001	1	117	1	118	0.2%	1.01 [0.06 , 15.93]
Oslo Diet-Heart 1966	2	206	1	206	0.2%	2.00 [0.18 , 21.89]
STARS 1992	0	27	1	28	0.3%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	4.1%	0.59 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	94.2%	1.03 [0.91 , 1.16]
Total (95% CI)		**20602**		**30350**	**100.0%**	**1.01 [0.89 , 1.13]**
Total events:	454		664			

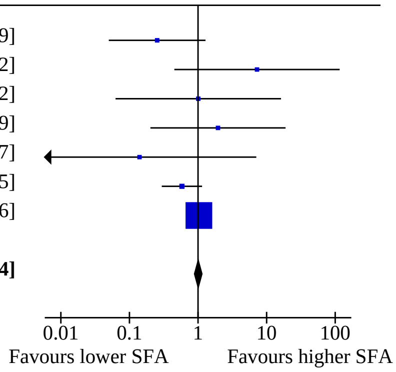


Heterogeneity: Chi² = 6.59, df = 6 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.11 (P = 0.92)
Test for subgroup differences: Not applicable

Footnotes
(1) During trial, Prentice 2017

Analysis 2.42. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 42: Stroke, SA Peto fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ley 2004	1	88	5	88	0.6%	0.25 [0.05 , 1.29]
MRC 1968	2	199	0	194	0.2%	7.24 [0.45 , 116.22]
Moy 2001	1	117	1	118	0.2%	1.01 [0.06 , 16.22]
Oslo Diet-Heart 1966	2	206	1	206	0.3%	1.95 [0.20 , 18.89]
STARS 1992	0	27	1	28	0.1%	0.14 [0.00 , 7.07]
Veterans Admin 1969	13	424	22	422	3.2%	0.58 [0.30 , 1.15]
WHI 2006 (1)	435	19541	634	29294	95.5%	1.03 [0.91 , 1.16]
Total (95% CI)		**20602**		**30350**	**100.0%**	**1.01 [0.89 , 1.14]**
Total events:	454		664			



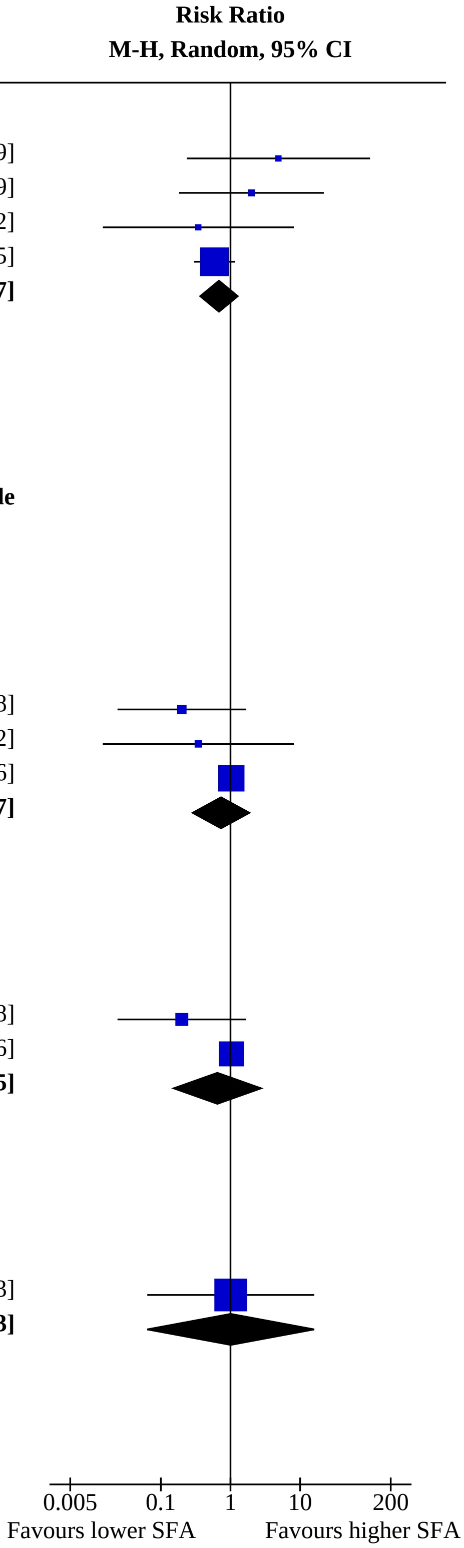
Heterogeneity: Chi² = 8.65, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 0.11 (P = 0.92)
Test for subgroup differences: Not applicable

Footnotes
(1) During trial, Prentice 2017

Analysis 2.43. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 43: Stroke, subgroup by any substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.43.1 replaced by PUFA						
MRC 1968	2	199	0	194	4.2%	4.88 [0.24 , 100.89]
Oslo Diet-Heart 1966	2	206	1	206	6.7%	2.00 [0.18 , 21.89]
STARS 1992	0	27	1	28	3.9%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	85.2%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**856**		**850**	**100.0%**	**0.68 [0.37 , 1.27]**
Total events:	17		24			
Heterogeneity: Tau² = 0.00; Chi² = 2.78, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
2.43.2 replaced by MUFA						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.43.3 replace by CHO						
Ley 2004	1	88	5	88	15.6%	0.20 [0.02 , 1.68]
STARS 1992	0	27	1	28	7.9%	0.35 [0.01 , 8.12]
WHI 2006 (1)	435	19541	634	29294	76.5%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19656**		**29410**	**100.0%**	**0.73 [0.29 , 1.87]**
Total events:	436		640			
Heterogeneity: Tau² = 0.30; Chi² = 2.73, df = 2 (P = 0.26); I² = 27%						
Test for overall effect: Z = 0.65 (P = 0.51)						
2.43.4 replaced by protein						
Ley 2004	1	88	5	88	28.1%	0.20 [0.02 , 1.68]
WHI 2006 (1)	435	19541	634	29294	71.9%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19629**		**29382**	**100.0%**	**0.65 [0.15 , 2.75]**
Total events:	436		639			
Heterogeneity: Tau² = 0.75; Chi² = 2.27, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.43.5 replacement unclear						
Moy 2001	1	117	1	118	100.0%	1.01 [0.06 , 15.93]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**1.01 [0.06 , 15.93]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 1.00)						

Test for subgroup differences: Chi² = 0.09, df = 3 (P = 0.99), I² = 0%



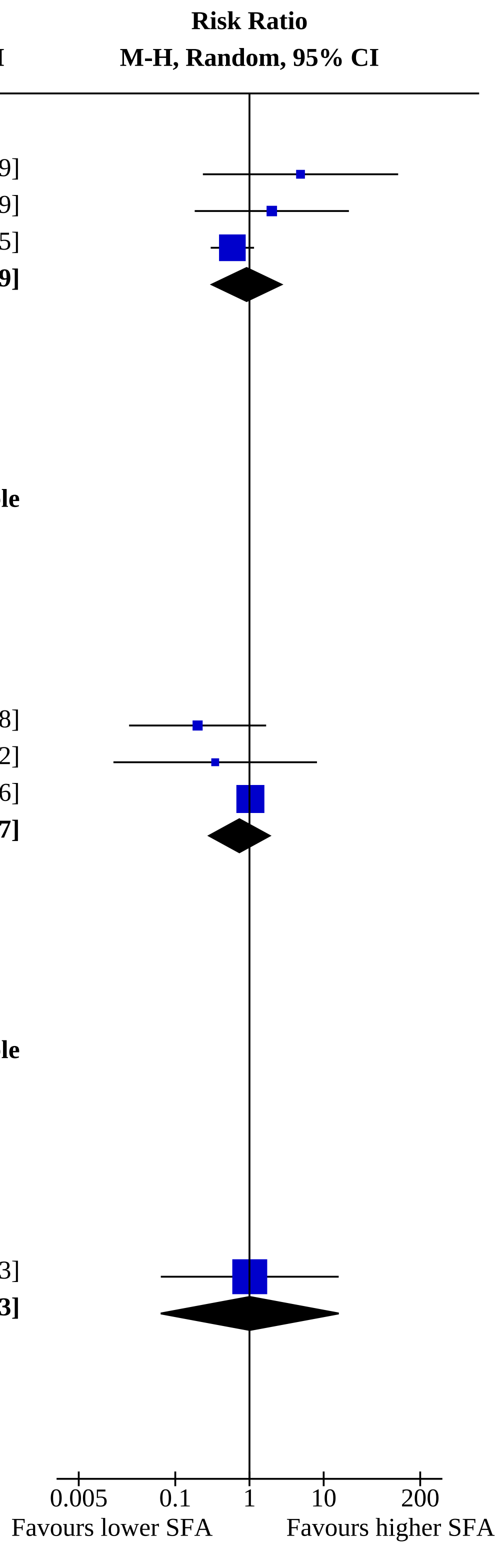
Footnotes

(1) During trial, Prentice 2017

Analysis 2.44. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 44: Stroke, subgroup by main substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
.44.1 replaced by PUFA						
MRC 1968	2	199	0	194	11.2%	4.88 [0.24 , 100.89]
Oslo Diet-Heart 1966	2	206	1	206	16.8%	2.00 [0.18 , 21.89]
Veterans Admin 1969	13	424	22	422	72.0%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**829**		**822**	**100.0%**	**0.92 [0.31 , 2.69]**
Total events:	17		23			
Heterogeneity: Tau² = 0.30; Chi² = 2.60, df = 2 (P = 0.27); I² = 23%						
Test for overall effect: Z = 0.16 (P = 0.87)						
.44.2 replaced by MUFA						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
.44.3 replace by CHO						
Ley 2004	1	88	5	88	15.6%	0.20 [0.02 , 1.68]
STARS 1992	0	27	1	28	7.9%	0.35 [0.01 , 8.12]
WHI 2006 (1)	435	19541	634	29294	76.5%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19656**		**29410**	**100.0%**	**0.73 [0.29 , 1.87]**
Total events:	436		640			
Heterogeneity: Tau² = 0.30; Chi² = 2.73, df = 2 (P = 0.26); I² = 27%						
Test for overall effect: Z = 0.65 (P = 0.51)						
.44.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
.44.5 replacement unclear						
Moy 2001	1	117	1	118	100.0%	1.01 [0.06 , 15.93]
Subtotal (95% CI)		**117**		**118**	**100.0%**	**1.01 [0.06 , 15.93]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 1.00)						

Test for subgroup differences: Chi² = 0.12, df = 2 (P = 0.94), I² = 0%



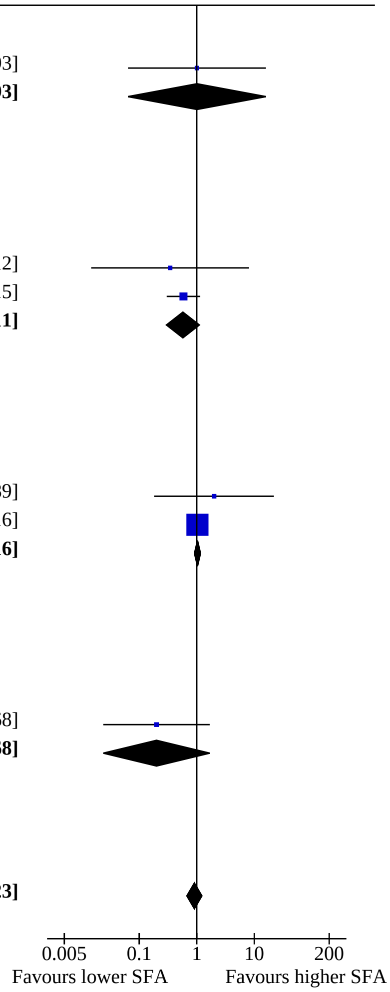
Footnotes

(1) During trial, Prentice 2017

Analysis 2.45. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 45: Stroke, subgroup by duration

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.45.1 up to 24mo						
Moy 2001	1	117	1	118	1.2%	1.01 [0.06 , 15.93]
Subtotal (95% CI)		**117**		**118**	**1.2%**	**1.01 [0.06 , 15.93]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 1.00)						
2.45.2 >24 to 48mo						
STARS 1992	0	27	1	28	0.9%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	16.3%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**451**		**450**	**17.2%**	**0.57 [0.30 , 1.11]**
Total events:	13		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
2.45.3 >48mo						
Oslo Diet-Heart 1966	2	206	1	206	1.6%	2.00 [0.18 , 21.89]
WHI 2006 (1)	435	19541	634	29294	78.1%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19747**		**29500**	**79.6%**	**1.03 [0.91 , 1.16]**
Total events:	437		635			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						
2.45.4 unclear duration						
Ley 2004	1	88	5	88	2.0%	0.20 [0.02 , 1.68]
Subtotal (95% CI)		**88**		**88**	**2.0%**	**0.20 [0.02 , 1.68]**
Total events:	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Total (95% CI)		**20403**		**30156**	**100.0%**	**0.91 [0.67 , 1.23]**
Total events:	452		664			
Heterogeneity: Tau² = 0.03; Chi² = 5.56, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 5.15, df = 3 (P = 0.16), I² = 41.8%						

Risk Ratio M-H, Random, 95% CI

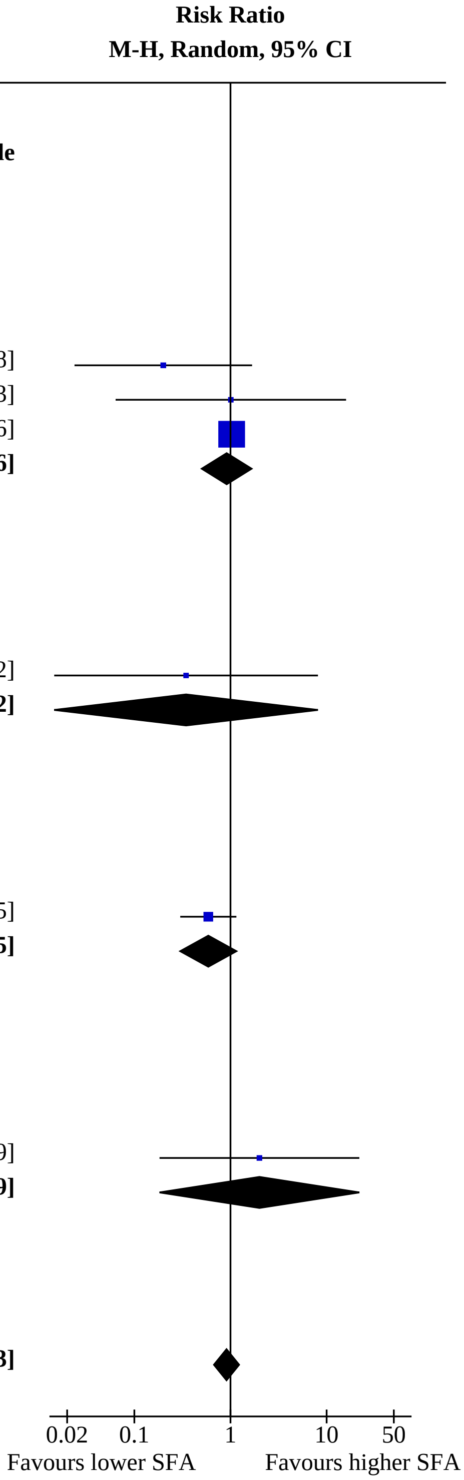


Footnotes

(1) During trial, Prentice 2017

Analysis 2.46. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 46: Stroke, subgroup by baseline SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.46.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.46.2 >12 to 15%E SFA baseline						
Ley 2004	1	88	5	88	2.0%	0.20 [0.02 , 1.68]
Moy 2001	1	117	1	118	1.2%	1.01 [0.06 , 15.93]
WHI 2006 (1)	435	19541	634	29294	78.1%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19746**		**29500**	**81.2%**	**0.91 [0.50 , 1.66]**
Total events:	437		640			
Heterogeneity: Tau² = 0.10; Chi² = 2.27, df = 2 (P = 0.32); I² = 12%						
Test for overall effect: Z = 0.30 (P = 0.76)						
2.46.3 >15 to 18%E SFA baseline						
STARS 1992	0	27	1	28	0.9%	0.35 [0.01 , 8.12]
Subtotal (95% CI)		**27**		**28**	**0.9%**	**0.35 [0.01 , 8.12]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
2.46.4 >18%E SFA baseline						
Veterans Admin 1969	13	424	22	422	16.3%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**424**		**422**	**16.3%**	**0.59 [0.30 , 1.15]**
Total events:	13		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
2.46.5 unclear						
Oslo Diet-Heart 1966	2	206	1	206	1.6%	2.00 [0.18 , 21.89]
Subtotal (95% CI)		**206**		**206**	**1.6%**	**2.00 [0.18 , 21.89]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**20403**		**30156**	**100.0%**	**0.91 [0.67 , 1.23]**
Total events:	452		664			
Heterogeneity: Tau² = 0.03; Chi² = 5.56, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 1.79, df = 3 (P = 0.62), I² = 0%						

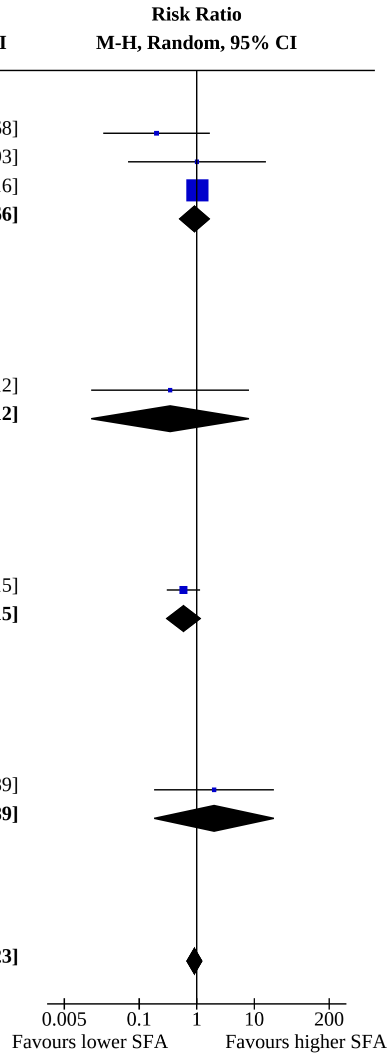


Footnotes

(1) During trial, Prentice 2017

Analysis 2.47. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 47: Stroke, subgroup by SFA change

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.47.1 up to 4%E difference						
Ley 2004	1	88	5	88	2.0%	0.20 [0.02 , 1.68]
Moy 2001	1	117	1	118	1.2%	1.01 [0.06 , 15.93]
WHI 2006 (1)	435	19541	634	29294	78.1%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19746**		**29500**	**81.2%**	**0.91 [0.50 , 1.66]**
Total events:	437		640			
Heterogeneity: Tau² = 0.10; Chi² = 2.27, df = 2 (P = 0.32); I² = 12%						
Test for overall effect: Z = 0.30 (P = 0.76)						
2.47.2 >4 to 8%E difference						
STARS 1992	0	27	1	28	0.9%	0.35 [0.01 , 8.12]
Subtotal (95% CI)		**27**		**28**	**0.9%**	**0.35 [0.01 , 8.12]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
2.47.3 >8%E difference						
Veterans Admin 1969	13	424	22	422	16.3%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**424**		**422**	**16.3%**	**0.59 [0.30 , 1.15]**
Total events:	13		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
2.47.4 unclear						
Oslo Diet-Heart 1966	2	206	1	206	1.6%	2.00 [0.18 , 21.89]
Subtotal (95% CI)		**206**		**206**	**1.6%**	**2.00 [0.18 , 21.89]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**20403**		**30156**	**100.0%**	**0.91 [0.67 , 1.23]**
Total events:	452		664			
Heterogeneity: Tau² = 0.03; Chi² = 5.56, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 1.79, df = 3 (P = 0.62), I² = 0%						

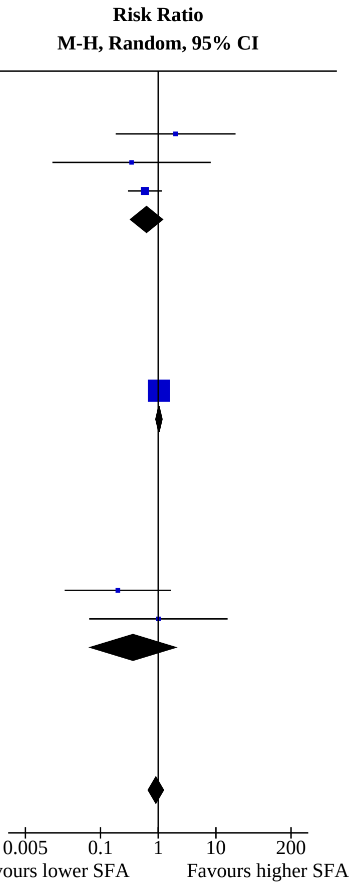


Footnotes

(1) During trial, Prentice 2017

Analysis 2.48. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 48: Stroke, subgroup by sex

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.48.1 Men						
Oslo Diet-Heart 1966	2	206	1	206	1.6%	2.00 [0.18 , 21.89]
STARS 1992	0	27	1	28	0.9%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	16.3%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**657**		**656**	**18.8%**	**0.63 [0.33 , 1.18]**
Total events:	15		24			
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 2 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
2.48.2 Women						
WHI 2006 (1)	435	19541	634	29294	78.1%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19541**		**29294**	**78.1%**	**1.03 [0.91 , 1.16]**
Total events:	435		634			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
2.48.3 Mixed, men and women						
Ley 2004	1	88	5	88	2.0%	0.20 [0.02 , 1.68]
Moy 2001	1	117	1	118	1.2%	1.01 [0.06 , 15.93]
Subtotal (95% CI)		**205**		**206**	**3.1%**	**0.37 [0.07 , 1.97]**
Total events:	2		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**20403**		**30156**	**100.0%**	**0.91 [0.67 , 1.23]**
Total events:	452		664			
Heterogeneity: Tau² = 0.03; Chi² = 5.56, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 3.65, df = 2 (P = 0.16), I² = 45.2%						

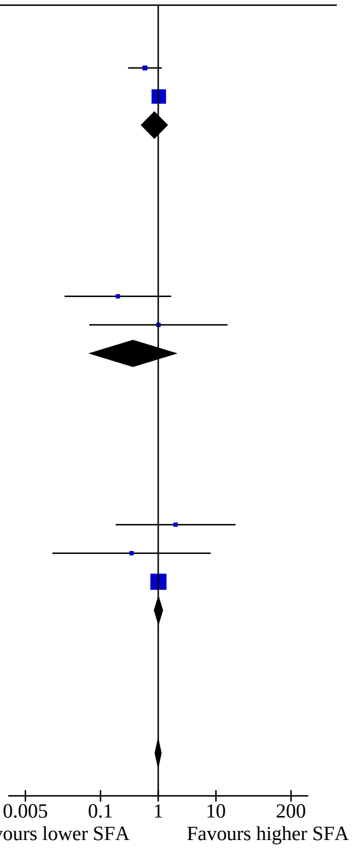


Footnotes
(1) During trial, Prentice 2017

Analysis 2.49. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 49: Stroke, subgroup by CVD risk

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.49.1 Low CVD risk						
Veterans Admin 1969	13	424	22	422	2.8%	0.59 [0.30 , 1.15]
WHI 2006 (1)	228	18633	334	27925	44.6%	1.02 [0.87 , 1.21]
Subtotal (95% CI)		**19057**		**28347**	**47.4%**	**0.86 [0.52 , 1.42]**
Total events:	241		356			
Heterogeneity: Tau² = 0.09; Chi² = 2.45, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.49.2 Moderate CVD risk						
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]
Subtotal (95% CI)		**205**		**206**	**0.4%**	**0.37 [0.07 , 1.97]**
Total events:	2		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
2.49.3 Existing CVD disease						
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]
WHI 2006	206	908	308	1369	51.9%	1.01 [0.86 , 1.18]
Subtotal (95% CI)		**1141**		**1603**	**52.2%**	**1.01 [0.86 , 1.18]**
Total events:	208		310			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**20403**		**30156**	**100.0%**	**1.00 [0.89 , 1.11]**
Total events:	451		672			
Heterogeneity: Tau² = 0.00; Chi² = 5.44, df = 6 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Test for subgroup differences: Chi² = 1.71, df = 2 (P = 0.42), I² = 0%						

