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Reduced or modified dietary fat for preventing cardiovascular disease (Review)

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Reduced or modified dietary fat for preventing cardiovascular disease.
Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD002137.
DOI: 10.1002/14651858.CD002137.pub3.

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[Intervention Review]

Reduced or modified dietary fat for preventing cardiovascular disease

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Editorial group: Cochrane Heart Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 11, 2017.

Citation: Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore HJ, Davey Smith G. Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD002137. DOI: 10.1002/14651858.CD002137.pub3.

ABSTRACT

Background

Reduction and modification of dietary fats have differing effects on cardiovascular risk factors (such as serum cholesterol), but their effects on important health outcomes are less clear.

Objectives

To assess the effect of reduction and/or modification of dietary fats on mortality, cardiovascular mortality, cardiovascular morbidity and individual outcomes including myocardial infarction, stroke and cancer diagnoses in randomised clinical trials of at least 6 months duration.

Search methods

For this review update, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE, were searched through to June 2010. References of Included studies and reviews were also checked.

Selection criteria

Trials fulfilled the following criteria: 1) randomised with appropriate control group, 2) intention to reduce or modify fat or cholesterol intake (excluding exclusively omega-3 fat interventions), 3) not multi factorial, 4) adult humans with or without cardiovascular disease, 5) intervention at least six months, 6) mortality or cardiovascular morbidity data available.

Data collection and analysis

Participant numbers experiencing health outcomes in each arm were extracted independently in duplicate and random effects meta-analyses, meta-regression, sub-grouping, sensitivity analyses and funnel plots were performed.

Main results

This updated review suggested that reducing saturated fat by reducing and/or modifying dietary fat reduced the risk of cardiovascular events by 14% (RR 0.86, 95% CI 0.77 to 0.96, 24 comparisons, 65,508 participants of whom 7% had a cardiovascular event, I^2 50%). Subgrouping suggested that this reduction in cardiovascular events was seen in studies of fat modification (not reduction - which related directly to the degree of effect on serum total and LDL cholesterol and triglycerides), of at least two years duration and in studies of men

(not of women). There were no clear effects of dietary fat changes on total mortality (RR 0.98, 95% CI 0.93 to 1.04, 71,790 participants) or cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04, 65,978 participants). This did not alter with sub-grouping or sensitivity analysis.

Few studies compared reduced with modified fat diets, so direct comparison was not possible.

Authors' conclusions

The findings are suggestive of a small but potentially important reduction in cardiovascular risk on modification of dietary fat, but not reduction of total fat, in longer trials. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates. The ideal type of unsaturated fat is unclear.

PLAIN LANGUAGE SUMMARY

Cutting down or changing the fat we eat may reduce our risk of heart disease

Modifying fat in our food (replacing some saturated (animal) fats with plant oils and unsaturated spreads) may reduce risk of heart and vascular disease, but it is not clear whether monounsaturated or polyunsaturated fats are more beneficial. There are no clear health benefits of replacing saturated fats with starchy foods (reducing the total amount of fat we eat). Heart and vascular disease includes heart attacks, angina, strokes, sudden cardiovascular death and the need for heart surgery. Modifying the fat we eat seems to protect us better if we adhere in doing so for at least two years. It is not clear whether people who are currently healthy benefit as much as those at increased risk of cardiovascular disease (people with hypertension, raised serum lipids or diabetes for example) and people who already have heart disease, but the suggestion is that they would all benefit to some extent.

BACKGROUND

In 1949 Ryle and Russell in Oxford documented a dramatic increase in coronary heart disease, 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 LDL cholesterol levels (Oliver 1953).

Meanwhile in 1949 in the US Gofman had separated lipids into lipoprotein classes through ultra centrifugation, describing the low density lipoproteins (LDL) as 'atherosclerogenic' (Gofman 1949). The following year Keys proposed that the concentration of plasma cholesterol was proportional to dietary saturated fat intake (Keys 1950), and this relationship was confirmed in work by Hegsted (Hegsted 1965; Hegsted 2000) who published an equation explaining the relationship in 1965 and subsequently in 2000, suggesting that dietary saturated fat increases serum cholesterol and so increases cardiovascular risk, while polyunsaturated fats 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 polyunsaturated intake (as percentage of energy) + 6.77 * Δ dietary cholesterol intake (in units of 100mg/day) – 0.53

The Seven Countries Study compared CHD mortality in 12000 men aged 40-59 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 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 diet 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, recent systematic reviews of the observational data have not confirmed these early studies. Skeaff 2009 included 28 US and European cohorts (including 6600 coronary heart disease deaths among 280,000 participants) investigating the effects of total, saturated, monounsaturated, trans and omega-3 fats on coronary heart disease deaths and events. They found no clear relationship between total, saturated or monounsaturated fat 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 polyunsaturated fats and omega-3 fats decreased them. Siri-Tarino 2010 included 21 prospective epidemiologic studies assessing the relationship between saturated fats and coronary heart disease, stroke and cardiovascular disease, finding that saturated fat intake was not associated with risk of coronary heart disease, stroke or cardiovascular disease. Observational studies are potentially powerful at providing associations between dietary factors and cardiovascular risk, but the scale of measurement error is such that detecting such effects may be difficult. Thus intervention studies are needed to clarify cause and effect, to ensure that confounding is not either hiding or generating true relationships. Trials also directly address the issue of whether altering dietary fat in adults is helpful in reducing the risk of cardiovascular diseases in the general population and in those at high risk. It is essential that intervention trials form the basis of evidence based practice in this area.

Most intervention studies have assessed the effect of dietary interventions on risk factors for heart disease, and separate work ties the effect of altering these risk factors to changes in disease incidence and mortality. Systematic review in this area follows the same pattern, so that there are systematic reviews of the effect of dietary fat advice on serum lipid levels (Brunner 1997; Brunner 2009; Clarke 1997; Denke 1995; Kodama 2009; Mensink 1992; Shafiq 2010; Weggemans 2001; Yu-Poth 1999) suggesting that dietary changes cause changes in serum lipids and reviews on the effect of lipid level alterations on cardiovascular morbidity and mortality (Briel 2009; De Caterina 2010; Law 1994; Robinson 2009; Rubins 1995; Walsh 1995), suggesting that changes in lipids do affect cardiovascular 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 cardiovascular disease. An example of this is the choice of substitution of saturated fats by carbohydrate, polyunsaturated fats or monounsaturated fats 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 cardiovascular morbidity and mortality, and on total mortality.

Substantial randomised controlled trial data on the effects of dietary fat on mortality and morbidity does exist - the first version of this systematic review included over 18,000 participants in trials of at least six months duration, reporting on over 1400 deaths, over 800 cardiovascular deaths, and over 1200 cardiovascular events (Hooper 2000, Hooper 2001). The review found no clear relationship between fat modification (reduction of saturated fats, including studies that replaced the missing calories with carbohydrates - low fat diets - and studies that replaced the missing calories with other fats - modified fat diets) and total or cardiovascular mortality, but did find that such modification reduced the rate of cardiovascular events by around 16% (rate ratio 0.84, 95% CI 0.72 to 0.99 compared with usual diet). Since 2000 several important new studies have been published. These include some very large studies that have modified dietary fat intake in women over several years (including the Women's Health Initiative that included over 2000 women with, and over 48,000 women without, cardiovascular disease at baseline for over eight years (WHI with CVD 2006; WHI without CVD 2006) and the Women's Healthy Eating and Living Study including over 3000 women for 11 years (WHEL 2007)) allowing us to add a substantial

body of new research on low fat diets (many of the large studies included in the first version of the review were of modified fat diets rather than reduced fat diets), as well as information on the effects of these changes in women (as previous large studies were mainly in men). The results of WHI in particular have raised many questions about both the effects of fat on health and on how we best conduct research to understand the relationship (Michels 2009; Prentice 2007; Stein 2006; Yngve 2006).

Public health dietary advice on prevention of cardiovascular disease has changed a little over time, with a focus on fat modification during the 1960s and fat reduction during the 1990s. Recent recommendations by the American Heart Association suggest that, among other dietary measures, Americans should "limit intake of saturated fat to 7% of energy, trans fat to 1% of energy, and cholesterol to 300 mg/day by choosing lean meats and vegetable alternatives, fat-free (skim) or low-fat (1% fat) dairy products and minimize intake of partially hydrogenated fats" (Lichtenstein 2006).

How effective are these alterations in dietary fat at reducing cardiovascular morbidity and mortality? Should we replace the energy from saturated and trans fats with carbohydrates, polyunsaturated or monounsaturated fats?

This systematic review aimed to assess the effects of reducing or modifying dietary fat on mortality, cardiovascular mortality and cardiovascular events, as well as on individual cardiovascular outcomes and total cancers, and cardiovascular risk factors. Additionally we used the whole database of studies to use meta-regression to explore effects of changes in total, saturated, polyunsaturated, monounsaturated, trans, weight and study duration on the primary outcomes. Finally we included studies that directly compare reduced with modified dietary fats.

OBJECTIVES

The aim of this systematic review was to assess the effect of change in dietary fats, which would be expected to result in lipid lowering, on mortality and cardiovascular morbidity, using all available randomised clinical trials. For this update interventions were classified as low fat, modified fat or combined low and modified fat diets and effects of each type of dietary intervention were assessed.