Risk Ratio
M-H, Random, 95% CI



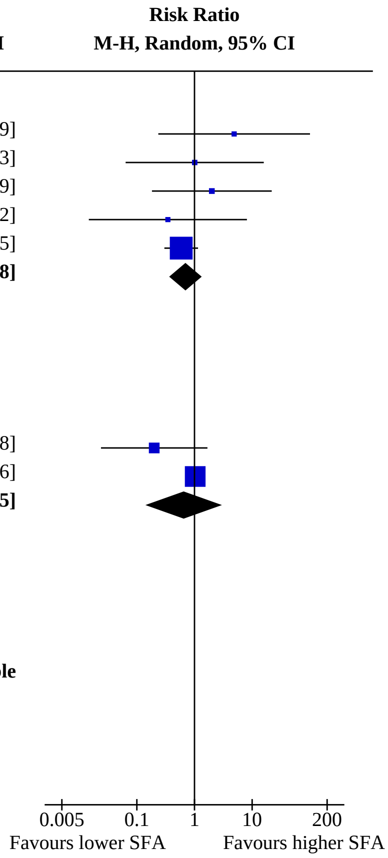
Footnotes

(1) Women without CVD at baseline

Analysis 2.50. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 50: Stroke, subgroup by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.50.1 serum chol reduced by at least 0.2mmol/L						
MRC 1968	2	199	0	194	4.0%	4.88 [0.24 , 100.89]
Moy 2001	1	117	1	118	4.8%	1.01 [0.06 , 15.93]
Oslo Diet-Heart 1966	2	206	1	206	6.4%	2.00 [0.18 , 21.89]
STARS 1992	0	27	1	28	3.7%	0.35 [0.01 , 8.12]
Veterans Admin 1969	13	424	22	422	81.1%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**973**		**968**	**100.0%**	**0.70 [0.38 , 1.28]**
Total events:	18		25			
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 4 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
2.50.2 serum chol reduced by <0.2mmol/L						
Ley 2004	1	88	5	88	28.1%	0.20 [0.02 , 1.68]
WHI 2006 (1)	435	19541	634	29294	71.9%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19629**		**29382**	**100.0%**	**0.65 [0.15 , 2.75]**
Total events:	436		639			
Heterogeneity: Tau² = 0.75; Chi² = 2.27, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.50.3 serum chol reduction unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

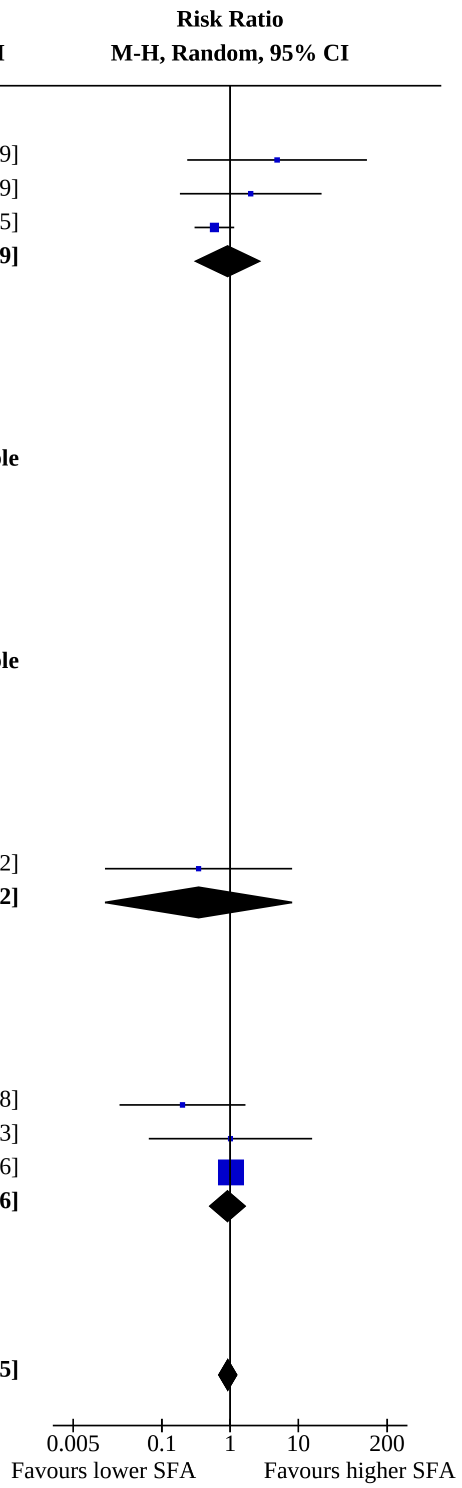


Footnotes

(1) During trial, Prentice 2017

Analysis 2.51. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 51: Stroke, subgroup decade of publication

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.51.1 1960s						
MRC 1968	2	199	0	194	1.0%	4.88 [0.24 , 100.89]
Oslo Diet-Heart 1966	2	206	1	206	1.6%	2.00 [0.18 , 21.89]
Veterans Admin 1969	13	424	22	422	16.4%	0.59 [0.30 , 1.15]
Subtotal (95% CI)		**829**		**822**	**19.0%**	**0.92 [0.31 , 2.69]**
Total events:	17		23			
Heterogeneity: Tau² = 0.30; Chi² = 2.60, df = 2 (P = 0.27); I² = 23%						
Test for overall effect: Z = 0.16 (P = 0.87)						
2.51.2 1970s						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.51.3 1980s						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.51.4 1990s						
STARS 1992	0	27	1	28	0.9%	0.35 [0.01 , 8.12]
Subtotal (95% CI)		**27**		**28**	**0.9%**	**0.35 [0.01 , 8.12]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
2.51.5 2000s						
Ley 2004	1	88	5	88	2.0%	0.20 [0.02 , 1.68]
Moy 2001	1	117	1	118	1.2%	1.01 [0.06 , 15.93]
WHI 2006 (1)	435	19541	634	29294	76.9%	1.03 [0.91 , 1.16]
Subtotal (95% CI)		**19746**		**29500**	**80.1%**	**0.91 [0.50 , 1.66]**
Total events:	437		640			
Heterogeneity: Tau² = 0.10; Chi² = 2.27, df = 2 (P = 0.32); I² = 12%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**20602**		**30350**	**100.0%**	**0.92 [0.68 , 1.25]**
Total events:	454		664			
Heterogeneity: Tau² = 0.03; Chi² = 6.59, df = 6 (P = 0.36); I² = 9%						
Test for overall effect: Z = 0.52 (P = 0.60)						
Test for subgroup differences: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%						



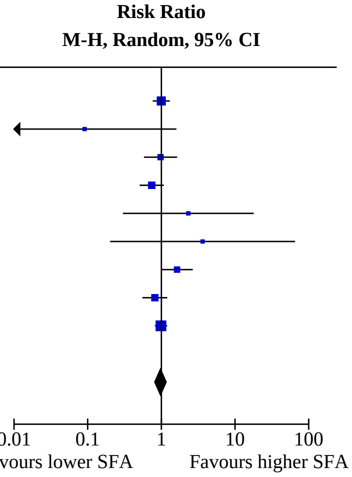
Footnotes

(1) During trial, Prentice 2017

Analysis 2.52. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 52: CORONARY HEART DISEASE MORTALITY

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	97	1018	97	1015	21.9%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.4%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	9.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	14.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	0.7%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.4%	3.63 [0.20 , 65.44]
Sydney Diet-Heart 1978	35	221	23	237	9.9%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	13.9%	0.82 [0.55 , 1.21]
WHI 2006 (1)	172	19541	261	29294	29.2%	0.99 [0.82 , 1.20]
Total (95% CI)		**21714**		**31445**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	415		512			

Heterogeneity: Tau² = 0.02; Chi² = 11.18, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable

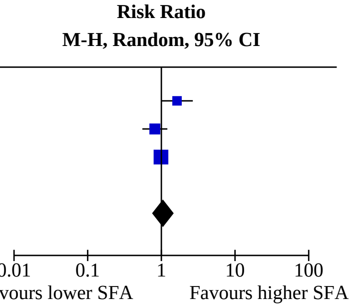


Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.53. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 53: CHD mortality, SA by low summary risk of bias

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Sydney Diet-Heart 1978	35	221	23	237	23.3%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	29.9%	0.82 [0.55 , 1.21]
WHI 2006 (1)	172	19541	261	29294	46.7%	0.99 [0.82 , 1.20]
Total (95% CI)		**20186**		**29953**	**100.0%**	**1.05 [0.77 , 1.43]**
Total events:	248		334			

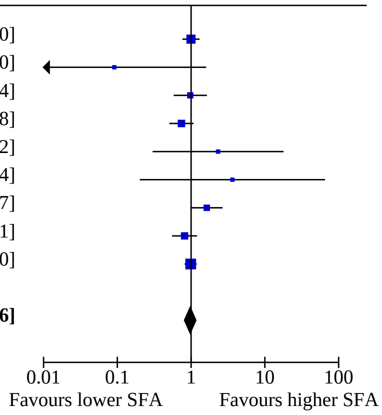
Heterogeneity: Tau² = 0.04; Chi² = 4.83, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.54. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 54: CHD mortality, SA aim to reduce SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	97	1018	97	1015	21.9%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.4%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	9.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	14.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	0.7%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.4%	3.63 [0.20 , 65.44]
Sydney Diet-Heart 1978	35	221	23	237	9.9%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	13.9%	0.82 [0.55 , 1.21]
WHI 2006 (1)	172	19541	261	29294	29.2%	0.99 [0.82 , 1.20]
Total (95% CI)		**21714**		**31445**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	415		512			

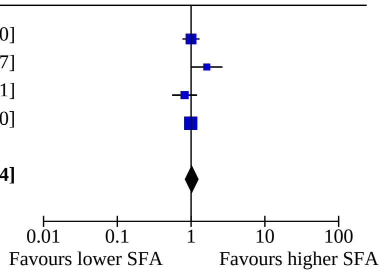


Heterogeneity: Tau² = 0.02; Chi² = 11.18, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.55. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 55: CHD mortality, SA statistically significant SFA reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	97	1018	97	1015	29.3%	1.00 [0.76 , 1.30]
Sydney Diet-Heart 1978	35	221	23	237	12.5%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	18.0%	0.82 [0.55 , 1.21]
WHI 2006 (1)	172	19541	261	29294	40.3%	0.99 [0.82 , 1.20]
Total (95% CI)		**21204**		**30968**	**100.0%**	**1.02 [0.84 , 1.24]**
Total events:	345		431			

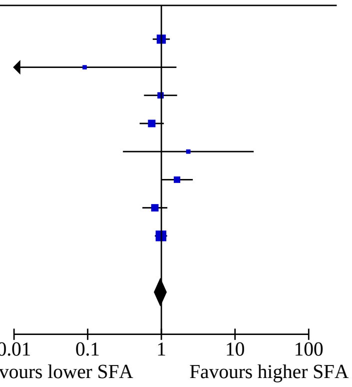


Heterogeneity: Tau² = 0.01; Chi² = 4.84, df = 3 (P = 0.18); I² = 38%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.56. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 56: CHD mortality, SA by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	97	1018	97	1015	21.9%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.4%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	9.3%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	14.7%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	0.7%	2.32 [0.30 , 17.92]
Sydney Diet-Heart 1978	35	221	23	237	10.0%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	14.1%	0.82 [0.55 , 1.21]
WHI 2006 (1)	172	19541	261	29294	28.9%	0.99 [0.82 , 1.20]
Total (95% CI)		**21688**		**31432**	**100.0%**	**0.97 [0.81 , 1.16]**
Total events:	412		512			

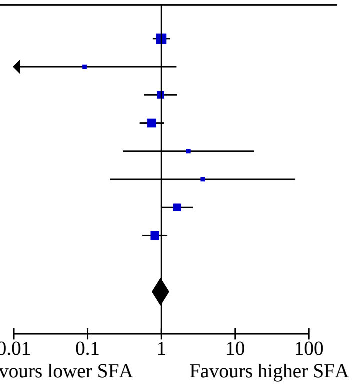


Heterogeneity: Tau² = 0.02; Chi² = 10.38, df = 7 (P = 0.17); I² = 33%
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.57. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 57: CHD mortality, SA excluding WHI

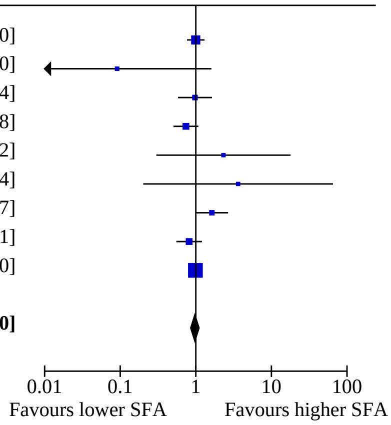
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	97	1018	97	1015	27.0%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.7%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	14.4%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	20.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	1.4%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.7%	3.63 [0.20 , 65.44]
Sydney Diet-Heart 1978	35	221	23	237	15.3%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	19.9%	0.82 [0.55 , 1.21]
Total (95% CI)		**2173**		**2151**	**100.0%**	**0.97 [0.76 , 1.24]**
Total events:	243		251			



Heterogeneity: Tau² = 0.04; Chi² = 11.13, df = 7 (P = 0.13); I² = 37%
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable

Analysis 2.58. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 58: CHD mortality, SA Mantel-Haenszel fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	97	1018	97	1015	21.1%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	1.2%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	5.5%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	10.8%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	0.3%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.1%	3.63 [0.20 , 65.44]
Sydney Diet-Heart 1978	35	221	23	237	4.8%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	10.9%	0.82 [0.55 , 1.21]
WHI 2006 (1)	172	19541	261	29294	45.3%	0.99 [0.82 , 1.20]
Total (95% CI)		**21714**		**31445**	**100.0%**	**0.97 [0.86 , 1.10]**
Total events:	415		512			

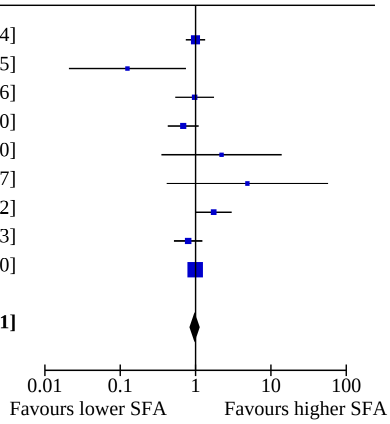


Heterogeneity: Chi² = 11.18, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.59. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 59: CHD mortality, SA Peto fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
DART 1989	97	1018	97	1015	20.8%	1.00 [0.74 , 1.34]
Houtsmuller 1979	0	51	5	51	0.6%	0.12 [0.02 , 0.75]
MRC 1968	25	199	25	194	5.2%	0.97 [0.54 , 1.76]
Oslo Diet-Heart 1966	37	206	50	206	8.2%	0.69 [0.43 , 1.10]
Rose corn oil 1965	5	28	1	13	0.5%	2.21 [0.35 , 13.90]
Rose olive 1965	3	26	0	13	0.3%	4.87 [0.41 , 57.37]
Sydney Diet-Heart 1978	35	221	23	237	6.0%	1.74 [1.00 , 3.02]
Veterans Admin 1969	41	424	50	422	9.6%	0.80 [0.52 , 1.23]
WHI 2006 (1)	172	19541	261	29294	48.8%	0.99 [0.81 , 1.20]
Total (95% CI)		**21714**		**31445**	**100.0%**	**0.97 [0.85 , 1.11]**
Total events:	415		512			



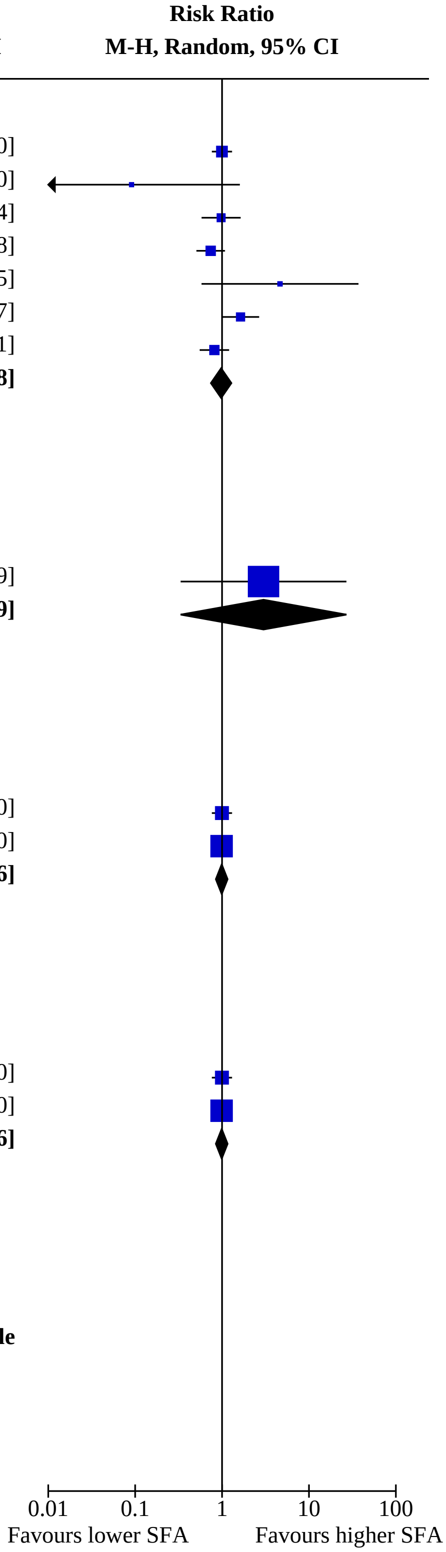
Heterogeneity: Chi² = 14.72, df = 8 (P = 0.06); I² = 46%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD death during trial, Prentice 2017

Analysis 2.60. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 60: CHD mortality, subgroup by any substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.60.1 replaced by PUFA						
DART 1989	97	1018	97	1015	25.6%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.9%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	15.2%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	20.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	26	1.6%	4.64 [0.58 , 37.15]
Sydney Diet-Heart 1978	35	221	23	237	16.1%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	20.0%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**2147**		**2151**	**100.0%**	**0.98 [0.74 , 1.28]**
Total events:	240		251			
Heterogeneity: Tau² = 0.06; Chi² = 11.81, df = 6 (P = 0.07); I² = 49%						
Test for overall effect: Z = 0.18 (P = 0.86)						
2.60.2 replaced by MUFA						
Rose olive 1965	3	26	1	26	100.0%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.33 , 26.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
2.60.3 replaced by CHO						
DART 1989	97	1018	97	1015	33.9%	1.00 [0.76 , 1.30]
WHI 2006 (1)	172	19541	261	29294	66.1%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**20559**		**30309**	**100.0%**	**0.99 [0.85 , 1.16]**
Total events:	269		358			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
2.60.4 replaced by protein						
DART 1989	97	1018	97	1015	33.9%	1.00 [0.76 , 1.30]
WHI 2006 (1)	172	19541	261	29294	66.1%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**20559**		**30309**	**100.0%**	**0.99 [0.85 , 1.16]**
Total events:	269		358			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
2.60.5 replacement unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 0.99, df = 3 (P = 0.80), I² = 0%



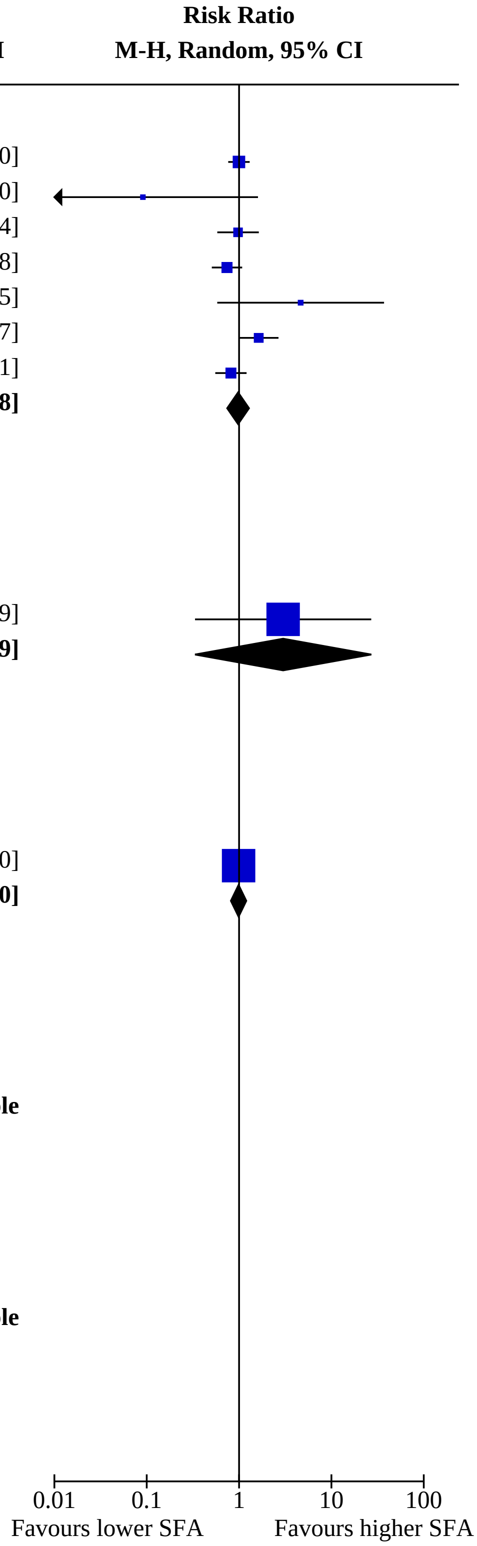
Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.61. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 61: CHD mortality, subgroup by main substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.61.1 replaced by PUFA						
DART 1989	97	1018	97	1015	25.6%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.9%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	15.2%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	20.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	26	1.6%	4.64 [0.58 , 37.15]
Sydney Diet-Heart 1978	35	221	23	237	16.1%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	20.0%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**2147**		**2151**	**100.0%**	**0.98 [0.74 , 1.28]**
Total events:	240		251			
Heterogeneity: Tau² = 0.06; Chi² = 11.81, df = 6 (P = 0.07); I² = 49%						
Test for overall effect: Z = 0.18 (P = 0.86)						
2.61.2 replaced by MUFA						
Rose olive 1965	3	26	1	26	100.0%	3.00 [0.33 , 26.99]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.33 , 26.99]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
2.61.3 replaced by CHO						
WHI 2006 (1)	172	19541	261	29294	100.0%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**19541**		**29294**	**100.0%**	**0.99 [0.82 , 1.20]**
Total events:	172		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
2.61.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.61.5 replacement unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 0.99, df = 2 (P = 0.61), I² = 0%



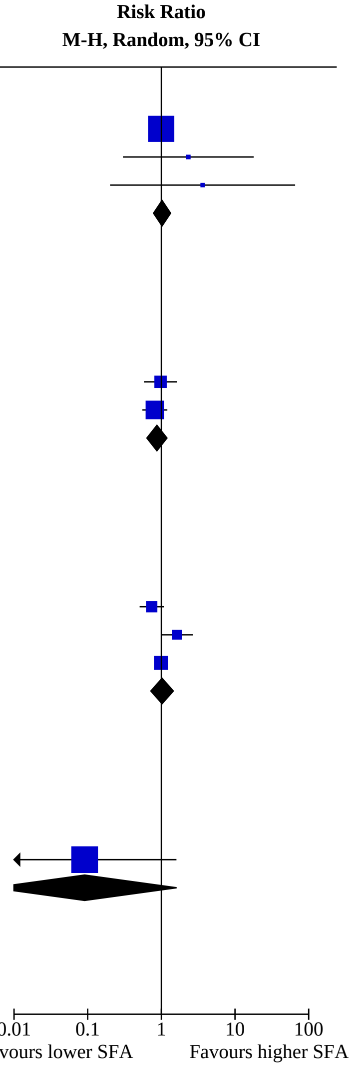
Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.62. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 62: CHD mortality, subgroup by duration

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.62.1 up to 24mo						
DART 1989	97	1018	97	1015	97.5%	1.00 [0.76 , 1.30]
Rose corn oil 1965	5	28	1	13	1.7%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.8%	3.63 [0.20 , 65.44]
Subtotal (95% CI)		**1072**		**1041**	**100.0%**	**1.02 [0.78 , 1.33]**
Total events:	105		98			
Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
2.62.2 >24 to 48months						
MRC 1968	25	199	25	194	36.2%	0.97 [0.58 , 1.64]
Veterans Admin 1969	41	424	50	422	63.8%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**623**		**616**	**100.0%**	**0.87 [0.64 , 1.19]**
Total events:	66		75			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
2.62.3 >48 months						
Oslo Diet-Heart 1966	37	206	50	206	31.5%	0.74 [0.51 , 1.08]
Sydney Diet-Heart 1978	35	221	23	237	25.1%	1.63 [1.00 , 2.67]
WHI 2006 (1)	172	19541	261	29294	43.4%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**19968**		**29737**	**100.0%**	**1.02 [0.72 , 1.45]**
Total events:	244		334			
Heterogeneity: Tau² = 0.06; Chi² = 6.22, df = 2 (P = 0.04); I² = 68%						
Test for overall effect: Z = 0.13 (P = 0.90)						
2.62.4 unclear duration						
Houtsmuller 1979	0	51	5	51	100.0%	0.09 [0.01 , 1.60]
Subtotal (95% CI)		**51**		**51**	**100.0%**	**0.09 [0.01 , 1.60]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						

Test for subgroup differences: Chi² = 3.31, df = 3 (P = 0.35), I² = 9.4%



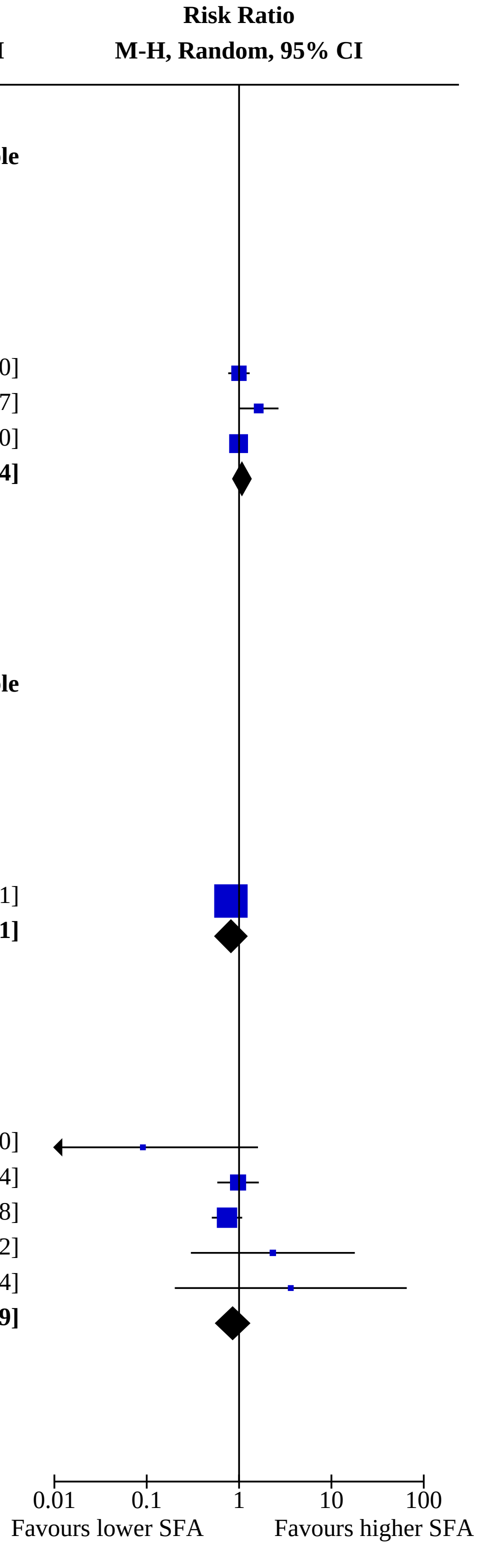
Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.63. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 63: CHD mortality, subgroup by baseline SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.63.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.63.2 >12% to 15%E SFA baseline						
DART 1989	97	1018	97	1015	35.9%	1.00 [0.76 , 1.30]
Sydney Diet-Heart 1978	35	221	23	237	15.9%	1.63 [1.00 , 2.67]
WHI 2006 (1)	172	19541	261	29294	48.2%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**20780**		**30546**	**100.0%**	**1.07 [0.86 , 1.34]**
Total events:	304		381			
Heterogeneity: Tau² = 0.02; Chi² = 3.58, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 0.63 (P = 0.53)						
2.63.3 >15 to 18%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.63.4 >18%E SFA baseline						
Veterans Admin 1969	41	424	50	422	100.0%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**424**		**422**	**100.0%**	**0.82 [0.55 , 1.21]**
Total events:	41		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.63.5 unclear						
Houtsmuller 1979	0	51	5	51	2.0%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	38.5%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	53.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	3.9%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	2.0%	3.63 [0.20 , 65.44]
Subtotal (95% CI)		**510**		**477**	**100.0%**	**0.85 [0.56 , 1.29]**
Total events:	70		81			
Heterogeneity: Tau² = 0.05; Chi² = 4.98, df = 4 (P = 0.29); I² = 20%						
Test for overall effect: Z = 0.76 (P = 0.45)						

Test for subgroup differences: Chi² = 1.94, df = 2 (P = 0.38), I² = 0%



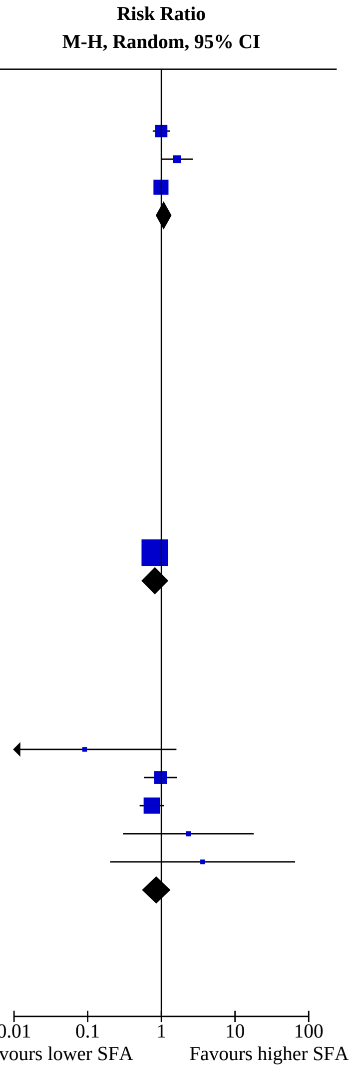
Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.64. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 64: CHD mortality, subgroup by SFA change

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.64.1 up to 4%E difference						
DART 1989	97	1018	97	1015	35.9%	1.00 [0.76 , 1.30]
Sydney Diet-Heart 1978	35	221	23	237	15.9%	1.63 [1.00 , 2.67]
WHI 2006 (1)	172	19541	261	29294	48.2%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**20780**		**30546**	**100.0%**	**1.07 [0.86 , 1.34]**
Total events:	304		381			
Heterogeneity: Tau² = 0.02; Chi² = 3.58, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 0.63 (P = 0.53)						
2.64.2 >4 to 8%E difference						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.64.3 >8%E difference						
Veterans Admin 1969	41	424	50	422	100.0%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**424**		**422**	**100.0%**	**0.82 [0.55 , 1.21]**
Total events:	41		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.64.4 unclear						
Houtsmuller 1979	0	51	5	51	2.0%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	38.5%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	53.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	3.9%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	2.0%	3.63 [0.20 , 65.44]
Subtotal (95% CI)		**510**		**477**	**100.0%**	**0.85 [0.56 , 1.29]**
Total events:	70		81			
Heterogeneity: Tau² = 0.05; Chi² = 4.98, df = 4 (P = 0.29); I² = 20%						
Test for overall effect: Z = 0.76 (P = 0.45)						

Test for subgroup differences: Chi² = 1.94, df = 2 (P = 0.38), I² = 0%

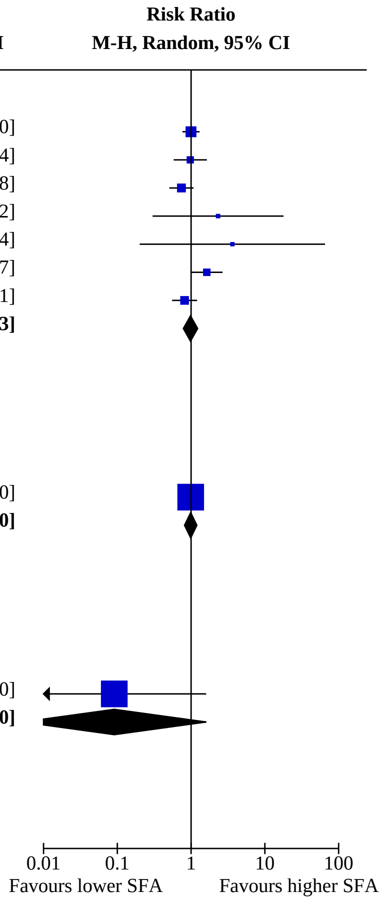


Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.65. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 65: CHD mortality, subgroup by sex

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.65.1 Men						
DART 1989	97	1018	97	1015	29.6%	1.00 [0.76 , 1.30]
MRC 1968	25	199	25	194	13.6%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	20.7%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	1.2%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.6%	3.63 [0.20 , 65.44]
Sydney Diet-Heart 1978	35	221	23	237	14.6%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	19.9%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**2122**		**2100**	**100.0%**	**0.98 [0.79 , 1.23]**
Total events:	243		246			
Heterogeneity: Tau² = 0.02; Chi² = 8.55, df = 6 (P = 0.20); I² = 30%						
Test for overall effect: Z = 0.16 (P = 0.87)						
2.65.2 Women						
WHI 2006 (1)	172	19541	261	29294	100.0%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**19541**		**29294**	**100.0%**	**0.99 [0.82 , 1.20]**
Total events:	172		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
2.65.3 Mixed, men and women						
Houtsmuller 1979	0	51	5	51	100.0%	0.09 [0.01 , 1.60]
Subtotal (95% CI)		**51**		**51**	**100.0%**	**0.09 [0.01 , 1.60]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						



Test for subgroup differences: Chi² = 2.64, df = 2 (P = 0.27), I² = 24.4%

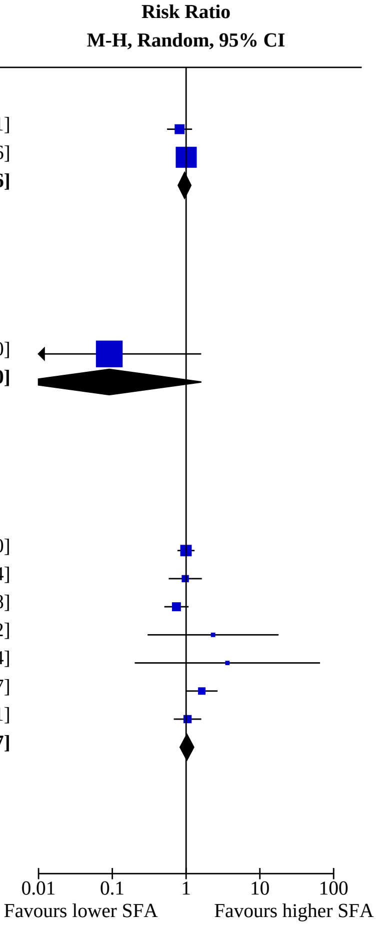
Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.66. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 66: CHD mortality, subgroup by CVD risk

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.66.1 Low CVD risk						
Veterans Admin 1969	41	424	50	422	25.2%	0.82 [0.55 , 1.21]
WHI 2006 (1)	124	18633	185	27925	74.8%	1.00 [0.80 , 1.26]
Subtotal (95% CI)		**19057**		**28347**	**100.0%**	**0.95 [0.78 , 1.16]**
Total events:	165		235			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
2.66.2 Moderate CVD risk						
Houtsmuller 1979	0	51	5	51	100.0%	0.09 [0.01 , 1.60]
Subtotal (95% CI)		**51**		**51**	**100.0%**	**0.09 [0.01 , 1.60]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
2.66.3 Existing CVD disease						
DART 1989	97	1018	97	1015	32.2%	1.00 [0.76 , 1.30]
MRC 1968	25	199	25	194	13.2%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	21.1%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	1.0%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.5%	3.63 [0.20 , 65.44]
Sydney Diet-Heart 1978	35	221	23	237	14.3%	1.63 [1.00 , 2.67]
WHI 2006 (2)	34	908	49	1369	17.7%	1.05 [0.68 , 1.61]
Subtotal (95% CI)		**2606**		**3047**	**100.0%**	**1.03 [0.83 , 1.27]**
Total events:	236		245			
Heterogeneity: Tau² = 0.02; Chi² = 7.69, df = 6 (P = 0.26); I² = 22%						
Test for overall effect: Z = 0.24 (P = 0.81)						

Test for subgroup differences: Chi² = 2.90, df = 2 (P = 0.23), I² = 31.0%



Footnotes

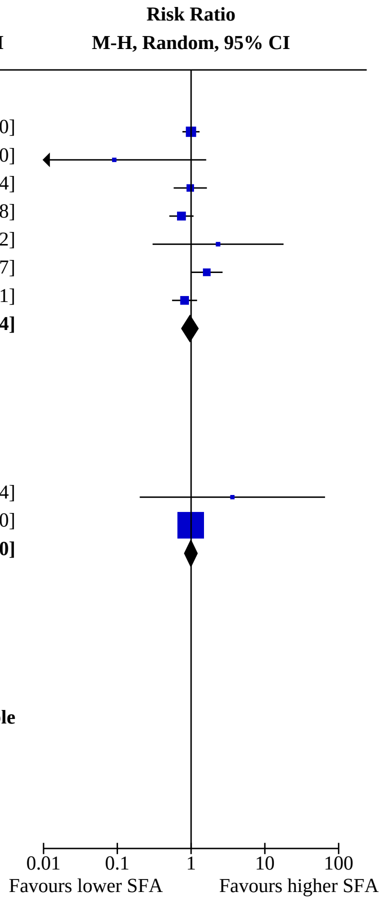
(1) Women without CVD at baseline

(2) Women with CVD at baseline

Analysis 2.67. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 67: CHD mortality, subgroup by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.67.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	97	1018	97	1015	27.0%	1.00 [0.76 , 1.30]
Houtsmuller 1979	0	51	5	51	0.7%	0.09 [0.01 , 1.60]
MRC 1968	25	199	25	194	14.6%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	20.6%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	1.4%	2.32 [0.30 , 17.92]
Sydney Diet-Heart 1978	35	221	23	237	15.5%	1.63 [1.00 , 2.67]
Veterans Admin 1969	41	424	50	422	20.0%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**2147**		**2138**	**100.0%**	**0.96 [0.75 , 1.24]**
Total events:	240		251			
Heterogeneity: Tau² = 0.04; Chi² = 10.31, df = 6 (P = 0.11); I² = 42%						
Test for overall effect: Z = 0.29 (P = 0.77)						
2.67.2 serum chol reduced by <0.2mmol/L						
Rose olive 1965	3	26	0	13	0.4%	3.63 [0.20 , 65.44]
WHI 2006 (1)	172	19541	261	29294	99.6%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**19567**		**29307**	**100.0%**	**0.99 [0.82 , 1.20]**
Total events:	175		261			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
2.67.3 serum chol reduction unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%

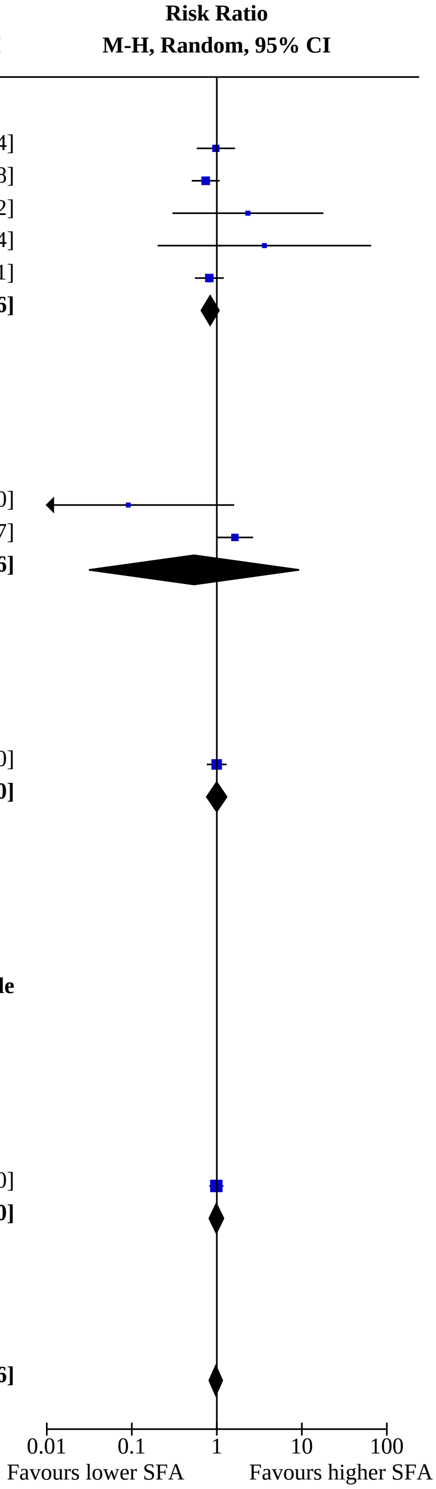


Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.68. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 68: CHD mortality, subgroup decade of publication

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.68.1 1960s						
MRC 1968	25	199	25	194	9.1%	0.97 [0.58 , 1.64]
Oslo Diet-Heart 1966	37	206	50	206	14.5%	0.74 [0.51 , 1.08]
Rose corn oil 1965	5	28	1	13	0.7%	2.32 [0.30 , 17.92]
Rose olive 1965	3	26	0	13	0.4%	3.63 [0.20 , 65.44]
Veterans Admin 1969	41	424	50	422	13.9%	0.82 [0.55 , 1.21]
Subtotal (95% CI)		**883**		**848**	**38.7%**	**0.84 [0.66 , 1.06]**
Total events:	111		126			
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 4 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
2.68.2 1970s						
Houtsmuller 1979	0	51	5	51	0.4%	0.09 [0.01 , 1.60]
Sydney Diet-Heart 1978	35	221	23	237	9.9%	1.63 [1.00 , 2.67]
Subtotal (95% CI)		**272**		**288**	**10.2%**	**0.54 [0.03 , 9.26]**
Total events:	35		28			
Heterogeneity: Tau² = 3.35; Chi² = 4.03, df = 1 (P = 0.04); I² = 75%						
Test for overall effect: Z = 0.43 (P = 0.67)						
2.68.3 1980s						
DART 1989	97	1018	97	1015	21.9%	1.00 [0.76 , 1.30]
Subtotal (95% CI)		**1018**		**1015**	**21.9%**	**1.00 [0.76 , 1.30]**
Total events:	97		97			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
2.68.4 1990s						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.68.5 2000s						
WHI 2006 (1)	172	19541	261	29294	29.2%	0.99 [0.82 , 1.20]
Subtotal (95% CI)		**19541**		**29294**	**29.2%**	**0.99 [0.82 , 1.20]**
Total events:	172		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**21714**		**31445**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	415		512			
Heterogeneity: Tau² = 0.02; Chi² = 11.18, df = 8 (P = 0.19); I² = 28%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 1.54, df = 3 (P = 0.67), I² = 0%						

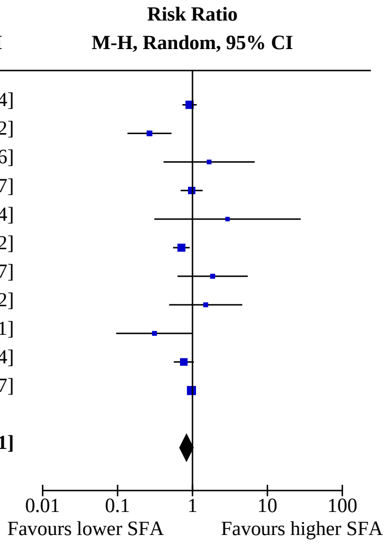


Footnotes

(1) CHD death during trial, Prentice 2017

Analysis 2.69. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 69: CORONARY HEART DISEASE EVENTS

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	17.5%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	6.2%	0.27 [0.14 , 0.52]
Ley 2004	5	88	3	88	1.9%	1.67 [0.41 , 6.76]
MRC 1968	50	199	50	194	13.6%	0.97 [0.69 , 1.37]
Moy 2001	3	135	1	132	0.8%	2.93 [0.31 , 27.84]
Oslo Diet-Heart 1966	64	206	90	206	16.3%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	2.9%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	2.8%	1.50 [0.49 , 4.62]
STARS 1992	3	27	10	28	2.5%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	14.5%	0.77 [0.56 , 1.04]
WHI 2006 (1)	590	19541	913	29294	21.0%	0.97 [0.87 , 1.07]
Total (95% CI)		**21743**		**31456**	**100.0%**	**0.83 [0.68 , 1.01]**
Total events:	936		1325			

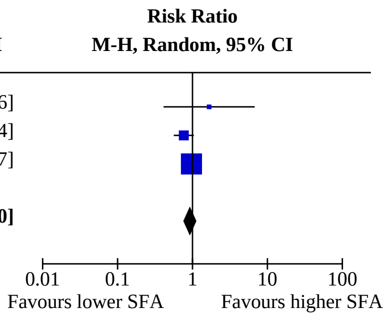


Heterogeneity: Tau² = 0.05; Chi² = 26.44, df = 10 (P = 0.003); I² = 62%
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.70. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 70: CHD events, SA by low summary risk of bias

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	5	88	3	88	1.6%	1.67 [0.41 , 6.76]
Veterans Admin 1969	60	424	78	422	24.7%	0.77 [0.56 , 1.04]
WHI 2006 (1)	590	19541	913	29294	73.7%	0.97 [0.87 , 1.07]
Total (95% CI)		**20053**		**29804**	**100.0%**	**0.92 [0.77 , 1.10]**
Total events:	655		994			

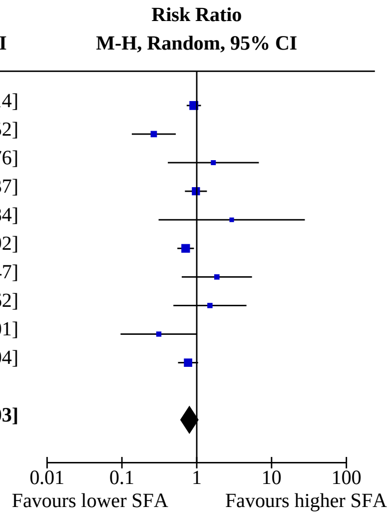


Heterogeneity: Tau² = 0.01; Chi² = 2.64, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.71. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 71: CHD events, SA excluding WHI