Specific questions included:

1. Does reducing saturated fat intake, by reducing and/or modifying dietary fat, in the longer term (at least six months) reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?
2. Does a long term reduced fat diet, compared with usual diet, reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?
3. Does a long term reduced fat diet alter classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?
4. Does a long term modified fat diet, compared with usual diet, reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?
5. Does a long term modified fat diet alter classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?
6. Does reducing and modifying dietary fat (as a combined intervention) in the longer term reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?
7. Does a long term reduced and modified fat diet (as a combined intervention) alter classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?
8. Are effects on mortality, cardiovascular mortality or cardiovascular morbidity moderated by differences in baseline cardiovascular risk, mode of intervention, control group total fat intake, control group saturated fat intake, gender, setting or decade of publication, or changes in total fat intake, saturated fat intake, polyunsaturated fat intake, monounsaturated fat intake, trans fat intake, dietary cholesterol, weight, serum LDL cholesterol, or study duration?
9. Is a long term reduced fat diet or a modified fat diet more effective in reducing mortality, cardiovascular mortality or cardiovascular morbidity (or individual effects such as myocardial infarction, stroke or cancer diagnoses)?
10. Is a long term reduced fat diet or a modified fat diet more acceptable to people trying to adhere to these diets?
11. Is a long term reduced fat diet or a modified fat diet more effective in altering classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials only. Randomization of individuals was accepted, or of larger groups where there were at least six of these groups randomized. Studies where allocation was not truly randomised (e.g. divisions based on days of the week or first letter of the family name were excluded) or where allocation was not stated as randomised (and no further information was available from the authors) were excluded.

Types of participants

Studies of adults (18 years or older, no upper age limit) at any risk of cardiovascular disease (with or without existing cardiovascular disease) were accepted. Participants could be of either gender, but those who were acutely ill, pregnant or lactating were excluded.

Types of interventions

All randomised controlled trials of interventions stating an intention to reduce or modify dietary fat or cholesterol, such as would be expected to result in improvement of serum lipid profile, were considered. These included an intention to reduce total fat intake, modify fat intake (while maintaining total fat intake), and reduction and modification of fat intake, all compared to a usual diet type control or modification of dietary fat compared to reduced total fat. The intervention had to be dietary advice, supplementation (of fats, oils or modified or low fat foods) or a

provided diet, and the control group usual diet, placebo or a control diet.

A low fat diet was considered to be one that aimed to reduce fat intake to < 30%E from fat, and at least partially replace the energy lost with carbohydrates (simple or complex), protein or fruit and vegetables. A modified fat diet was considered to be one that aimed to include 30% or more energy from total fats, and included higher levels of mono-unsaturated or poly-unsaturated fats than a 'usual' diet.

Interventions excluded (unless they were present in addition to those above) were addition of alpha-linolenic acid, omega-3 fats or fish oils (as the effect of these is dealt with in a separate review), high fibre diets and garlic (as pulses, fruits and vegetables may have various effects other than lipid lowering) or exploration of varying forms of carbohydrate (unless also specifically low in fat or fat modified). Also excluded were all multiple risk factor interventions other than diet or supplementation (unless the effects of diet or supplementation could be separated, as in a factorial design, so the additional intervention was consistent or randomised between the intervention and control groups), and studies that aimed for weight loss in one arm but not the other. Atkins-type diet 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 or modified fats and encouraged physical activity in one arm and compared with encouraging physical activity in the control were included; studies that reduced or modified fats and encouraged physical activity in one arm and compared with no intervention in the control were excluded; studies that reduced or modified 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:

The main outcomes were total and cardiovascular mortality and combined cardiovascular events. Combined cardiovascular events included any of the following data available from a trial: cardiovascular deaths, cardiovascular morbidity (non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events, atrial fibrillation) and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty).

Secondary outcomes:

Secondary outcomes included individual types of cardiovascular events, including total myocardial infarction, non-fatal myocardial infarction, stroke (fatal and non-fatal), diabetes diagnosis, cancer deaths and cancer diagnoses, and quality of life measures (including informal outcomes such as feelings of health, time off work).

Tertiary outcomes:

Tertiary outcomes were process outcomes, and included changes in saturated and total fat intakes, and classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride).

Trials were only included where primary outcome data (mortality or cardiovascular morbidity) could be collected (by communication with authors if necessary). Studies where it was known that no events occurred were included, and their data used to assess tertiary outcomes.

Search methods for identification of studies

Electronic searches

The initial searches were run in March to June 1998 and included *The Cochrane Library*, MEDLINE, EMBASE, CAB Abstracts, CVRCT Registry, SIGLE, bibliographies and experts. A comprehensive search strategy was developed to search for nutrition based randomised controlled trials with morbidity or mortality outcomes.