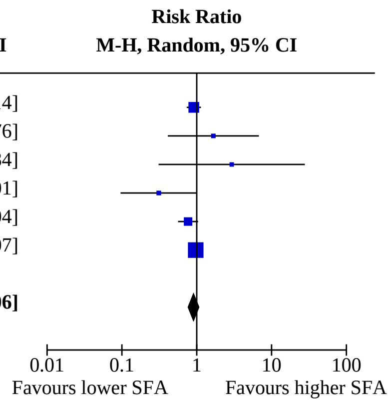
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	20.2%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	9.0%	0.27 [0.14 , 0.52]
Ley 2004	5	88	3	88	3.0%	1.67 [0.41 , 6.76]
MRC 1968	50	199	50	194	16.8%	0.97 [0.69 , 1.37]
Moy 2001	3	135	1	132	1.2%	2.93 [0.31 , 27.84]
Oslo Diet-Heart 1966	64	206	90	206	19.2%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	4.6%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	4.3%	1.50 [0.49 , 4.62]
STARS 1992	3	27	10	28	4.0%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	17.7%	0.77 [0.56 , 1.04]
Total (95% CI)		**2202**		**2162**	**100.0%**	**0.80 [0.62 , 1.03]**
Total events:	346		412			



Heterogeneity: Tau² = 0.07; Chi² = 22.03, df = 9 (P = 0.009); I² = 59%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable

Analysis 2.72. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 72: CHD events, SA statistically significant SFA reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	28.4%	0.91 [0.73 , 1.14]
Ley 2004	5	88	3	88	1.3%	1.67 [0.41 , 6.76]
Moy 2001	3	135	1	132	0.5%	2.93 [0.31 , 27.84]
STARS 1992	3	27	10	28	1.8%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	18.5%	0.77 [0.56 , 1.04]
WHI 2006 (1)	590	19541	913	29294	49.6%	0.97 [0.87 , 1.07]
Total (95% CI)		**21233**		**30979**	**100.0%**	**0.91 [0.77 , 1.06]**
Total events:	793		1149			



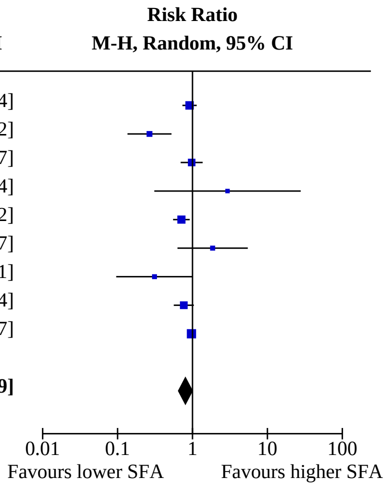
Heterogeneity: Tau² = 0.01; Chi² = 7.12, df = 5 (P = 0.21); I² = 30%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable

Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.73. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 73: CHD events, SA by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	18.3%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	6.7%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	14.3%	0.97 [0.69 , 1.37]
Moy 2001	3	135	1	132	0.8%	2.93 [0.31 , 27.84]
Oslo Diet-Heart 1966	64	206	90	206	17.0%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	3.2%	1.86 [0.63 , 5.47]
STARS 1992	3	27	10	28	2.7%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	15.2%	0.77 [0.56 , 1.04]
WHI 2006 (1)	590	19541	913	29294	21.8%	0.97 [0.87 , 1.07]
Total (95% CI)		**21629**		**31355**	**100.0%**	**0.80 [0.65 , 0.99]**
Total events:	922		1319			

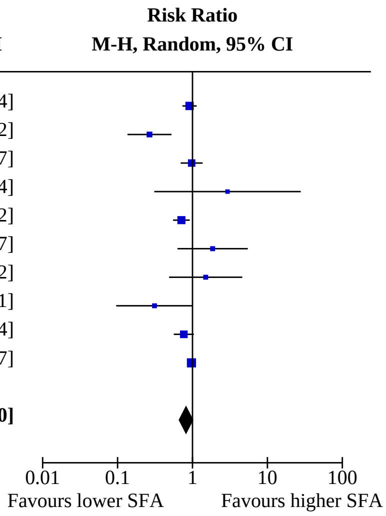


Heterogeneity: Tau² = 0.05; Chi² = 24.92, df = 8 (P = 0.002); I² = 68%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.74. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 74: CHD events, SA aim to reduce SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	132	1018	144	1015	17.8%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	6.4%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	13.8%	0.97 [0.69 , 1.37]
Moy 2001	3	135	1	132	0.8%	2.93 [0.31 , 27.84]
Oslo Diet-Heart 1966	64	206	90	206	16.6%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	3.0%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	2.8%	1.50 [0.49 , 4.62]
STARS 1992	3	27	10	28	2.6%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	14.8%	0.77 [0.56 , 1.04]
WHI 2006 (1)	590	19541	913	29294	21.3%	0.97 [0.87 , 1.07]
Total (95% CI)		**21655**		**31368**	**100.0%**	**0.82 [0.67 , 1.00]**
Total events:	931		1322			

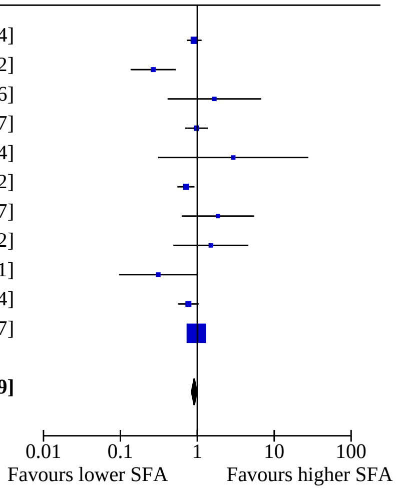


Heterogeneity: Tau² = 0.05; Chi² = 25.71, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 1.92 (P = 0.05)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.75. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 75: CHD events, SA Mantel-Haenszel fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	132	1018	144	1015	12.6%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	2.6%	0.27 [0.14 , 0.52]
Ley 2004	5	88	3	88	0.3%	1.67 [0.41 , 6.76]
MRC 1968	50	199	50	194	4.4%	0.97 [0.69 , 1.37]
Moy 2001	3	135	1	132	0.1%	2.93 [0.31 , 27.84]
Oslo Diet-Heart 1966	64	206	90	206	7.9%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	0.4%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	0.3%	1.50 [0.49 , 4.62]
STARS 1992	3	27	10	28	0.9%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	6.8%	0.77 [0.56 , 1.04]
WHI 2006 (1)	590	19541	913	29294	63.8%	0.97 [0.87 , 1.07]
Total (95% CI)		**21743**		**31456**	**100.0%**	**0.91 [0.84 , 0.99]**
Total events:	936		1325			

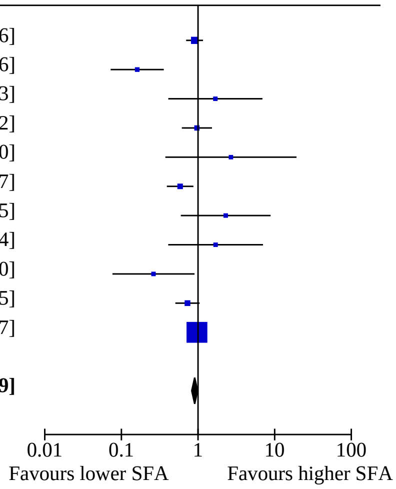


Heterogeneity: Chi² = 26.44, df = 10 (P = 0.003); I² = 62%
Test for overall effect: Z = 2.24 (P = 0.03)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.76. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 76: CHD events, SA Peto fixed-effect

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
DART 1989	132	1018	144	1015	12.0%	0.90 [0.70 , 1.16]
Houtsmuller 1979	8	51	30	51	1.2%	0.16 [0.07 , 0.36]
Ley 2004	5	88	3	88	0.4%	1.68 [0.41 , 6.93]
MRC 1968	50	199	50	194	3.8%	0.97 [0.61 , 1.52]
Moy 2001	3	135	1	132	0.2%	2.69 [0.37 , 19.30]
Oslo Diet-Heart 1966	64	206	90	206	4.9%	0.58 [0.39 , 0.87]
Rose corn oil 1965	12	28	3	13	0.4%	2.30 [0.60 , 8.85]
Rose olive 1965	9	26	3	13	0.4%	1.70 [0.41 , 7.04]
STARS 1992	3	27	10	28	0.5%	0.26 [0.08 , 0.90]
Veterans Admin 1969	60	424	78	422	5.8%	0.73 [0.51 , 1.05]
WHI 2006 (1)	590	19541	913	29294	70.4%	0.97 [0.87 , 1.07]
Total (95% CI)		**21743**		**31456**	**100.0%**	**0.90 [0.83 , 0.99]**
Total events:	936		1325			

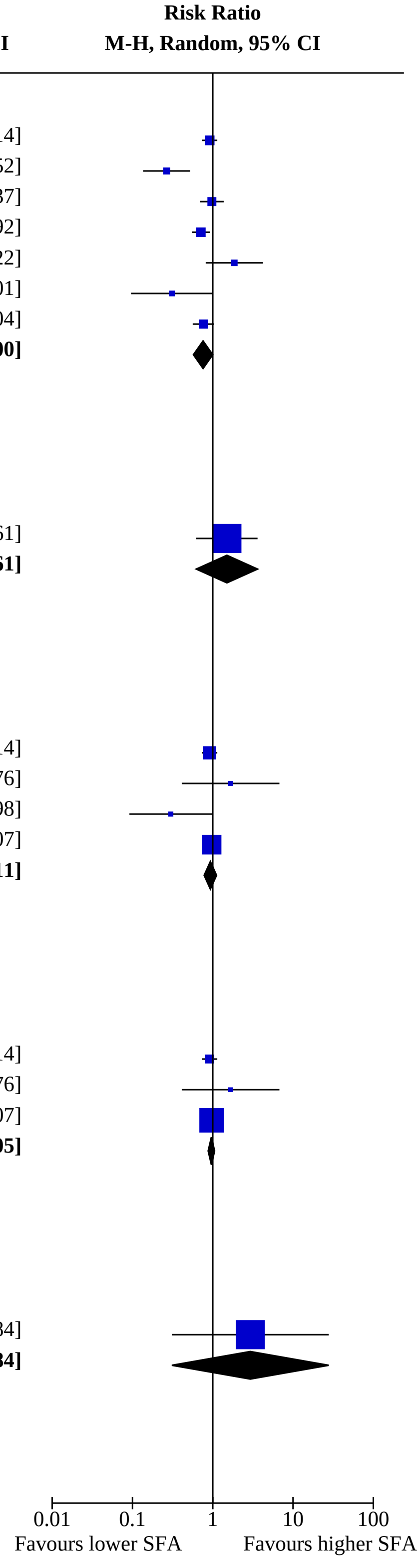


Heterogeneity: Chi² = 33.99, df = 10 (P = 0.0002); I² = 71%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable

Footnotes
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.77. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 77: CHD events, subgroup by any substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.77.1 replaced by PUFA						
DART 1989	132	1018	144	1015	21.1%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	9.9%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	17.9%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	20.2%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	6	26	7.7%	1.86 [0.82 , 4.22]
STARS 1992	3	27	10	28	4.5%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	18.7%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**1953**		**1942**	**100.0%**	**0.76 [0.57 , 1.00]**
Total events:	329		408			
Heterogeneity: Tau² = 0.08; Chi² = 20.25, df = 6 (P = 0.002); I² = 70%						
Test for overall effect: Z = 1.97 (P = 0.05)						
2.77.2 replaced by MUFA						
Rose olive 1965	9	26	6	26	100.0%	1.50 [0.62 , 3.61]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.50 [0.62 , 3.61]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.77.3 replaced by CHO						
DART 1989	132	1018	144	1015	35.2%	0.91 [0.73 , 1.14]
Ley 2004	5	88	3	88	1.6%	1.67 [0.41 , 6.76]
STARS 1992	3	30	10	30	2.2%	0.30 [0.09 , 0.98]
WHI 2006 (1)	590	19541	913	29294	61.0%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**20677**		**30427**	**100.0%**	**0.93 [0.78 , 1.11]**
Total events:	730		1070			
Heterogeneity: Tau² = 0.01; Chi² = 4.49, df = 3 (P = 0.21); I² = 33%						
Test for overall effect: Z = 0.76 (P = 0.44)						
2.77.4 replaced by protein						
DART 1989	132	1018	144	1015	17.7%	0.91 [0.73 , 1.14]
Ley 2004	5	88	3	88	0.4%	1.67 [0.41 , 6.76]
WHI 2006 (1)	590	19541	913	29294	81.9%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**20647**		**30397**	**100.0%**	**0.96 [0.88 , 1.05]**
Total events:	727		1060			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.77.5 replacement unclear						
Moy 2001	3	135	1	132	100.0%	2.93 [0.31 , 27.84]
Subtotal (95% CI)		**135**		**132**	**100.0%**	**2.93 [0.31 , 27.84]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						



Test for subgroup differences: Chi² = 4.64, df = 4 (P = 0.33), I² = 13.8%

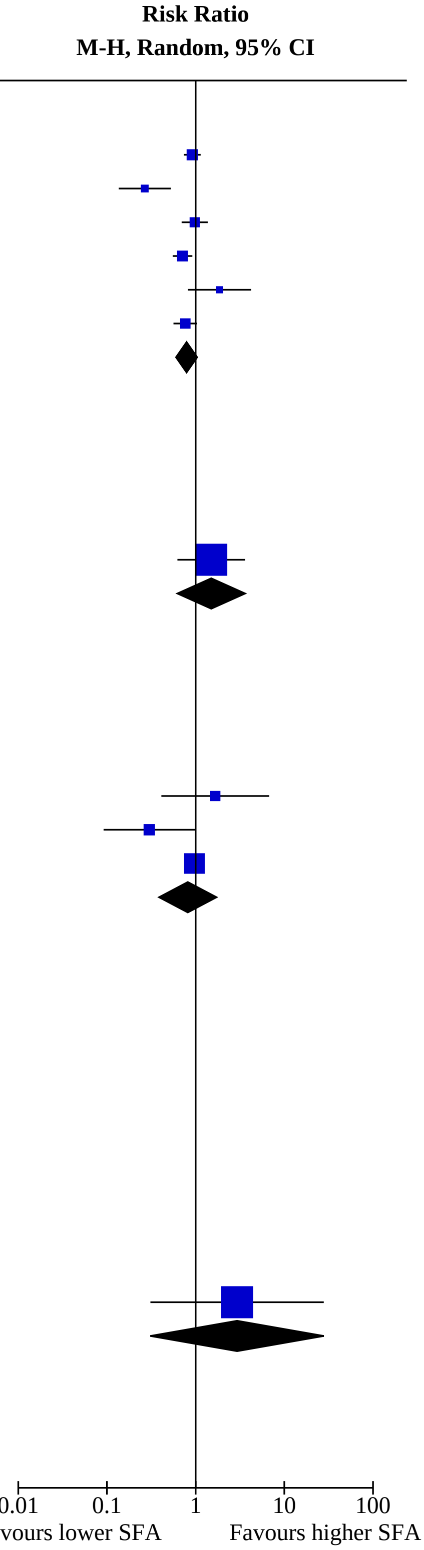
Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.78. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 78: CHD events, subgroup by main substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.78.1 replaced by PUFA						
DART 1989	132	1018	144	1015	22.4%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	10.1%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	18.7%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	21.3%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	6	26	7.8%	1.86 [0.82 , 4.22]
Veterans Admin 1969	60	424	78	422	19.7%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**1926**		**1914**	**100.0%**	**0.79 [0.60 , 1.04]**
Total events:	326		398			
Heterogeneity: Tau² = 0.07; Chi² = 17.71, df = 5 (P = 0.003); I² = 72%						
Test for overall effect: Z = 1.68 (P = 0.09)						
2.78.2 replaced by MUFA						
Rose olive 1965	9	26	6	26	100.0%	1.50 [0.62 , 3.61]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.50 [0.62 , 3.61]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.78.3 replaced by CHO						
Ley 2004	5	88	3	88	19.0%	1.67 [0.41 , 6.76]
STARS 1992	3	30	10	30	23.5%	0.30 [0.09 , 0.98]
WHI 2006 (1)	590	19541	913	29294	57.5%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**19659**		**29412**	**100.0%**	**0.82 [0.39 , 1.72]**
Total events:	598		926			
Heterogeneity: Tau² = 0.25; Chi² = 4.31, df = 2 (P = 0.12); I² = 54%						
Test for overall effect: Z = 0.54 (P = 0.59)						
2.78.4 replaced by protein						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.78.5 replacement unclear						
Moy 2001	3	135	1	132	100.0%	2.93 [0.31 , 27.84]
Subtotal (95% CI)		**135**		**132**	**100.0%**	**2.93 [0.31 , 27.84]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						

Test for subgroup differences: Chi² = 3.05, df = 3 (P = 0.38), I² = 1.7%

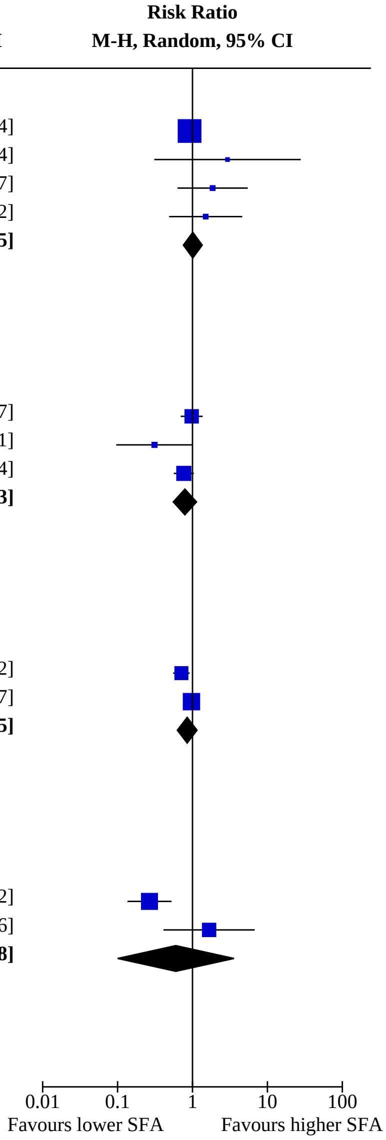


Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.79. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 79: CHD events, subgroup by duration

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.79.1 up to 24 months						
DART 1989	132	1018	144	1015	85.1%	0.91 [0.73 , 1.14]
Moy 2001	3	135	1	132	1.6%	2.93 [0.31 , 27.84]
Rose corn oil 1965	12	28	3	13	6.9%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	6.4%	1.50 [0.49 , 4.62]
Subtotal (95% CI)		**1207**		**1173**	**100.0%**	**1.01 [0.76 , 1.35]**
Total events:	156		151			
Heterogeneity: Tau² = 0.01; Chi² = 3.17, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 0.06 (P = 0.95)						
2.79.2 >24 to 48 months						
MRC 1968	50	199	50	194	44.3%	0.97 [0.69 , 1.37]
STARS 1992	3	27	10	28	8.2%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	47.5%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**650**		**644**	**100.0%**	**0.79 [0.55 , 1.13]**
Total events:	113		138			
Heterogeneity: Tau² = 0.04; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 1.28 (P = 0.20)						
2.79.3 >48 months						
Oslo Diet-Heart 1966	64	206	90	206	42.6%	0.71 [0.55 , 0.92]
WHI 2006 (1)	590	19541	913	29294	57.4%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**19747**		**29500**	**100.0%**	**0.85 [0.63 , 1.15]**
Total events:	654		1003			
Heterogeneity: Tau² = 0.04; Chi² = 4.91, df = 1 (P = 0.03); I² = 80%						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.79.4 unclear duration						
Houtsmuller 1979	8	51	30	51	55.8%	0.27 [0.14 , 0.52]
Ley 2004	5	88	3	88	44.2%	1.67 [0.41 , 6.76]
Subtotal (95% CI)		**139**		**139**	**100.0%**	**0.60 [0.10 , 3.58]**
Total events:	13		33			
Heterogeneity: Tau² = 1.37; Chi² = 5.35, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Chi² = 1.42, df = 3 (P = 0.70), I² = 0%						



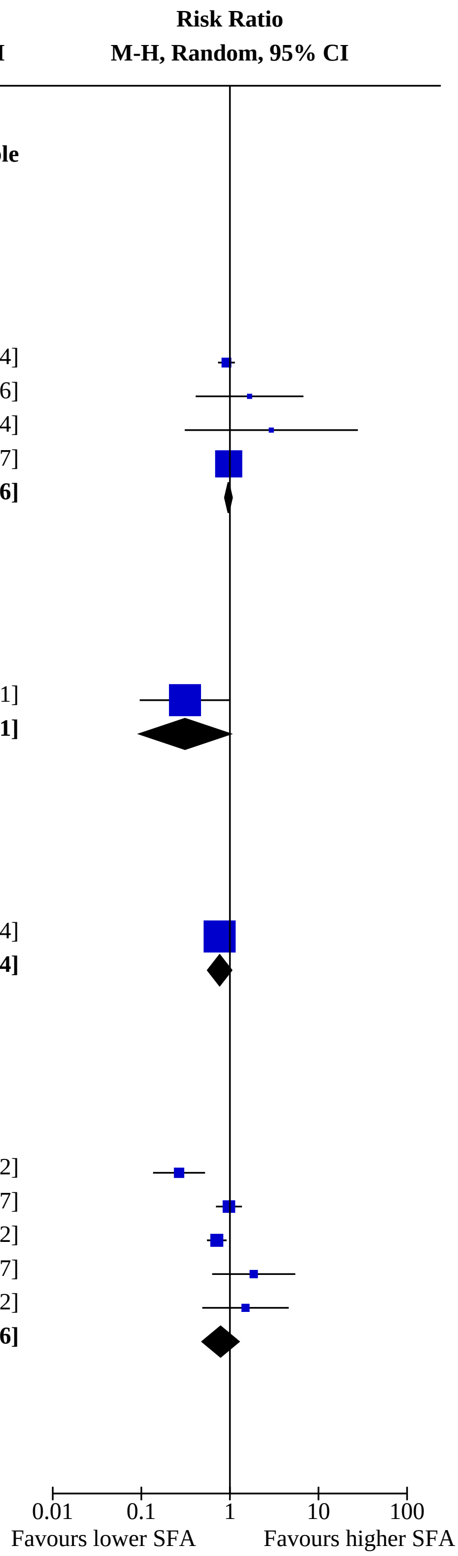
Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.80. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 80: CHD events, subgroup by baseline SFA

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.80.1 up to 12%E SFA baseline						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.80.2 >12 to 15%E SFA baseline						
DART 1989	132	1018	144	1015	17.6%	0.91 [0.73 , 1.14]
Ley 2004	5	88	3	88	0.4%	1.67 [0.41 , 6.76]
Moy 2001	3	135	1	132	0.2%	2.93 [0.31 , 27.84]
WHI 2006 (1)	590	19541	913	29294	81.8%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**20782**		**30529**	**100.0%**	**0.96 [0.88 , 1.06]**
Total events:	730		1061			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 3 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
2.80.3 >15 to 18%E SFA baseline						
STARS 1992	3	27	10	28	100.0%	0.31 [0.10 , 1.01]
Subtotal (95% CI)		**27**		**28**	**100.0%**	**0.31 [0.10 , 1.01]**
Total events:	3		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
2.80.4 >18%E SFA baseline						
Veterans Admin 1969	60	424	78	422	100.0%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**424**		**422**	**100.0%**	**0.77 [0.56 , 1.04]**
Total events:	60		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
2.80.5 unclear						
Houtsmuller 1979	8	51	30	51	19.5%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	27.6%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	29.4%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	12.1%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	11.5%	1.50 [0.49 , 4.62]
Subtotal (95% CI)		**510**		**477**	**100.0%**	**0.78 [0.49 , 1.26]**
Total events:	143		176			
Heterogeneity: Tau² = 0.18; Chi² = 15.59, df = 4 (P = 0.004); I² = 74%						
Test for overall effect: Z = 1.00 (P = 0.32)						

Test for subgroup differences: Chi² = 5.89, df = 3 (P = 0.12), I² = 49.1%



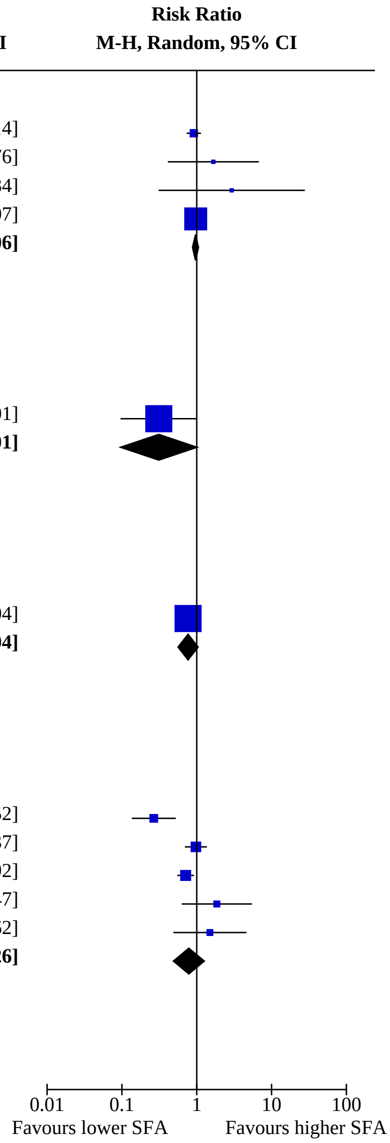
Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.81. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 81: CHD events, subgroup by SFA change

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.81.1 up to 4%E difference						
DART 1989	132	1018	144	1015	17.6%	0.91 [0.73 , 1.14]
Ley 2004	5	88	3	88	0.4%	1.67 [0.41 , 6.76]
Moy 2001	3	135	1	132	0.2%	2.93 [0.31 , 27.84]
WHI 2006 (1)	590	19541	913	29294	81.8%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**20782**		**30529**	**100.0%**	**0.96 [0.88 , 1.06]**
Total events:	730		1061			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 3 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
2.81.2 >4 to 8%E difference						
STARS 1992	3	27	10	28	100.0%	0.31 [0.10 , 1.01]
Subtotal (95% CI)		**27**		**28**	**100.0%**	**0.31 [0.10 , 1.01]**
Total events:	3		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
2.81.3 >8%E difference						
Veterans Admin 1969	60	424	78	422	100.0%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**424**		**422**	**100.0%**	**0.77 [0.56 , 1.04]**
Total events:	60		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
2.81.4 unclear						
Houtsmuller 1979	8	51	30	51	19.5%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	27.6%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	29.4%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	12.1%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	11.5%	1.50 [0.49 , 4.62]
Subtotal (95% CI)		**510**		**477**	**100.0%**	**0.78 [0.49 , 1.26]**
Total events:	143		176			
Heterogeneity: Tau² = 0.18; Chi² = 15.59, df = 4 (P = 0.004); I² = 74%						
Test for overall effect: Z = 1.00 (P = 0.32)						

Test for subgroup differences: Chi² = 5.89, df = 3 (P = 0.12), I² = 49.1%



Footnotes

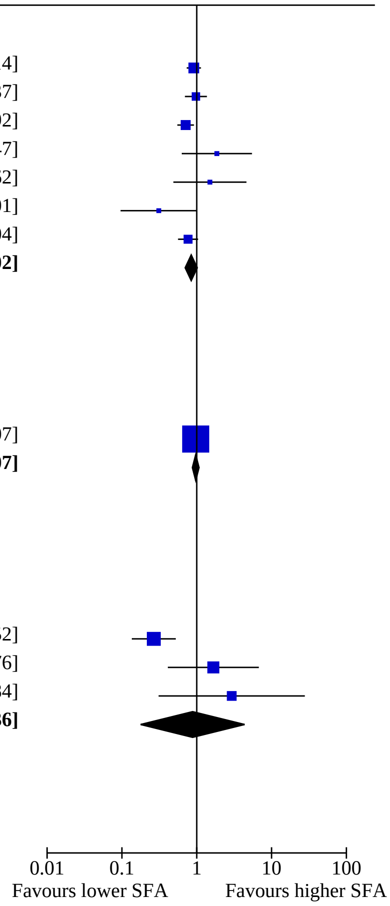
(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.82. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 82: CHD events, subgroup by sex

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.82.1 Men						
DART 1989	132	1018	144	1015	28.5%	0.91 [0.73 , 1.14]
MRC 1968	50	199	50	194	18.4%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	24.9%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	2.8%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	2.6%	1.50 [0.49 , 4.62]
STARS 1992	3	27	10	28	2.4%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	20.5%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**1928**		**1891**	**100.0%**	**0.84 [0.70 , 1.02]**
Total events:	330		378			
Heterogeneity: Tau² = 0.02; Chi² = 9.12, df = 6 (P = 0.17); I² = 34%						
Test for overall effect: Z = 1.79 (P = 0.07)						
2.82.2 Women						
WHI 2006 (1)	590	19541	913	29294	100.0%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**19541**		**29294**	**100.0%**	**0.97 [0.87 , 1.07]**
Total events:	590		913			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.82.3 Mixed, men and women						
Houtsmuller 1979	8	51	30	51	42.2%	0.27 [0.14 , 0.52]
Ley 2004	5	88	3	88	33.8%	1.67 [0.41 , 6.76]
Moy 2001	3	135	1	132	24.0%	2.93 [0.31 , 27.84]
Subtotal (95% CI)		**274**		**271**	**100.0%**	**0.88 [0.18 , 4.36]**
Total events:	16		34			
Heterogeneity: Tau² = 1.46; Chi² = 8.38, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 0.16 (P = 0.88)						

Test for subgroup differences: Chi² = 1.64, df = 2 (P = 0.44), I² = 0%

Risk Ratio M-H, Random, 95% CI

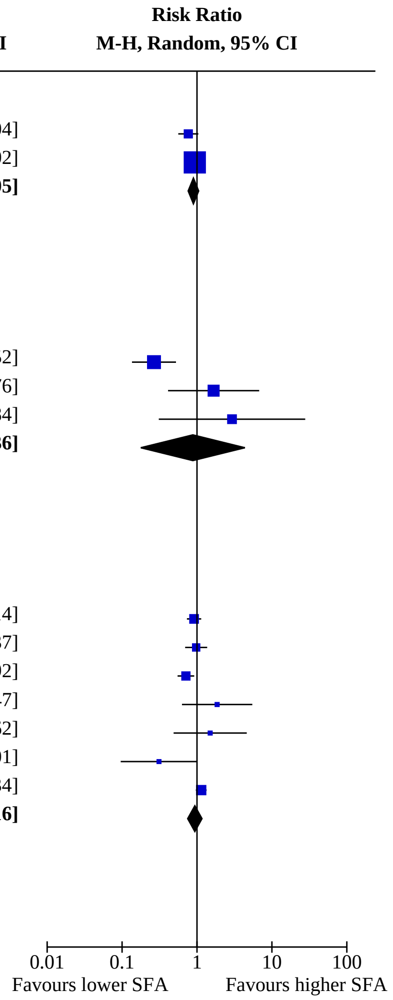


Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.83. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 83: CHD events, subgroup by CVD risk

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.83.1 Low CVD risk						
Veterans Admin 1969	60	424	78	422	21.4%	0.77 [0.56 , 1.04]
WHI 2006 (1)	806	18633	1292	27925	78.6%	0.93 [0.86 , 1.02]
Subtotal (95% CI)		**19057**		**28347**	**100.0%**	**0.90 [0.76 , 1.05]**
Total events:	866		1370			
Heterogeneity: Tau² = 0.01; Chi² = 1.50, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 1.34 (P = 0.18)						
2.83.2 Moderate CVD risk						
Houtsmuller 1979	8	51	30	51	42.2%	0.27 [0.14 , 0.52]
Ley 2004	5	88	3	88	33.8%	1.67 [0.41 , 6.76]
Moy 2001	3	135	1	132	24.0%	2.93 [0.31 , 27.84]
Subtotal (95% CI)		**274**		**271**	**100.0%**	**0.88 [0.18 , 4.36]**
Total events:	16		34			
Heterogeneity: Tau² = 1.46; Chi² = 8.38, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 0.16 (P = 0.88)						
2.83.3 Existing CVD disease						
DART 1989	132	1018	144	1015	23.7%	0.91 [0.73 , 1.14]
MRC 1968	50	199	50	194	17.9%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	21.9%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	3.6%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	3.4%	1.50 [0.49 , 4.62]
STARS 1992	3	27	10	28	3.1%	0.31 [0.10 , 1.01]
WHI 2006 (2)	194	908	257	1369	26.4%	1.14 [0.96 , 1.34]
Subtotal (95% CI)		**2412**		**2838**	**100.0%**	**0.94 [0.75 , 1.16]**
Total events:	464		557			
Heterogeneity: Tau² = 0.04; Chi² = 15.05, df = 6 (P = 0.02); I² = 60%						
Test for overall effect: Z = 0.59 (P = 0.55)						
Test for subgroup differences: Chi² = 0.10, df = 2 (P = 0.95), I² = 0%						



Footnotes

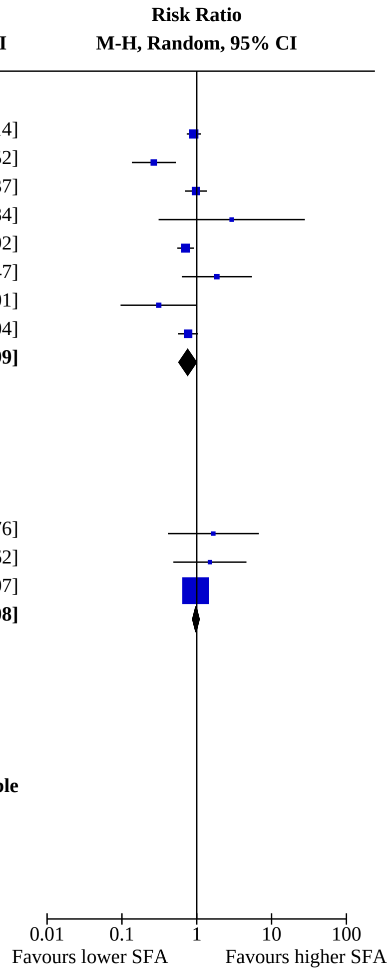
(1) Women without CVD at baseline

(2) Women with CVD at baseline

Analysis 2.84. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 84: CHD events, subgroup by TC reduction

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.84.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	132	1018	144	1015	21.7%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	9.8%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	18.1%	0.97 [0.69 , 1.37]
Moy 2001	3	135	1	132	1.4%	2.93 [0.31 , 27.84]
Oslo Diet-Heart 1966	64	206	90	206	20.6%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	5.0%	1.86 [0.63 , 5.47]
STARS 1992	3	27	10	28	4.3%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	19.0%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**2088**		**2061**	**100.0%**	**0.76 [0.58 , 0.99]**
Total events:	332		406			
Heterogeneity: Tau² = 0.07; Chi² = 19.84, df = 7 (P = 0.006); I² = 65%						
Test for overall effect: Z = 2.03 (P = 0.04)						
2.84.2 serum chol reduced by <0.2mmol/L						
Ley 2004	5	88	3	88	0.5%	1.67 [0.41 , 6.76]
Rose olive 1965	9	26	3	13	0.8%	1.50 [0.49 , 4.62]
WHI 2006 (1)	590	19541	913	29294	98.7%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**19655**		**29395**	**100.0%**	**0.97 [0.88 , 1.08]**
Total events:	604		919			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
2.84.3 serum chol reduction unclear						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Test for subgroup differences: Chi² = 3.00, df = 1 (P = 0.08), I² = 66.6%

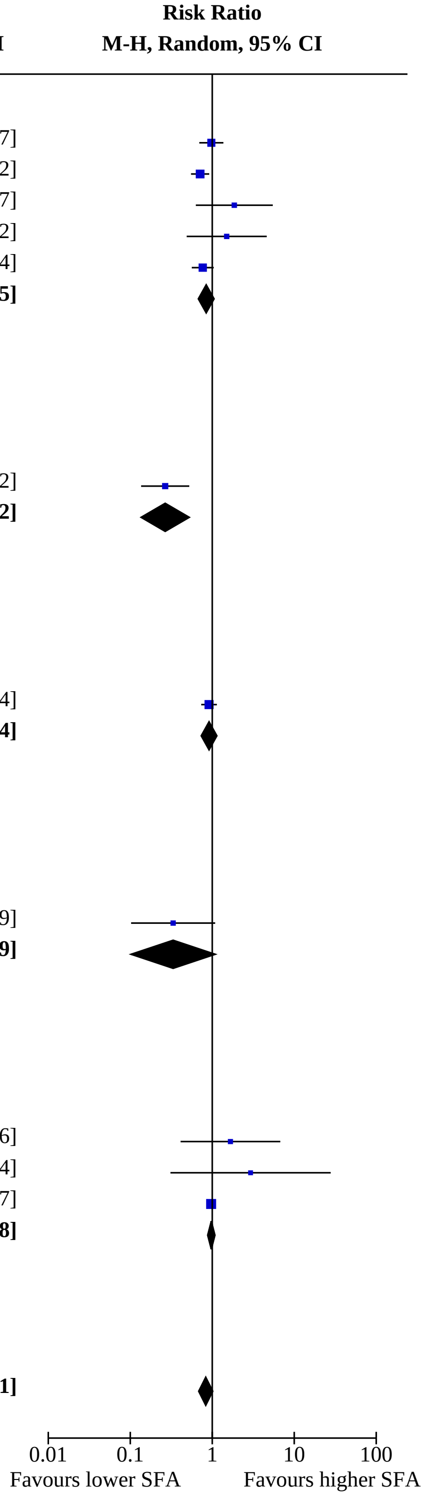


Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.85. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 85: CHD events, subgroup decade of publication

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.85.1 1960s						
MRC 1968	50	199	50	194	13.5%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	16.3%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	3	13	2.9%	1.86 [0.63 , 5.47]
Rose olive 1965	9	26	3	13	2.7%	1.50 [0.49 , 4.62]
Veterans Admin 1969	60	424	78	422	14.5%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**883**		**848**	**50.0%**	**0.84 [0.68 , 1.05]**
Total events:	195		224			
Heterogeneity: Tau² = 0.02; Chi² = 5.70, df = 4 (P = 0.22); I² = 30%						
Test for overall effect: Z = 1.51 (P = 0.13)						
2.85.2 1970s						
Houtsmuller 1979	8	51	30	51	6.2%	0.27 [0.14 , 0.52]
Subtotal (95% CI)		**51**		**51**	**6.2%**	**0.27 [0.14 , 0.52]**
Total events:	8		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.83 (P = 0.0001)						
2.85.3 1980s						
DART 1989	132	1018	144	1015	17.6%	0.91 [0.73 , 1.14]
Subtotal (95% CI)		**1018**		**1015**	**17.6%**	**0.91 [0.73 , 1.14]**
Total events:	132		144			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
2.85.4 1990s						
STARS 1992	3	27	10	30	2.5%	0.33 [0.10 , 1.09]
Subtotal (95% CI)		**27**		**30**	**2.5%**	**0.33 [0.10 , 1.09]**
Total events:	3		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
2.85.5 2000s						
Ley 2004	5	88	3	88	1.8%	1.67 [0.41 , 6.76]
Moy 2001	3	135	1	132	0.7%	2.93 [0.31 , 27.84]
WHI 2006 (1)	590	19541	913	29294	21.2%	0.97 [0.87 , 1.07]
Subtotal (95% CI)		**19764**		**29514**	**23.8%**	**0.97 [0.88 , 1.08]**
Total events:	598		917			
Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**21743**		**31458**	**100.0%**	**0.83 [0.68 , 1.01]**
Total events:	936		1325			
Heterogeneity: Tau² = 0.05; Chi² = 26.03, df = 10 (P = 0.004); I² = 62%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Test for subgroup differences: Chi² = 17.51, df = 4 (P = 0.002), I² = 77.2%						



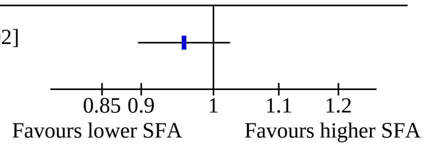
Footnotes

(1) CHD events including CHD death & MI, Prentice 2017

Analysis 2.86. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 86: DIABETES DIAGNOSES

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
WHI 2006	1303	19541	2039	29294	0.96 [0.90 , 1.02]	

Test for subgroup differences: Not applicable



Comparison 3. SFA reduction vs usual diet - secondary blood outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Total cholesterol, mmol/L	14	7115	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.36, -0.13]
3.2 TC, mmol/L, subgroup by any replacement	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2.1 replaced by PUFA	9	3888	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.47, -0.19]
3.2.2 replace by MUFA	1	24	Mean Difference (IV, Random, 95% CI)	0.30 [-0.93, 1.53]
3.2.3 replace by CHO	6	5094	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.32, -0.04]
3.2.4 replace by protein	4	4986	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.27, -0.04]
3.2.5 replacement unclear	1	72	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.64, -0.04]
3.3 TC, mmol/L, subgroup by main replacement	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.3.1 replaced by PUFA	8	3838	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.37, -0.19]
3.3.2 replace by MUFA	1	24	Mean Difference (IV, Random, 95% CI)	0.30 [-0.93, 1.53]
3.3.3 replace by CHO	4	3181	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.40, 0.01]
3.3.4 replace by protein	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.3.5 replacement unclear	1	72	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.64, -0.04]
3.4 LDL cholesterol, mmol/L	5	3291	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.33, -0.05]
3.5 LDL, mmol/L, subgroup by any replacement	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.5.1 replaced by PUFA	1	50	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.90, -0.06]
3.5.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.5.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.35, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.4 replace by protein	2	2935	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.15, -0.04]
3.5.5 replacement unclear	2	306	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.51, -0.08]
3.6 LDL, mmol/L, subgroup by main replacement	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.6.1 replaced by PUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.6.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.6.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.35, 0.02]
3.6.4 replace by protein	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.6.5 replacement unclear	2	306	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.51, -0.08]
3.7 HDL cholesterol, mmol/L	6	5147	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
3.8 HDL, mmol/L, subgroup by any replacement	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.8.1 replaced by PUFA	2	1905	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
3.8.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.8.3 replace by CHO	4	4840	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.00]
3.8.4 replace by protein	3	4790	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.00]
3.8.5 replacement unclear	2	307	Mean Difference (IV, Random, 95% CI)	0.01 [-0.10, 0.12]
3.9 HDL, mmol/L, subgroup by main replacement	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.9.1 replaced by PUFA	1	1855	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.02]
3.9.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.9.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
3.9.4 replace by protein	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.9.5 replacement unclear	2	307	Mean Difference (IV, Random, 95% CI)	0.01 [-0.10, 0.12]
3.10 Triglycerides, mmol/L	7	3845	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.21, 0.04]
3.11 TG, mmol/L, subgroup by any replacement	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.11.1 replaced by PUFA	3	604	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.35, -0.02]
3.11.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

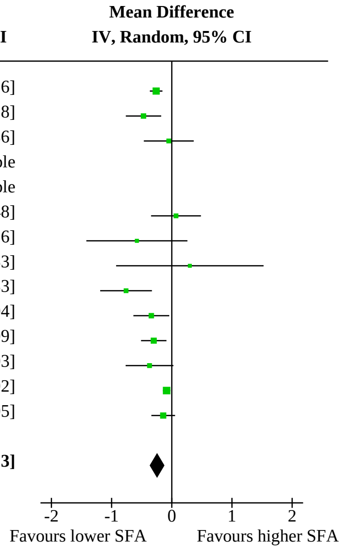
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.32, 0.25]
3.11.4 replace by protein	2	2935	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.09]
3.11.5 replacement unclear	2	306	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.52, 0.33]
3.12 TG, mmol/L, subgroup by main replacement	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.12.1 replaced by PUFA	2	554	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.30, -0.01]
3.12.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.12.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.32, 0.25]
3.12.4 replace by protein	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.12.5 replacement unclear	2	306	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.52, 0.33]
3.13 total cholesterol /HDL ratio	3	2985	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.33, 0.13]
3.14 TC /HDL ratio, subgroup by any replacement	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.14.1 replaced by PUFA	1	50	Mean Difference (IV, Random, 95% CI)	-0.58 [-1.33, 0.17]
3.14.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.14.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.33, 0.13]
3.14.4 replace by protein	2	2935	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.21, 0.04]
3.14.5 replacement unclear	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.15 TC /HDL ratio, subgroup by main replacement	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.15.1 replaced by PUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.15.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.15.3 replace by CHO	3	2985	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.33, 0.13]
3.15.4 replace by protein	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.15.5 replacement unclear	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.16 LDL /HDL ratio	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.17 Lp(a), mmol/L	2	2882	Mean Difference (IV, Random, 95% CI)	0.00 [-0.00, 0.00]
3.18 Lp(a), mmol/L, subgroup by any replacement	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.18.1 replaced by PUFA	1	50	Mean Difference (IV, Random, 95% CI)	0.00 [-1.37, 1.37]
3.18.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.18.3 replace by CHO	2	2882	Mean Difference (IV, Random, 95% CI)	0.00 [-0.00, 0.00]
3.18.4 replace by protein	1	2832	Mean Difference (IV, Random, 95% CI)	0.00 [-0.00, 0.00]
3.18.5 replacement unclear	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.19 Lp(a), mmol/L, subgroup by main replacement	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.19.1 replaced by PUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.19.2 replace by MUFA	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.19.3 replace by CHO	2	2882	Mean Difference (IV, Random, 95% CI)	0.00 [-0.00, 0.00]
3.19.4 replace by protein	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.19.5 replacement unclear	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.20 Insulin sensitivity	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.20.1 HbA1c (glycosylated haemoglobin), %	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.20.2 GTT (glucose tolerance test), glucose at 2 hours, mmol/L	3	249	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.55, -0.82]
3.20.3 HOMA	1	2832	Mean Difference (IV, Random, 95% CI)	0.00 [-0.04, 0.04]

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

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
DART 1989	6.31	1.14	924	6.57	1.16	931	17.0%	-0.26 [-0.36 , -0.16]
Houtsmuller 1979	6.43	0.65	48	6.9	0.81	48	8.3%	-0.47 [-0.76 , -0.18]
Ley 2004	-0.2	0.79	51	-0.15	1.3	52	5.3%	-0.05 [-0.46 , 0.36]
MRC 1968	-1.11	0	88	-0.47	0	89		Not estimable
Oslo Diet-Heart 1966	6.12	0	168	7.19	0	161		Not estimable
Oxford Retinopathy 1978	4.94	0.82	29	4.87	0.79	29	5.3%	0.07 [-0.34 , 0.48]
Rose corn oil 1965	-0.78	0.923	13	-0.2	1.031	9	1.6%	-0.58 [-1.42 , 0.26]
Rose olive 1965	0.1	2.023	15	-0.2	1.031	9	0.8%	0.30 [-0.93 , 1.53]
STARS 1992	6.17	0.459	26	6.93	0.98	24	5.0%	-0.76 [-1.19 , -0.33]
Simon 1997	4.87	0.87	34	5.21	0.18	38	8.2%	-0.34 [-0.64 , -0.04]
Sydney Diet-Heart 1978	6.5	1.2	221	6.8	1.1	237	11.6%	-0.30 [-0.51 , -0.09]
Veterans Admin 1969	4.93	3.72	423	5.3	1.87	420	5.6%	-0.37 [-0.77 , 0.03]
WHI 2006	-0.264	0.828	1133	-0.178	0.825	1699	18.9%	-0.09 [-0.15 , -0.02]
WINS 2006	-0.0005	0.728	96	0.142	0.675	100	12.3%	-0.14 [-0.34 , 0.05]
Total (95% CI)			**3269**			**3846**	**100.0%**	**-0.24 [-0.36 , -0.13]**

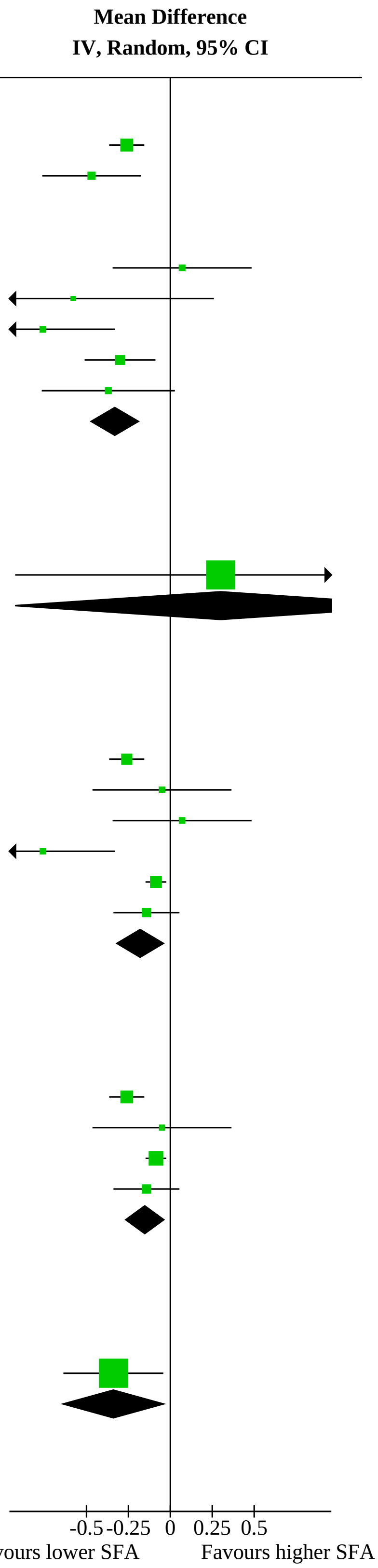
Heterogeneity: Tau² = 0.02; Chi² = 27.85, df = 11 (P = 0.003); I² = 60%
Test for overall effect: Z = 4.32 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 2: TC, mmol/L, subgroup by any replacement

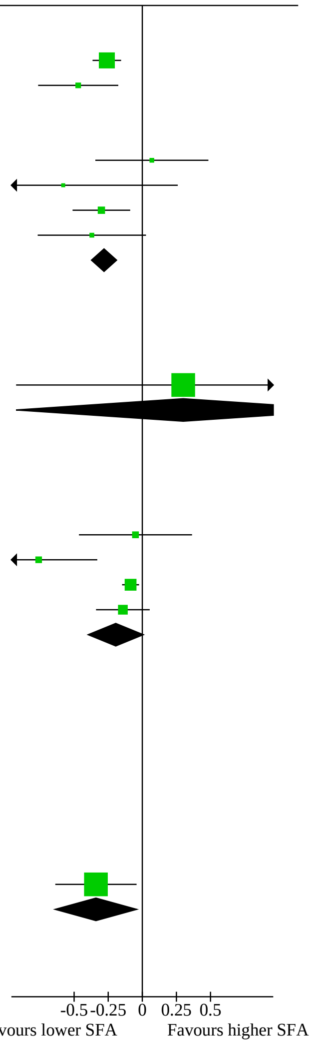
	Lower SFA			HIgher SFA				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
3.2.1 replaced by PUFA								
DART 1989	6.31	1.14	924	6.57	1.16	931	33.9%	-0.26 [-0.36 , -0.16]
Houtsmuller 1979	6.43	0.65	48	6.9	0.81	48	14.8%	-0.47 [-0.76 , -0.18]
MRC 1968	-1.11	0	88	-0.47	0	89		Not estimable
Oslo Diet-Heart 1966	6.12	0	168	7.19	0	161		Not estimable
Oxford Retinopathy 1978	4.94	0.82	29	4.87	0.79	29	9.0%	0.07 [-0.34 , 0.48]
Rose corn oil 1965	-0.78	0.923	13	-0.2	1.031	9	2.6%	-0.58 [-1.42 , 0.26]
STARS 1992	6.17	0.459	26	6.93	0.98	24	8.5%	-0.76 [-1.19 , -0.33]
Sydney Diet-Heart 1978	6.5	1.2	221	6.8	1.1	237	21.5%	-0.30 [-0.51 , -0.09]
Veterans Admin 1969	4.93	3.72	423	5.3	1.87	420	9.6%	-0.37 [-0.77 , 0.03]
Subtotal (95% CI)			**1940**			**1948**	**100.0%**	**-0.33 [-0.47 , -0.19]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.85$, df = 6 (P = 0.13); $I^2 = 39\%$								
Test for overall effect: Z = 4.62 (P < 0.00001)								
3.2.2 replace by MUFA								
Rose olive 1965	0.1	2.023	15	-0.2	1.031	9	100.0%	0.30 [-0.93 , 1.53]
Subtotal (95% CI)			**15**			**9**	**100.0%**	**0.30 [-0.93 , 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								
3.2.3 replace by CHO								
DART 1989	6.31	1.14	924	6.57	1.16	931	26.8%	-0.26 [-0.36 , -0.16]
Ley 2004	-0.2	0.79	51	-0.15	1.3	52	8.2%	-0.05 [-0.46 , 0.36]
Oxford Retinopathy 1978	4.94	0.82	29	4.87	0.79	29	8.2%	0.07 [-0.34 , 0.48]
STARS 1992	6.17	0.459	26	6.93	0.98	24	7.8%	-0.76 [-1.19 , -0.33]
WHI 2006	-0.264	0.828	1133	-0.178	0.825	1699	29.7%	-0.09 [-0.15 , -0.02]
WINS 2006	-0.0005	0.728	96	0.142	0.675	100	19.3%	-0.14 [-0.34 , 0.05]
Subtotal (95% CI)			**2259**			**2835**	**100.0%**	**-0.18 [-0.32 , -0.04]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 17.09$, df = 5 (P = 0.004); $I^2 = 71\%$								
Test for overall effect: Z = 2.55 (P = 0.01)								
3.2.4 replace by protein								
DART 1989	6.31	1.14	924	6.57	1.16	931	33.3%	-0.26 [-0.36 , -0.16]
Ley 2004	-0.2	0.79	51	-0.15	1.3	52	6.4%	-0.05 [-0.46 , 0.36]
WHI 2006	-0.264	0.828	1133	-0.178	0.825	1699	40.9%	-0.09 [-0.15 , -0.02]
WINS 2006	-0.0005	0.728	96	0.142	0.675	100	19.3%	-0.14 [-0.34 , 0.05]
Subtotal (95% CI)			**2204**			**2782**	**100.0%**	**-0.15 [-0.27 , -0.04]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.01$, df = 3 (P = 0.05); $I^2 = 63\%$								
Test for overall effect: Z = 2.64 (P = 0.008)								
3.2.5 replacement unclear								
Simon 1997	4.87	0.87	34	5.21	0.18	38	100.0%	-0.34 [-0.64 , -0.04]
Subtotal (95% CI)			**34**			**38**	**100.0%**	**-0.34 [-0.64 , -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								

Test for subgroup differences: $Chi^2 = 5.40$, df = 4 (P = 0.25), $I^2 = 25.9\%$



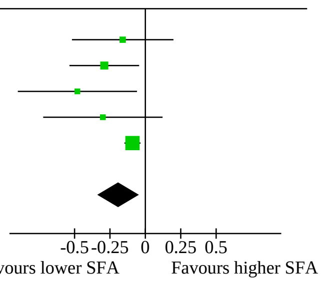
Analysis 3.3. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 3: TC, mmol/L, subgroup by main replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 replaced by PUFA								
DART 1989	6.31	1.14	924	6.57	1.16	931	61.4%	-0.26 [-0.36 , -0.16]
Houtsmuller 1979	6.43	0.65	48	6.9	0.81	48	9.5%	-0.47 [-0.76 , -0.18]
MRC 1968	-1.11	0	88	-0.47	0	89		Not estimable
Oslo Diet-Heart 1966	6.12	0	168	7.19	0	161		Not estimable
Oxford Retinopathy 1978	4.94	0.82	29	4.87	0.79	29	4.8%	0.07 [-0.34 , 0.48]
Rose corn oil 1965	-0.78	0.923	13	-0.2	1.031	9	1.2%	-0.58 [-1.42 , 0.26]
Sydney Diet-Heart 1978	6.5	1.2	221	6.8	1.1	237	17.8%	-0.30 [-0.51 , -0.09]
Veterans Admin 1969	4.93	3.72	423	5.3	1.87	420	5.3%	-0.37 [-0.77 , 0.03]
Subtotal (95% CI)			**1914**			**1924**	**100.0%**	**-0.28 [-0.37 , -0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 5.21, df = 5 (P = 0.39); I² = 4%								
Test for overall effect: Z = 5.98 (P < 0.00001)								
3.3.2 replace by MUFA								
Rose olive 1965	0.1	2.023	15	-0.2	1.031	9	100.0%	0.30 [-0.93 , 1.53]
Subtotal (95% CI)			**15**			**9**	**100.0%**	**0.30 [-0.93 , 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								
3.3.3 replace by CHO								
Ley 2004	-0.2	0.79	51	-0.15	1.3	52	15.1%	-0.05 [-0.46 , 0.36]
STARS 1992	6.17	0.459	26	6.93	0.98	24	14.4%	-0.76 [-1.19 , -0.33]
WHI 2006	-0.264	0.828	1133	-0.178	0.825	1699	40.4%	-0.09 [-0.15 , -0.02]
WINS 2006	-0.0005	0.728	96	0.142	0.675	100	30.0%	-0.14 [-0.34 , 0.05]
Subtotal (95% CI)			**1306**			**1875**	**100.0%**	**-0.19 [-0.40 , 0.01]**
Heterogeneity: Tau² = 0.03; Chi² = 9.48, df = 3 (P = 0.02); I² = 68%								
Test for overall effect: Z = 1.89 (P = 0.06)								
3.3.4 replace by protein								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.3.5 replacement unclear								
Simon 1997	4.87	0.87	34	5.21	0.18	38	100.0%	-0.34 [-0.64 , -0.04]
Subtotal (95% CI)			**34**			**38**	**100.0%**	**-0.34 [-0.64 , -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								
Test for subgroup differences: Chi² = 1.63, df = 3 (P = 0.65), I² = 0%								



Analysis 3.4. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 4: LDL cholesterol, mmol/L

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
Ley 2004	-0.32	0.64	51	-0.16	1.15	52	11.7%	-0.16 [-0.52 , 0.20]
Moy 2001	-0.69	1.1	117	-0.4	0.8	118	20.0%	-0.29 [-0.54 , -0.04]
STARS 1992	4.19	0.51	26	4.67	0.931	24	9.0%	-0.48 [-0.90 , -0.06]
Simon 1997	2.79	0.82	34	3.09	0.99	37	9.0%	-0.30 [-0.72 , 0.12]
WHI 2006	-0.251	0.758	1133	-0.16	0.753	1699	50.3%	-0.09 [-0.15 , -0.03]
Total (95% CI)			**1361**			**1930**	**100.0%**	**-0.19 [-0.33 , -0.05]**
Heterogeneity: Tau² = 0.01; Chi² = 6.30, df = 4 (P = 0.18); I² = 37%								
Test for overall effect: Z = 2.73 (P = 0.006)								
Test for subgroup differences: Not applicable								

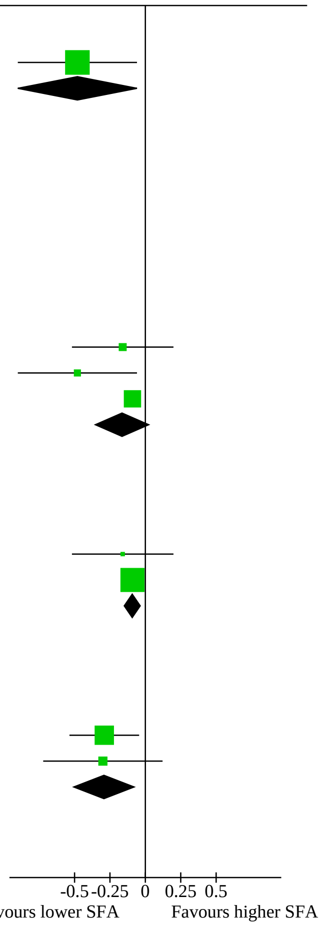


Analysis 3.5. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 5: LDL, mmol/L, subgroup by any replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.5.1 replaced by PUFA								
STARS 1992	4.19	0.51	26	4.67	0.931	24	100.0%	-0.48 [-0.90 , -0.06]
Subtotal (95% CI)			**26**			**24**	**100.0%**	**-0.48 [-0.90 , -0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								
3.5.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.5.3 replace by CHO								
Ley 2004	-0.32	0.64	51	-0.16	1.15	52	19.7%	-0.16 [-0.52 , 0.20]
STARS 1992	4.19	0.51	26	4.67	0.931	24	15.5%	-0.48 [-0.90 , -0.06]
WHI 2006	-0.251	0.758	1133	-0.16	0.753	1699	64.8%	-0.09 [-0.15 , -0.03]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.16 [-0.35 , 0.02]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.33$, df = 2 (P = 0.19); $I^2 = 40\%$								
Test for overall effect: Z = 1.72 (P = 0.09)								
3.5.4 replace by protein								
Ley 2004	-0.32	0.64	51	-0.16	1.15	52	2.5%	-0.16 [-0.52 , 0.20]
WHI 2006	-0.251	0.758	1133	-0.16	0.753	1699	97.5%	-0.09 [-0.15 , -0.03]
Subtotal (95% CI)			**1184**			**1751**	**100.0%**	**-0.09 [-0.15 , -0.04]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$								
Test for overall effect: Z = 3.24 (P = 0.001)								
3.5.5 replacement unclear								
Moy 2001	-0.69	1.1	117	-0.4	0.8	118	74.6%	-0.29 [-0.54 , -0.04]
Simon 1997	2.79	0.82	34	3.09	0.99	37	25.4%	-0.30 [-0.72 , 0.12]
Subtotal (95% CI)			**151**			**155**	**100.0%**	**-0.29 [-0.51 , -0.08]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$								
Test for overall effect: Z = 2.70 (P = 0.007)								

Test for subgroup differences: $Chi^2 = 6.44$, df = 3 (P = 0.09), $I^2 = 53.4\%$

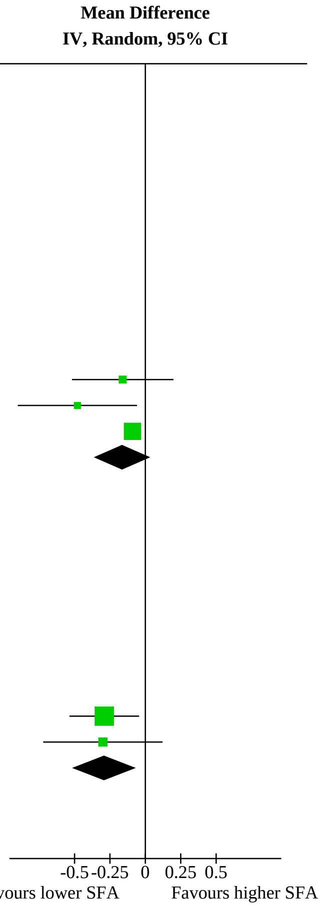
Mean Difference
IV, Random, 95% CI



Analysis 3.6. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 6: LDL, mmol/L, subgroup by main replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.6.1 replaced by PUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.6.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.6.3 replace by CHO								
Ley 2004	-0.32	0.64	51	-0.16	1.15	52	19.7%	-0.16 [-0.52 , 0.20]
STARS 1992	4.19	0.51	26	4.67	0.931	24	15.5%	-0.48 [-0.90 , -0.06]
WHI 2006	-0.251	0.758	1133	-0.16	0.753	1699	64.8%	-0.09 [-0.15 , -0.03]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.16 [-0.35 , 0.02]**
Heterogeneity: Tau² = 0.01; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 1.72 (P = 0.09)								
3.6.4 replace by protein								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.6.5 replacement unclear								
Moy 2001	-0.69	1.1	117	-0.4	0.8	118	74.6%	-0.29 [-0.54 , -0.04]
Simon 1997	2.79	0.82	34	3.09	0.99	37	25.4%	-0.30 [-0.72 , 0.12]
Subtotal (95% CI)			**151**			**155**	**100.0%**	**-0.29 [-0.51 , -0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%								
Test for overall effect: Z = 2.70 (P = 0.007)								

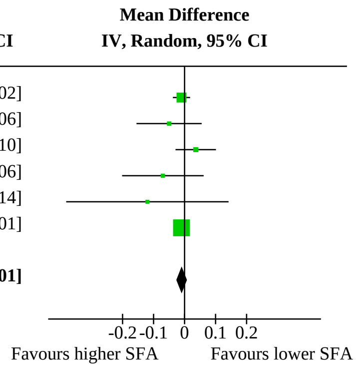
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%



Analysis 3.7. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 7: HDL cholesterol, mmol/L

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
DART 1989	1.04	0.31	924	1.05	0.3	931	28.9%	-0.01 [-0.04 , 0.02]
Ley 2004	0.01	0.14	51	0.06	0.36	52	2.0%	-0.05 [-0.16 , 0.06]
Moy 2001	0.044	0.3	117	0.008	0.2	118	5.2%	0.04 [-0.03 , 0.10]
STARS 1992	1.14	0.153	26	1.21	0.294	24	1.3%	-0.07 [-0.20 , 0.06]
Simon 1997	1.44	0.58	34	1.56	0.55	38	0.3%	-0.12 [-0.38 , 0.14]
WHI 2006	-0.018	0.243	1133	-0.008	0.264	1699	62.2%	-0.01 [-0.03 , 0.01]
Total (95% CI)			**2285**			**2862**	**100.0%**	**-0.01 [-0.02 , 0.01]**

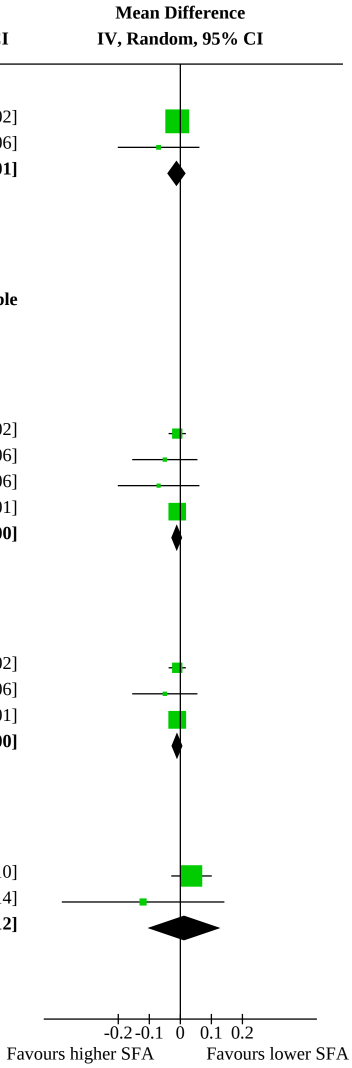
Heterogeneity: Tau² = 0.00; Chi² = 3.94, df = 5 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 8: HDL, mmol/L, subgroup by any replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.8.1 replaced by PUFA								
DART 1989	1.04	0.31	924	1.05	0.3	931	95.7%	-0.01 [-0.04 , 0.02]
STARS 1992	1.14	0.153	26	1.21	0.294	24	4.3%	-0.07 [-0.20 , 0.06]
Subtotal (95% CI)			**950**			**955**	**100.0%**	**-0.01 [-0.04 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%								
Test for overall effect: Z = 0.91 (P = 0.36)								
3.8.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.8.3 replace by CHO								
DART 1989	1.04	0.31	924	1.05	0.3	931	30.6%	-0.01 [-0.04 , 0.02]
Ley 2004	0.01	0.14	51	0.06	0.36	52	2.1%	-0.05 [-0.16 , 0.06]
STARS 1992	1.14	0.153	26	1.21	0.294	24	1.4%	-0.07 [-0.20 , 0.06]
WHI 2006	-0.018	0.243	1133	-0.008	0.264	1699	65.9%	-0.01 [-0.03 , 0.01]
Subtotal (95% CI)			**2134**			**2706**	**100.0%**	**-0.01 [-0.03 , 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 3 (P = 0.73); I² = 0%								
Test for overall effect: Z = 1.49 (P = 0.14)								
3.8.4 replace by protein								
DART 1989	1.04	0.31	924	1.05	0.3	931	31.0%	-0.01 [-0.04 , 0.02]
Ley 2004	0.01	0.14	51	0.06	0.36	52	2.2%	-0.05 [-0.16 , 0.06]
WHI 2006	-0.018	0.243	1133	-0.008	0.264	1699	66.8%	-0.01 [-0.03 , 0.01]
Subtotal (95% CI)			**2108**			**2682**	**100.0%**	**-0.01 [-0.03 , 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 2 (P = 0.76); I² = 0%								
Test for overall effect: Z = 1.38 (P = 0.17)								
3.8.5 replacement unclear								
Moy 2001	0.044	0.3	117	0.008	0.2	118	84.4%	0.04 [-0.03 , 0.10]
Simon 1997	1.44	0.58	34	1.56	0.55	38	15.6%	-0.12 [-0.38 , 0.14]
Subtotal (95% CI)			**151**			**156**	**100.0%**	**0.01 [-0.10 , 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%								
Test for overall effect: Z = 0.21 (P = 0.84)								

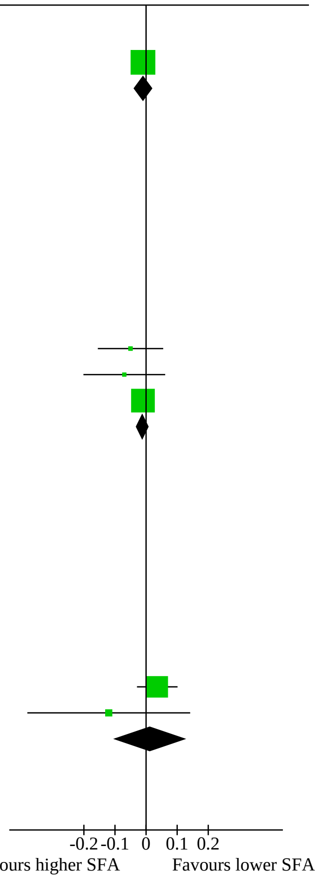
Test for subgroup differences: Chi² = 0.18, df = 3 (P = 0.98), I² = 0%



Analysis 3.9. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 9: HDL, mmol/L, subgroup by main replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.9.1 replaced by PUFA								
DART 1989	1.04	0.31	924	1.05	0.3	931	100.0%	-0.01 [-0.04 , 0.02]
Subtotal (95% CI)			**924**			**931**	**100.0%**	**-0.01 [-0.04 , 0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
3.9.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.9.3 replace by CHO								
Ley 2004	0.01	0.14	51	0.06	0.36	52	3.1%	-0.05 [-0.16 , 0.06]
STARS 1992	1.14	0.153	26	1.21	0.294	24	2.0%	-0.07 [-0.20 , 0.06]
WHI 2006	-0.018	0.243	1133	-0.008	0.264	1699	95.0%	-0.01 [-0.03 , 0.01]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.01 [-0.03 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 2 (P = 0.52); I² = 0%								
Test for overall effect: Z = 1.32 (P = 0.19)								
3.9.4 replace by protein								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.9.5 replacement unclear								
Moy 2001	0.044	0.3	117	0.008	0.2	118	84.4%	0.04 [-0.03 , 0.10]
Simon 1997	1.44	0.58	34	1.56	0.55	38	15.6%	-0.12 [-0.38 , 0.14]
Subtotal (95% CI)			**151**			**156**	**100.0%**	**0.01 [-0.10 , 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%								
Test for overall effect: Z = 0.21 (P = 0.84)								
Test for subgroup differences: Chi² = 0.19, df = 2 (P = 0.91), I² = 0%								

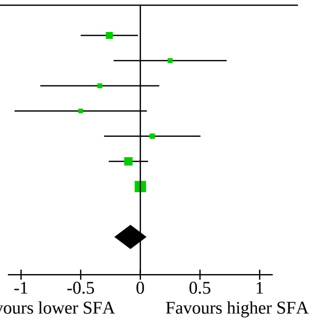
Mean Difference IV, Random, 95% CI



Analysis 3.10. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 10: Triglycerides, mmol/L

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
Houtsmuller 1979	0.79	0.6	48	1.05	0.6	48	15.9%	-0.26 [-0.50 , -0.02]
Ley 2004	0.37	0.71	51	0.12	1.59	52	6.0%	0.25 [-0.22 , 0.72]
Moy 2001	-0.4	2	117	-0.06	1.9	118	5.5%	-0.34 [-0.84 , 0.16]
STARS 1992	1.85	1.02	26	2.35	0.98	24	4.6%	-0.50 [-1.05 , 0.05]
Simon 1997	1.35	1.05	34	1.25	0.61	37	7.8%	0.10 [-0.30 , 0.50]
Sydney Diet-Heart 1978	1.6	0.9	221	1.7	0.9	237	22.9%	-0.10 [-0.26 , 0.06]
WHI 2006	0.011	0.005	1133	0.011	0.003	1699	37.5%	0.00 [-0.00 , 0.00]
Total (95% CI)			**1630**			**2215**	**100.0%**	**-0.08 [-0.21 , 0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 12.13, df = 6 (P = 0.06); I² = 51%								
Test for overall effect: Z = 1.29 (P = 0.20)								
Test for subgroup differences: Not applicable								

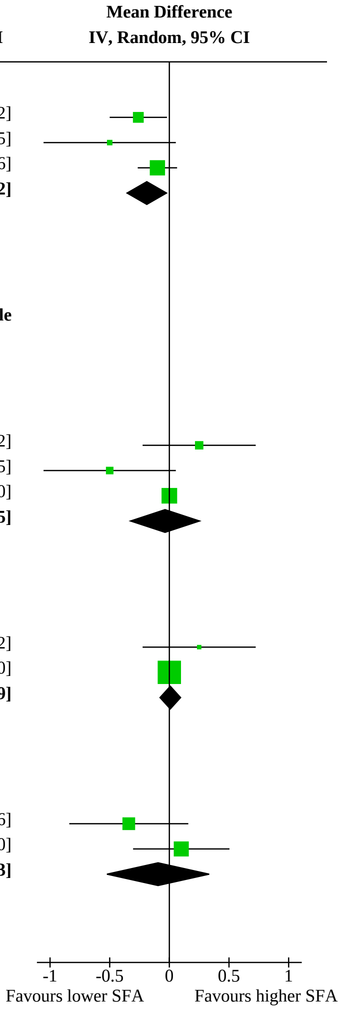
Mean Difference IV, Random, 95% CI



Analysis 3.11. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 11: TG, mmol/L, subgroup by any replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.11.1 replaced by PUFA								
Houtsmuller 1979	0.79	0.6	48	1.05	0.6	48	34.8%	-0.26 [-0.50 , -0.02]
STARS 1992	1.85	1.02	26	2.35	0.98	24	8.3%	-0.50 [-1.05 , 0.05]
Sydney Diet-Heart 1978	1.6	0.9	221	1.7	0.9	237	56.9%	-0.10 [-0.26 , 0.06]
Subtotal (95% CI)			**295**			**309**	**100.0%**	**-0.19 [-0.35 , -0.02]**
Heterogeneity: Tau² = 0.01; Chi² = 2.59, df = 2 (P = 0.27); I² = 23%								
Test for overall effect: Z = 2.24 (P = 0.03)								
3.11.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.11.3 replace by CHO								
Ley 2004	0.37	0.71	51	0.12	1.59	52	22.8%	0.25 [-0.22 , 0.72]
STARS 1992	1.85	1.02	26	2.35	0.98	24	18.6%	-0.50 [-1.05 , 0.05]
WHI 2006	0.011	0.005	1133	0.011	0.003	1699	58.7%	0.00 [-0.00 , 0.00]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.04 [-0.32 , 0.25]**
Heterogeneity: Tau² = 0.04; Chi² = 4.19, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 0.24 (P = 0.81)								
3.11.4 replace by protein								
Ley 2004	0.37	0.71	51	0.12	1.59	52	3.2%	0.25 [-0.22 , 0.72]
WHI 2006	0.011	0.005	1133	0.011	0.003	1699	96.8%	0.00 [-0.00 , 0.00]
Subtotal (95% CI)			**1184**			**1751**	**100.0%**	**0.01 [-0.08 , 0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 1 (P = 0.30); I² = 6%								
Test for overall effect: Z = 0.18 (P = 0.86)								
3.11.5 replacement unclear								
Moy 2001	-0.4	2	117	-0.06	1.9	118	44.2%	-0.34 [-0.84 , 0.16]
Simon 1997	1.35	1.05	34	1.25	0.61	37	55.8%	0.10 [-0.30 , 0.50]
Subtotal (95% CI)			**151**			**155**	**100.0%**	**-0.09 [-0.52 , 0.33]**
Heterogeneity: Tau² = 0.04; Chi² = 1.80, df = 1 (P = 0.18); I² = 45%								
Test for overall effect: Z = 0.43 (P = 0.66)								

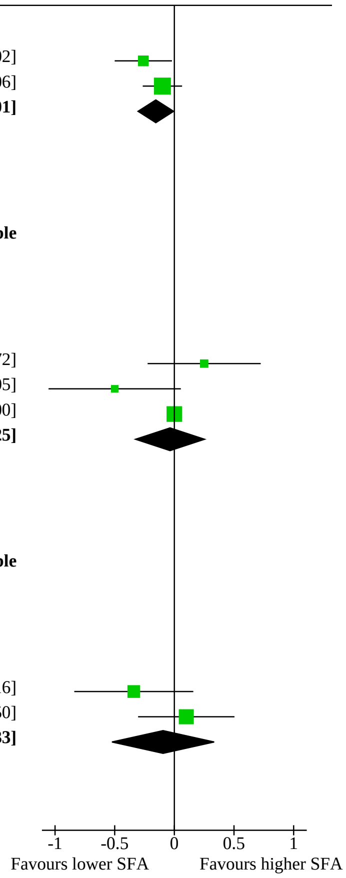
Test for subgroup differences: Chi² = 4.36, df = 3 (P = 0.22), I² = 31.2%



Analysis 3.12. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 12: TG, mmol/L, subgroup by main replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.12.1 replaced by PUFA								
Houtsmuller 1979	0.79	0.6	48	1.05	0.6	48	34.5%	-0.26 [-0.50 , -0.02]
Sydney Diet-Heart 1978	1.6	0.9	221	1.7	0.9	237	65.5%	-0.10 [-0.26 , 0.06]
Subtotal (95% CI)			**269**			**285**	**100.0%**	**-0.16 [-0.30 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%								
Test for overall effect: Z = 2.04 (P = 0.04)								
3.12.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.12.3 replace by CHO								
Ley 2004	0.37	0.71	51	0.12	1.59	52	22.8%	0.25 [-0.22 , 0.72]
STARS 1992	1.85	1.02	26	2.35	0.98	24	18.6%	-0.50 [-1.05 , 0.05]
WHI 2006	0.011	0.005	1133	0.011	0.003	1699	58.7%	0.00 [-0.00 , 0.00]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.04 [-0.32 , 0.25]**
Heterogeneity: Tau² = 0.04; Chi² = 4.19, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 0.24 (P = 0.81)								
3.12.4 replace by protein								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.12.5 replacement unclear								
Moy 2001	-0.4	2	117	-0.06	1.9	118	44.2%	-0.34 [-0.84 , 0.16]
Simon 1997	1.35	1.05	34	1.25	0.61	37	55.8%	0.10 [-0.30 , 0.50]
Subtotal (95% CI)			**151**			**155**	**100.0%**	**-0.09 [-0.52 , 0.33]**
Heterogeneity: Tau² = 0.04; Chi² = 1.80, df = 1 (P = 0.18); I² = 45%								
Test for overall effect: Z = 0.43 (P = 0.66)								

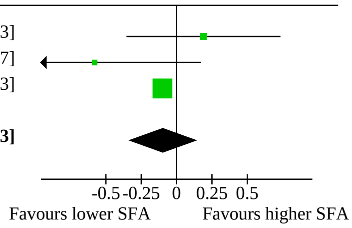
Test for subgroup differences: Chi² = 0.54, df = 2 (P = 0.76), I² = 0%



Analysis 3.13. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 13: total cholesterol /HDL ratio

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
Ley 2004	-0.34	1	51	-0.53	1.73	52	14.6%	0.19 [-0.35 , 0.73]
STARS 1992	5.5	0.918	26	6.08	1.666	24	8.3%	-0.58 [-1.33 , 0.17]
WHI 2006	-0.2	0.8	1133	-0.1	1	1699	77.0%	-0.10 [-0.17 , -0.03]
Total (95% CI)			**1210**			**1775**	**100.0%**	**-0.10 [-0.33 , 0.13]**

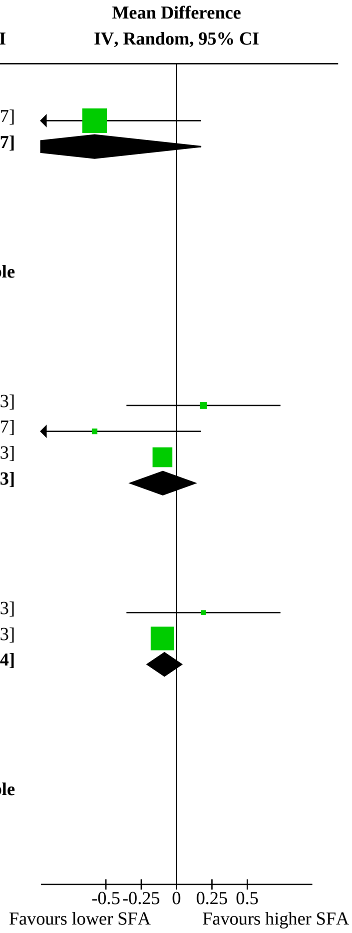
Heterogeneity: Tau² = 0.02; Chi² = 2.65, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 3.14. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 14: TC /HDL ratio, subgroup by any replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.14.1 replaced by PUFA								
STARS 1992	5.5	0.918	26	6.08	1.666	24	100.0%	-0.58 [-1.33 , 0.17]
Subtotal (95% CI)			**26**			**24**	**100.0%**	**-0.58 [-1.33 , 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.51 (P = 0.13)								
3.14.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.14.3 replace by CHO								
Ley 2004	-0.34	1	51	-0.53	1.73	52	14.6%	0.19 [-0.35 , 0.73]
STARS 1992	5.5	0.918	26	6.08	1.666	24	8.3%	-0.58 [-1.33 , 0.17]
WHI 2006	-0.2	0.8	1133	-0.1	1	1699	77.0%	-0.10 [-0.17 , -0.03]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.10 [-0.33 , 0.13]**
Heterogeneity: Tau² = 0.02; Chi² = 2.65, df = 2 (P = 0.27); I² = 24%								
Test for overall effect: Z = 0.83 (P = 0.40)								
3.14.4 replace by protein								
Ley 2004	-0.34	1	51	-0.53	1.73	52	4.8%	0.19 [-0.35 , 0.73]
WHI 2006	-0.2	0.8	1133	-0.1	1	1699	95.2%	-0.10 [-0.17 , -0.03]
Subtotal (95% CI)			**1184**			**1751**	**100.0%**	**-0.09 [-0.21 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 1 (P = 0.30); I² = 7%								
Test for overall effect: Z = 1.39 (P = 0.17)								
3.14.5 replacement unclear								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

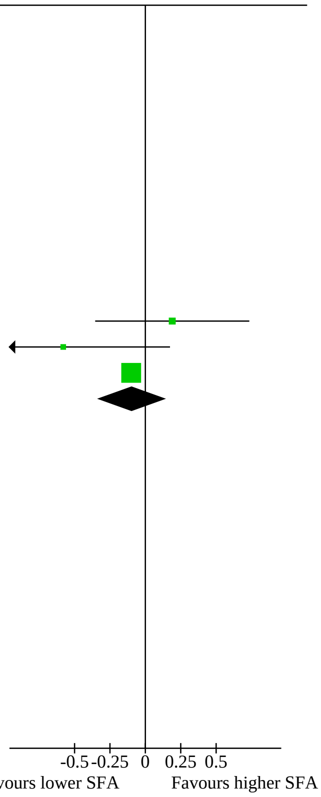
Test for subgroup differences: Chi² = 1.61, df = 2 (P = 0.45), I² = 0%



Analysis 3.15. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 15: TC /HDL ratio, subgroup by main replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.15.1 replaced by PUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.15.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.15.3 replace by CHO								
Ley 2004	-0.34	1	51	-0.53	1.73	52	14.6%	0.19 [-0.35 , 0.73]
STARS 1992	5.5	0.918	26	6.08	1.666	24	8.3%	-0.58 [-1.33 , 0.17]
WHI 2006	-0.2	0.8	1133	-0.1	1	1699	77.0%	-0.10 [-0.17 , -0.03]
Subtotal (95% CI)			**1210**			**1775**	**100.0%**	**-0.10 [-0.33 , 0.13]**
Heterogeneity: Tau² = 0.02; Chi² = 2.65, df = 2 (P = 0.27); I² = 24%								
Test for overall effect: Z = 0.83 (P = 0.40)								
3.15.4 replace by protein								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.15.5 replacement unclear								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

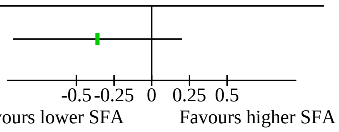
Test for subgroup differences: Not applicable



Analysis 3.16. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 16: LDL /HDL ratio

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Mean Difference IV, Random, 95% CI
STARS 1992	3.74	0.71	26	4.1	1.22	24	-0.36 [-0.92 , 0.20]

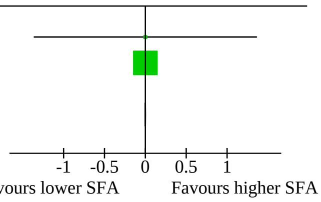
Test for subgroup differences: Not applicable



Analysis 3.17. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 17: Lp(a), mmol/L

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
STARS 1992	0.96	1.89	26	0.96	2.89	24	0.0%	0.00 [-1.37 , 1.37]
WHI 2006	0.03	0.02	1133	0.03	0.02	1699	100.0%	0.00 [-0.00 , 0.00]
Total (95% CI)			**1159**			**1723**	**100.0%**	**0.00 [-0.00 , 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

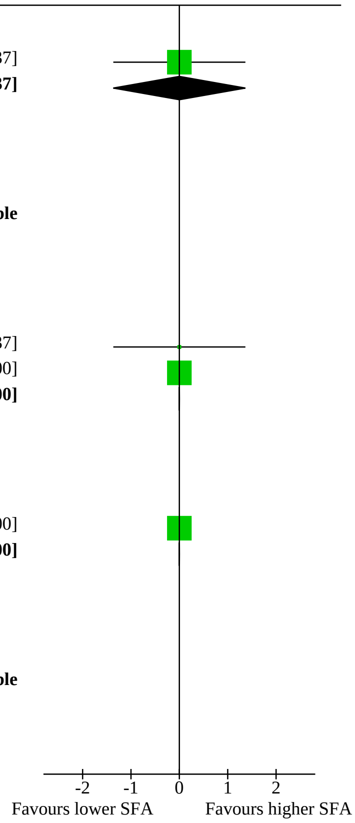


Analysis 3.18. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 18: Lp(a), mmol/L, subgroup by any replacement

	Lower SFA			HIgher SFA				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
3.18.1 replaced by PUFA								
STARS 1992	0.96	1.89	26	0.96	2.89	24	100.0%	0.00 [-1.37 , 1.37]
Subtotal (95% CI)			**26**			**24**	**100.0%**	**0.00 [-1.37 , 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.18.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.18.3 replace by CHO								
STARS 1992	0.96	1.89	26	0.96	2.89	24	0.0%	0.00 [-1.37 , 1.37]
WHI 2006	0.03	0.02	1133	0.03	0.02	1699	100.0%	0.00 [-0.00 , 0.00]
Subtotal (95% CI)			**1159**			**1723**	**100.0%**	**0.00 [-0.00 , 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.18.4 replace by protein								
WHI 2006	0.03	0.02	1133	0.03	0.02	1699	100.0%	0.00 [-0.00 , 0.00]
Subtotal (95% CI)			**1133**			**1699**	**100.0%**	**0.00 [-0.00 , 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.18.5 replacement unclear								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

Test for subgroup differences: Chi² = 0.00, df = 2 (P = 1.00), I² = 0%

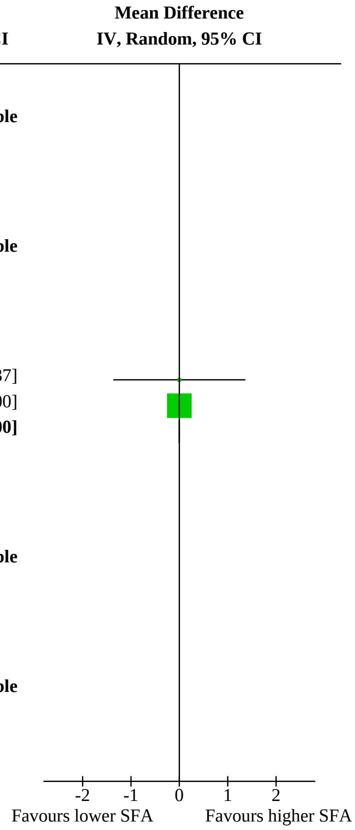
Mean Difference
IV, Random, 95% CI



Analysis 3.19. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 19: Lp(a), mmol/L, subgroup by main replacement

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.19.1 replaced by PUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.19.2 replace by MUFA								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.19.3 replace by CHO								
STARS 1992	0.96	1.89	26	0.96	2.89	24	0.0%	0.00 [-1.37 , 1.37]
WHI 2006	0.03	0.02	1133	0.03	0.02	1699	100.0%	0.00 [-0.00 , 0.00]
Subtotal (95% CI)			**1159**			**1723**	**100.0%**	**0.00 [-0.00 , 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.19.4 replace by protein								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.19.5 replacement unclear								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

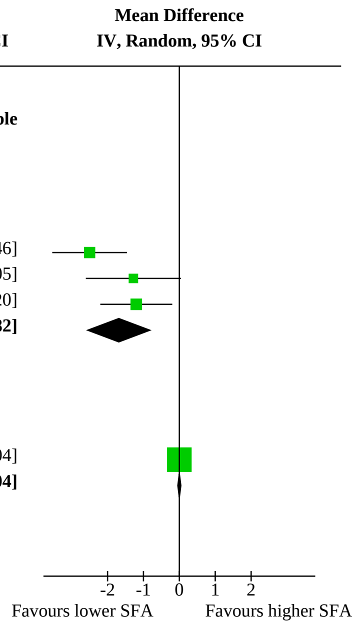
Test for subgroup differences: Not applicable



Analysis 3.20. Comparison 3: SFA reduction vs usual diet - secondary blood outcomes, Outcome 20: Insulin sensitivity

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	HIgher SFA Mean	HIgher SFA SD	HIgher SFA Total	Weight	Mean Difference IV, Random, 95% CI
3.20.1 HbA1c (glycosylated haemoglobin), %								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.20.2 GTT (glucose tolerance test), glucose at 2 hours, mmol/L								
Houtsmuller 1979	7.7	2.5	48	10.2	2.7	48	35.8%	-2.50 [-3.54 , -1.46]
Ley 2004	1.02	2.9	51	2.3	3.9	52	27.0%	-1.28 [-2.61 , 0.05]
STARS 1992	4.6	1.7	26	5.8	1.9	24	37.2%	-1.20 [-2.20 , -0.20]
Subtotal (95% CI)			**125**			**124**	**100.0%**	**-1.69 [-2.55 , -0.82]**
Heterogeneity: Tau² = 0.26; Chi² = 3.61, df = 2 (P = 0.16); I² = 45%								
Test for overall effect: Z = 3.83 (P = 0.0001)								
3.20.3 HOMA								
WHI 2006	1.1	0.5	1133	1.1	0.6	1699	100.0%	0.00 [-0.04 , 0.04]
Subtotal (95% CI)			**1133**			**1699**	**100.0%**	**0.00 [-0.04 , 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								

Test for subgroup differences: Chi² = 14.65, df = 1 (P = 0.0001), I² = 93.2%



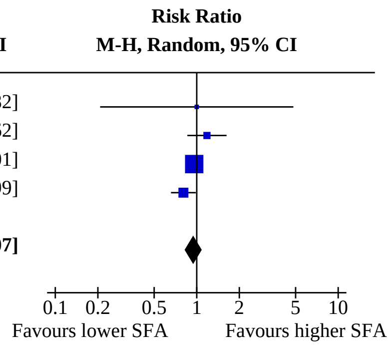
Comparison 4. SFA reduction vs usual diet - secondary outcomes including potential adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Cancer diagnoses	4	52294	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.07]
4.2 Cancer deaths	5	52283	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.61, 1.64]
4.3 Weight, kg	6	43062	Mean Difference (IV, Random, 95% CI)	-1.77 [-3.54, -0.01]
4.4 BMI, kg/m2	6	43894	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.72, -0.12]
4.5 Systolic Blood Pressure, mmHg	5	3812	Mean Difference (IV, Random, 95% CI)	-0.19 [-1.36, 0.97]
4.6 Diastolic Blood Pressure, mmHg	5	3812	Mean Difference (IV, Random, 95% CI)	-0.36 [-1.03, 0.32]
4.7 Quality of Life	1	40130	Mean Difference (IV, Random, 95% CI)	0.04 [0.01, 0.07]

Analysis 4.1. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 1: Cancer diagnoses

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
Ley 2004	3	88	3	88	0.6%	1.00 [0.21 , 4.82]
Veterans Admin 1969	70	424	59	422	12.8%	1.18 [0.86 , 1.62]
WHI 2006	1946	19541	3040	29294	61.7%	0.96 [0.91 , 1.01]
WINS 2006	124	975	231	1462	24.9%	0.80 [0.66 , 0.99]
Total (95% CI)		**21028**		**31266**	**100.0%**	**0.94 [0.83 , 1.07]**
Total events:	2143		3333			

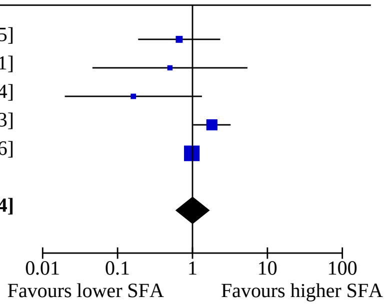
Heterogeneity: Tau² = 0.01; Chi² = 4.47, df = 3 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.91 (P = 0.37)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 2: Cancer deaths

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
DART 1989	4	1018	6	1015	11.7%	0.66 [0.19 , 2.35]
Ley 2004	1	88	2	88	3.9%	0.50 [0.05 , 5.41]
MRC 1968	1	199	6	194	4.9%	0.16 [0.02 , 1.34]
Veterans Admin 1969	31	424	17	422	29.8%	1.81 [1.02 , 3.23]
WHI 2006	950	19541	1454	29294	49.6%	0.98 [0.90 , 1.06]
Total (95% CI)		**21270**		**31013**	**100.0%**	**1.00 [0.61 , 1.64]**
Total events:	987		1485			

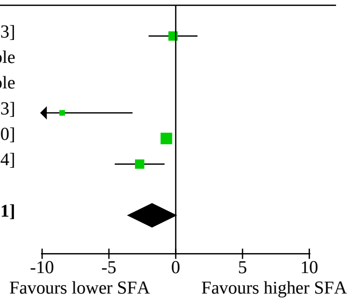
Heterogeneity: Tau² = 0.13; Chi² = 7.84, df = 4 (P = 0.10); I² = 49%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 3: Weight, kg

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	Higher SFA Mean	Higher SFA SD	Higher SFA Total	Weight	Mean Difference IV, Random, 95% CI
Ley 2004	1.06	4.57	51	1.26	4.9	52	26.9%	-0.20 [-2.03 , 1.63]
MRC 1968	0	0	88	-3	0	89		Not estimable
Oslo Diet-Heart 1966	-2.5	0	168	-0.5	0	161		Not estimable
Simon 1997	63.4	11.1	34	71.9	11.7	38	8.7%	-8.50 [-13.77 , -3.23]
WHI 2006 (1)	-0.8	10.1	16297	-0.1	10.1	25056	37.7%	-0.70 [-0.90 , -0.50]
WINS 2006	70.6	14.6	380	73.3	14.9	648	26.7%	-2.70 [-4.56 , -0.84]
Total (95% CI)			**17018**			**26044**	**100.0%**	**-1.77 [-3.54 , -0.01]**

Heterogeneity: Tau² = 2.14; Chi² = 13.06, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable

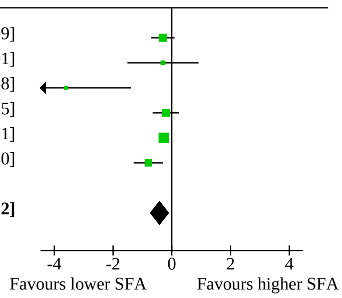


Footnotes
(1) Change from baseline to 7,5 years

Analysis 4.4. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 4: BMI, kg/m2

Study or Subgroup	Lower SFA Mean	Lower SFA SD	Lower SFA Total	Higher SFA Mean	Higher SFA SD	Higher SFA Total	Weight	Mean Difference IV, Random, 95% CI
Moy 2001	-0.1	1	117	0.21	2	118	21.4%	-0.31 [-0.71 , 0.09]
Oxford Retinopathy 1978	-1	2.8	29	-0.7	1.8	29	5.3%	-0.30 [-1.51 , 0.91]
Simon 1997	23.8	4.7	34	27.4	4.9	38	1.8%	-3.60 [-5.82 , -1.38]
Sydney Diet-Heart 1978	24.3	1.5	179	24.5	2.8	192	19.5%	-0.20 [-0.65 , 0.25]
WHI 2006 (1)	0.03	3.2	16230	0.3	3.1	24943	34.3%	-0.27 [-0.33 , -0.21]
WINS 2006	26.8	5.608	755	27.6	5.368	1230	17.8%	-0.80 [-1.30 , -0.30]
Total (95% CI)			**17344**			**26550**	**100.0%**	**-0.42 [-0.72 , -0.12]**

Heterogeneity: Tau² = 0.07; Chi² = 13.00, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 2.72 (P = 0.006)
Test for subgroup differences: Not applicable

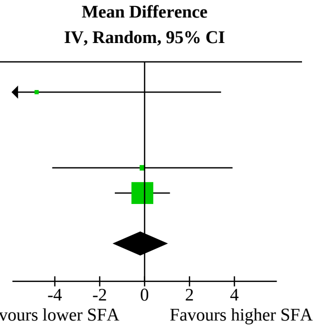


Footnotes
(1) Change to 7.5 years

Analysis 4.5. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 5: Systolic Blood Pressure, mmHg

	Lower SFA			Higher SFA				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ley 2004	-3.5	17.71	51	1.31	24.37	52	2.0%	-4.81 [-13.03 , 3.41]
MRC 1968	2	0	88	0	0	89		Not estimable
Oslo Diet-Heart 1966	158.2	0	168	154.3	0	161		Not estimable
Sydney Diet-Heart 1978	136.4	17.8	179	136.5	21.6	192	8.4%	-0.10 [-4.12 , 3.92]
WHI 2006	-2.2	16.3	1133	-2.1	16.4	1699	89.6%	-0.10 [-1.33 , 1.13]
Total (95% CI)			**1619**			**2193**	**100.0%**	**-0.19 [-1.36 , 0.97]**

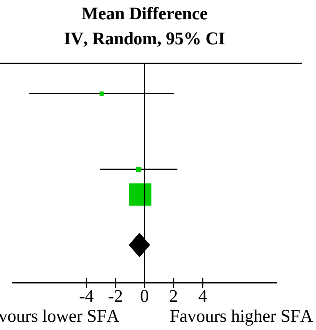
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 6: Diastolic Blood Pressure, mmHg

	Lower SFA			Higher SFA				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ley 2004	-7.16	12	51	-4.2	13.85	52	1.8%	-2.96 [-7.96 , 2.04]
MRC 1968	-1	0	88	3	0	89		Not estimable
Oslo Diet-Heart 1966	98.6	0	168	95.5	0	161		Not estimable
Sydney Diet-Heart 1978	87.5	12.3	179	87.9	13.8	192	6.5%	-0.40 [-3.06 , 2.26]
WHI 2006	-2.6	9.4	1133	-2.3	9.4	1699	91.7%	-0.30 [-1.01 , 0.41]
Total (95% CI)			**1619**			**2193**	**100.0%**	**-0.36 [-1.03 , 0.32]**

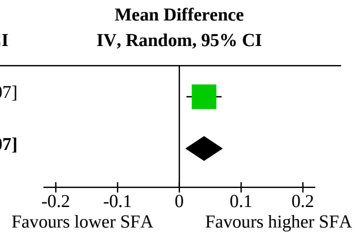
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4: SFA reduction vs usual diet - secondary outcomes including potential adverse effects, Outcome 7: Quality of Life

	Lower SFA			HIgher SFA				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
WHI 2006 (1)	0.07	1.41	15788	0.03	1.44	24342	100.0%	0.04 [0.01 , 0.07]
Total (95% CI)			**15788**			**24342**	**100.0%**	**0.04 [0.01 , 0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Not applicable



Footnotes
(1) Change in Global Quality of Life to trial close-out (0 worst to 10 best), Assaf 2016

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 sessions	Advice (behaviour techniques learning)
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 every 2 months	Advice and supplement (oil)

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

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-month 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 2006	Postmenopausal women aged 50 - 79 with or without CVD at baseline	Low and High	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

MI: myocardial infarction
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
Houtsmuller 1979	102	0	0	102	102	0	0	102	102	0
Ley 2004	176	176	176	176	176	0	176	0	176	0

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

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
Sydney Diet-Heart 1978	458	458	458	458	0	0	0	458	0	0
Veterans Admin 1969	846	846	846	846	846	846	846	846	846	0
WHI 2006	48,835	48,835	48,835	48,835	48,835	48,835	48,835	48,835	48,835	48,835
WINS 2006	2437	2437	0	0	0	0	0	0	0	0
Total Participants	56,675	55,858	53,421	53,758	53,167	52,834	50,952	53,159	53,199	48,835
Percent of participants for this outcome	100%	99%	94%	95%	94%	93%	90%	94%	94%	86%

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).
CHD: coronary heart disease
CV: cardiovascular
CVD: cardiovascular disease

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

	Participants	Total cho-	LDL cholesterol	HDL cholesterol	Triglycerides	TG/HDL ratio	Total choles-	LDL/HDL ratio	LP (a)	Insulin sensitivity

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

		les- terol					terol/HDL ratio			
Black 1994	133	0	0	0	0	0	0	0	0	0
DART 1989	2033	1855	0	1855	0	0	0	0	0	0
Houtsmuller 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	60	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
WHI 2006	48,835	2832	2832	2832	2832	0	2832	0	2832	2832
WINS 2006	2437	196	0	0	0	0	0	0	0	0
Total Participants	56,675	7115	3291	5147	3845	0	2985	50	2882	3081
Percent of participants for this outcome	100%	13%	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).
HDL: high density lipoprotein

LDL: low density lipoprotein
Lp(a): lipoprotein (a)
TG: triglyceride

Table 4. Meta-regression of effects of SFA reduction on cardiovascular events

Regression factor	No. of studies	Con-stant	Coefficient (95% CI)	P value	Proportion of between study vari-ation ex-plained
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%

*Gender was coded as follows: 0 = women, 1 = mixed, 2 = men

****CVD risk at baseline was coded as follows: 1 = Low CVD risk, 2 = Moderate CVD risk, 3 = existing CVD

CHO: carbohydrate

CI: confidence interval

CVD: cardiovascular disease

E: energy

MUFA: monounsaturated fatty acid

PUFA: polyunsaturated fatty fat

SFA: saturated fatty acid

TC: total cholesterol

Table 5. 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	0.89 (0.66 to 1.20)	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	0.89 (0.66 to 1.20)	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	0.96 (0.83 to 1.10)	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)	0.95 (0.67 to 1.35)	0.88 (0.66 to 1.18)	0.93 (0.80 to 1.08)	0.89 (0.58 to 1.35)	0.87 (0.58 to 1.33)	1.05 (0.77 to 1.43)	0.82 (0.60 to 1.13)
11%E	0.99 (0.88 to 1.12)	0.92 (0.65 to 1.31)	0.86 (0.66 to 1.13)	0.94 (0.84 to 1.06)	0.89 (0.58 to 1.35)	0.76 (0.45 to 1.30)	1.02 (0.84 to 1.24)	0.85 (0.63 to 1.15)
12%E	0.98 (0.91 to 1.07)	0.95 (0.75 to 1.21)	0.90 (0.74 to 1.08)	0.94 (0.85 to 1.04)	0.90 (0.72 to 1.14)	0.93 (0.55 to 1.25)	1.02 (0.84 to 1.24)	0.90 (0.77 to 1.06)
13%E	1.02 (0.83 to 1.25)	0.93 (0.63 to 1.38)	0.87 (0.65 to 1.17)	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
E: energy
MI: myocardial infarction
N/A: not applicable (no relevant studies)
RR: risk ratio
SFA: saturated fat, as percentage of energy

APPENDICES

Appendix 1. Search strategies 2019

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) Date added to CENTRAL trials database: 05/03/2014-15/10/2019

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. limit 33 to ed=20140305-20191015

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. limit 39 to dd=20140305-20191015

Clinicaltrials.gov

Condition or disease: Cardiovascular Diseases OR CVD OR "heart disease"

Intervention/treatment: Dietary Fats OR saturated OR unsaturated OR fat

Study type: Interventional Studies (Clinical Trials)

ICTRP

Condition: Cardiovascular Diseases OR CVD OR heart disease

Intervention: Dietary Fats OR saturated OR unsaturated OR fat

FEEDBACK

Jeffery Heileson and Chaz McIntosh, May 2020

Summary

Dear Editors,

We recently read with interest the updated systematic review, “Reduction in saturated fat intake for cardiovascular disease”.[1] After a careful review of the analysis, some notable flaws were identified that may be of interest to the Cochrane Heart Group and the authors:

1) As discussed elsewhere,[2] the inclusion of the Oslo Diet-Heart Study (ODHS) seems to violate one of the inclusion criteria (“not multifactorial”). Briefly, the ODHS experimental group (polyunsaturated [PUFA]) was counselled to increase fruits, vegetables, nuts, and fish, while avoiding sugar.[3] Interestingly, the PUFA group was not only counselled, but supplemented with cod liver oil and sardines (5/d EPA+DHA and 610 IU vitamin D). Lastly, the PUFA group restricted trans-fat (TFA) intake, while the control (saturated fat [SFA]) group consumed nearly 10% of total energy as TFA.

2) Similarly, the St Thomas Atherosclerosis Regression Study (STARS) was recently excluded from a Cochrane systematic review for being multifactorial.[4] Also of note, the PUFA group ate about 15g/d less TFA and doubled their EPA+DHA intake compared to the SFA group.[5] While Analysis 1.43 excluded trials with additional interventions for CVD events, this analysis was not replicated for all-cause mortality (ACM), CVD mortality, CHD mortality, or CHD events.

3) Inclusion of the Houtsmuller trial may be questionable.[6] A previous Cochrane systematic review notes that there were “concerns of fraud” in Houtsmuller’s later research and how the study was “extremely vague across all publications about its methods”.[4] Moreover, the specific source of fat used in the control group – vaguely described as “saturated margarines” – is likely not animal sourced and may well be hydrogenated vegetable oil.[7]

4) During the early trials, SFA interventions also reduced TFA intake. Namely, the ODHS, LA Vets trial, and MRC, all reduced TFA intake by at least 2% of total energy in the PUFA groups. While not explicitly a component of the selection criteria, TFA intake should be taken into consideration as a major confounding variable.

5) The reduction in “combined cardiovascular events” was driven by softer endpoints more susceptible to bias. For instance, about 85% of the events in Houtsmuller et al were due to angina,[6] 71% of the events in STARS were “patients requiring increased anti-anginal treatment” or “cardiac surgery”,[8] and 42% of the events in MRC were “those not classified as major, which include 'acquired angina'”.[9] Similarly, results from LA Vets were only significant after adding secondary soft endpoints. Given that virtually all dietary trials were not sufficiently blinded, inclusion of these softer endpoints may be inappropriate and introduce bias. Notably, Ramsden et al did not evaluate non-fatal endpoints because of “several critical deficiencies in the collection and reporting of non-fatal CHD events in these RCTs”.[10]

6) The exclusion of the Sydney Diet-Heart Study (SDHS) for "combined cardiovascular events" is puzzling and should be elucidated further within the text. The SDHS did report cardiovascular mortality endpoints which appears to fit the definition of "combined cardiovascular events" as noted on page 7.[1] Also, Cochrane's omega-6 PUFA review shows that the SDHA was included in that analysis for CVD events, CHD events, and strokes.[4] Since the Sydney study is one of the few "low summary risk of bias" trials for CVD events,[1] it would seem important to include it where possible.

7) The authors stated, "This clearly indicates that the cardiovascular effects of reducing saturated fat rely on changes in atherosclerosis via serum cholesterol." Meta-regression and subgroup analysis are observational; hence, this statement seems to go beyond the evidence provided. The degree of cholesterol reduction did not influence ACM, CVD mortality, or CHD mortality. The relationship between CVD and CHD events and total cholesterol could have been driven by the higher omega-3 intake and lower TFA intake in the experimental groups as well as the intervention.

We'd like to thank the authors for their hard work and rigorous analysis. We hope that our comments contribute to the research process in a meaningful way and improve future analysis.

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Reply

Thank you for your thoughts. We did not include studies that were multifactorial in terms of smoking, exercise, drugs etc, but did allow concurrent dietary changes. We ran a sensitivity analysis assessing effects on CVD events in trials where additional dietary interventions were not included. "Sensitivity analysis omitting trials which included dietary interventions in addition to changes to dietary fat (for example, changes to fruit and vegetable or fibre intake) we excluded three trials (Oslo Diet-Heart 1966; STARS 1992; WHI 2006). This analysis also suggested that reducing saturated fat (rather than other dietary changes) reduced risk of cardiovascular events: RR 0.86 (95% CI 0.67 to 1.09, Analysis 1.43)."

We aimed to gather trans fatty acid data from all included studies and to include changes to trans fats, alongside changes to MUFA, PUFA etc in the meta-regression. This was not possible for trans fats due to the lack of data within included studies. Without the data we can only speculate as to changes in trans fats.

The Sydney Diet-Heart Study should appear in the "combined cardiovascular events" analysis, and we have updated the analysis to include the Sydney Diet-Heart Study CVD deaths within the CVD events analysis. This alters the "bottom line" for the CVD events forest plot to RR 0.83 (95% CI 0.70 to 0.98, I2 67%). This altered effect size has been worked through the review, and does not alter the main conclusions of the review.

Contributors

Feedback editor: William Cayley

Lead author: Lee Hooper

George Henderson, May 2020

Summary

The introduction to this meta-analysis includes an error uncorrected from the 2015 version.
Oliver 1953 measured total cholesterol, not LDL cholesterol. Further, it is relevant that every subject in Oliver 1953 had been eating the same hospital diet for at least 5 weeks before the cholesterol samples were taken, which does not support a diet-heart interpretation of the results.[1] (The presence of FH in the sample, and/or survivorship bias, are probably more reasonable interpretations)
The section headed "Agreements and disagreements with other studies or reviews" has not addressed any written after 2014, meaning that this section has not been updated. There are several analyses of the diet heart trials since 2015 that should have been addressed (indeed, that should have been read before the current Cochrane review was designed). Some are listed below.[2,3.4]
The discussion of Siri-Tarino 2010 in "Agreements and disagreements with other studies or reviews" claims that adjustment for lipids has confounded its null result, however Siri-Tarino at al had already addressed this by isolating studies not adjusted for lipids with no difference in their null result. This is quite understandable as adjusting for lipids also means adjusting for TG and HDL, cardiometabolic risk markers which can be beneficially influenced by saturated fat and worsened by carbohydrate.
Studies which do not adjust for lipids can be non-significantly favourable to saturated fat, for example the Malmo DCS, a high-quality observational study using a 7-day food diary and more rigorous exclusion criteria than is usual, or the 2019 dose-response meta-analysis of observational studies by Zhu et al.[5,6]
The claim that greater lowering of LDL in trials being associated with greater reduction of events supports the diet-heart hypothesis may be unsound. Persons in good metabolic health are at significantly lower risk of CVD events despite other risk factors.[7] Persons who are obese, have diabetes, or the metabolic syndrome do not usually experience drops in LDL cholesterol when fat in the diet is changed; the subjects in the feeding studies cited, who did experience such drops, were healthy volunteers.[8,9,10]

It is also relevant that from 2004 the Swedish population began to reject diet-heart advice, to such an extent that butter sales rose and margarine sales dropped; cholesterol levels also rose.[11] Yet as recently as 2018 mortality from, and incidence of, AMI was continuing to decline in Sweden. In fact incidence of AMI had stayed stable from 1987 to 2005, after which it began to drop from 42,263 PA to 25,789 PA in 2018.[12]

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Reply

Thank you for your thoughts, comments and suggested references. There is a vast literature on effects on health of saturated fat. We limited our introduction to systematic reviews of effects of reducing saturated fats on CVD, and there do not appear to be any further substantial ones that we missed.

In discussing the Siri-Tarino 2010 meta-analysis of observational studies our focus is on comparison with effects observed in our systematic review of trials, and the problems of knowing what factors to adjust for in observational studies where different dietary factors are very highly correlated.

In meta-regression the studies that reduced saturated fat the most also reduced CVD events the most, and greater reductions in total serum cholesterol levels reduced CVD events more. This explained much of the heterogeneity between studies. Overall, the relationship with serum total cholesterol was clearest (P = 0.04, accounting for 99% of between-study variation). Apparent heterogeneity was accounted for by a dose-effect; where SFA reduction resulted in greater serum cholesterol reduction, the reduction in CVD events was greater (see section "Effects of interventions" and additional Table 4).

Our review assessed effects of saturated fat on CVD, but it is not the only element of our lifestyles that affects CVD risk. Within Sweden smoking, physical activity, alcohol intake, medication levels for lipids and blood pressure etc etc will have changed alongside fat intakes, highlighting some of the problems of interpreting observational data. What happens to levels of CVD in Sweden reflects all of these changes, and does not detract from our review of effects of reducing saturated fats. This is not a systematic review of observational studies.

Contributors

Feedback editor: William Cayley

Lead author: Lee Hooper

Kevin Schwanz, July 2020

Summary

The major problem with this review is that the studies included do not test saturated fat. They are not a simple decrease in saturated fat intake, nor are they a simple substitution of saturated fat for unsaturated fat or other nutrient. A prime example of this is the Women's Health Initiative Study. The intervention group decreased saturated fat intake compared to controls, but they also decrease MUFA, PUFA, trans-fat, and cholesterol intake while increasing intake of fiber, fruits/vegetables, and grains. Thus, the study tells us nothing about the specific effects of saturated fat. The same can be said for most, if not all, of the other included studies. What is the rationale for including these studies in a review about the effects of saturated fat?

Reply

Thank you for your comments. As you know it is never possible to make a single change to dietary intake – if one nutrient is altered then its energy will be replaced by another nutrient. But more than that, we eat foods, so nutrients are grouped (the basis of our interest in dietary patterns). However good and explicit your dietary advice to a patient post-MI you will never be able to effect a simple reduction in saturated fat and an increase in (for example) complex carbohydrate – other dietary changes will also happen. If a patient reduces their cheese intake their calcium intake will also fall, if that patient reduces their red meat intake their iron intake will fall. For this reason we focused on including studies that reduced saturated fat intake, regardless of what replaced it. The thinking is that this gives us the best idea of the effect of reducing saturated fat and as different studies replaced the saturated fat with slightly different nutrients any effect of these replacements will tend to be diluted out. However, because we included some trials that explicitly aimed to make additional dietary changes (for example, to reduce saturated fat and increase fruit and vegetable intake, like WHI) we ran sensitivity analyses to check effects omitting these trials (see analysis 1.43). When omitting these studies we have less power to see the effect of reducing saturated fat, but the effect size is very similar, suggesting that the effects we see are driven by the reduction in saturated fat, not the other dietary changes.

Contributors

Feedback editor: William Cayley

Lead author: Lee Hooper

WHAT'S NEW

Date	Event	Description
21 August 2020	Amended	Data for the Sydney Diet-Heart 1978 were added to primary outcome combined CVD events. This has slightly altered the effect of reducing saturated fat on combined cardiovascular events, from

Date	Event	Description
		RR 0.79 (95% CI 0.66 to 0.93) to RR 0.83 (95% CI 0.70 to 0.98), but has not changed the overall conclusion. This suggests a reduction in cardiovascular events by 17% (moderate quality GRADE evidence). Additionally, some aspects of the review methods have been better explained, and points added to the discussion.
21 August 2020	New citation required but conclusions have not changed	Feedback incorporated, conclusions unchanged.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 6, 2015

Date	Event	Description
9 January 2020	New citation required but conclusions have not changed	No new trials included, but four ongoing trials and one study awaiting assessment, and we found new data for two of the already included trials (WHI 2006; WINS 2006). We updated assessment of risk of bias, including assessment of summary risk of bias for each trial, and carrying out sensitivity analyses omitting trials not at low summary risk of bias. We updated assessment of small study bias by comparing results of fixed- and random-effects meta-analyses. Data, results, GRADE assessment and conclusions updated.
29 December 2019	New search has been performed	Searches updated to October 2019, searches of trials registers added.
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. 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, all authors took part in assessment of the results of the updated search, and assessment of inclusion of potentially relevant studies. All authors edited, proof-read and agreed the final version of the review.

LH was the principal author of earlier versions (Hooper 2000; Hooper 2001; Hooper 2012; Hooper 2015a), originated and was primarily responsible for planning and carrying out this systematic review, liaising with WHO NUGAG, carrying out the statistical analyses, and writing the first draft of this review.

AA, OFJ, CK, EF and LH were responsible for data extraction and assessment of validity.

DECLARATIONS OF INTEREST

Lee Hooper: LH is a member of the World Health Organization Nutrition Guidance Expert Advisory Group (NUGAG). WHO paid for her travel, accommodation and expenses to attend NUGAG meetings in Geneva, China and South Korea where the evidence of effects of dietary fats on health was discussed and guidance developed. LH's institution was given grant funding from WHO to carry out the 2019 update of this systematic review, to update a systematic review on the relationship between total fat intake and body weight and a series of systematic reviews on the health effects of polyunsaturated fatty acids.

Nicole Martin: None known

Asmaa Abdelhamid: None known

Oluseyi Florence Jimoh: This review was funded by a grant from the World Health Organization.

Eve Foster: None known

Christian Kirk: None known

SOURCES OF SUPPORT

Internal sources

- University of East Anglia, UK

  Help with acquiring papers for previous versions of this review, and allowing time for Lee Hooper to work on the review
- University of Manchester, UK

  Support with collection of papers for the first version of this 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
- World Health Organization, Other

  WHO funded the most recent update of this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is the result of updating the searches for Hooper 2015a. The objective and outcomes have been widened since the protocol 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