MEDLINE on SilverPlatter was searched for randomised controlled trials on diet and cardiovascular disease or mortality from 1966 to May 1998. An additional MEDLINE (SilverPlatter 1966 to June 1998) search strategy was run to collect papers where only lipid outcomes were mentioned (see Appendix 1 for details of both searches). These search strategies were adapted for use on *The Cochrane Library* (Issue 2, 1998), EMBASE (Ovid online to May 1998), the CVRCT Registry (May 1998), CAB Abstracts (Ovid online, 1973 to March 1998) and SIGLE (to January 1999). Published systematic reviews addressing diet and heart health were sought as a source of RCTs using similar strategies on MEDLINE (Silver Platter, 1966-March 1998) and *The Cochrane Library* (Issue 1, 1998).

Cochrane Review Groups in areas related to this review include the Diabetes Group (now the Endocrine and Metabolic Disorders Group), Stroke Group, Renal Group, Hypertension Group and Peripheral Vascular Disease Group. The groups were contacted and asked to search their trial registers for relevant trials.

The review authors updated the searches in June 2010, and modified searches were run on Cochrane Central Register of Controlled Trials (CENTRAL on *The Cochrane Library*), Ovid MEDLINE and EMBASE. Modification was due to altered database accessibility as well as altered recommended RCT filters. The searches for the earlier review were run as a wider search for studies for several reviews (including a variety of dietary factors), the recent searches were focused on dietary fat interventions only. As databases other than these three had not provided any included studies during the first version of the review, and the numbers of titles and abstracts were not feasible to handle for the update, these were the only databases used for this update. The search strategies used for the update search are shown in Appendix 2.

No language restrictions were applied to the searches.

Searching other resources

Bibliographies of all identified systematic reviews, major non-systematic reviews and included trials were searched for further trials for the first review and the update. Experts in the field were contacted for references to studies not yet identified by the search process. Attempts were made to obtain translations of relevant non-English articles, or contact with the author was established to enable assessment of eligibility.

Data collection and analysis

Selection of studies

Articles were only rejected on initial screen if the reviewer could determine from the title and abstract that the article was not a report of a randomized 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 6 months duration; or the intervention was multi-factorial. When a title/abstract could not be rejected with certainty, the full text of the article was obtained for further evaluation.

The inclusion of studies was assessed independently by two assessors (LH and one of RLT, DS, FR, HM, Indra Tumur and Dorotheé Fagard) and differences between reviewers' results resolved by discussion and, when necessary, in consultation with a third reviewer (Rudolph Reimersma, see acknowledgements). Trials were categorised as "possible" (where all inclusion criteria appeared to be met or where the ascertainment, or otherwise, of outcome events was uncertain, to be resolved by writing to the author) or "excluded". Attempts were made to contact all authors of "possible" trials in order to confirm or ascertain whether inclusion criteria were met.

Data extraction and management

A data extraction form was designed for this review. 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 patient years in trial were extracted. Where provided, data on risk factors for cardiovascular disease including blood pressure, lipids and weight were collected.

Baseline risk of cardiovascular disease was defined 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.

Original reports of trial results were independently extracted by two reviewers (LH and one of CDS, RLT, DS, FR, HM, Indra Tumur, Dorotheé Fagard, Rudolph Reimersma), differences were resolved by discussion.

Assessment of risk of bias in included studies

Trial quality characteristics were assessed using the Cochane Collaboration's tool for assessment of risk of bias; studies already included were re-assessed using this tool (Higgins 2011). All validity data were extracted by two reviewers independently (LH and one of CDS, RLT, DS, FR, HM, Indra Tumur, Dorotheé Fagard, Rudolph Reimersma), and differences resolved by discussion.

Measures of treatment effect

Primary measures of interest were the effect of intervention on:

1. total and cardiovascular mortality
2. combined cardiovascular events (including cardiovascular deaths, non-fatal myocardial infarction, stroke, angina, heart failure, peripheral vascular disease, angioplasty and coronary artery bypass grafting)
3. quality of life measures.

Unit of analysis issues

We did not include any cluster randomised trials in this review, and cross-over studies (such as the Finnish Mental Hospital study, Finnish Mental Hosp 1972) were excluded as this design would be inappropriate for assessing effects on cardiovascular events or mortality.

Where there was more than one relevant intervention arm but only one control arm the relevant intervention arms were either pooled to create a single pair-wise comparison (where the intervention arms were equivalently appropriate for this review) as described in the Cochrane Handbook (Higgins 2011). Intervention arms that were not appropriate for this review, or less appropriate than another arm, were excluded. When two arms were appropriate for different subgroups then the control group was used once with each intervention arm, but the subgroups were not pooled overall.

When assessing event data we aimed to avoid counting more than one outcome event for any one individual within any one comparison. Where we were unclear (for example, where a paper reported numbers of heart attacks, but did not report the number of people who experienced a heart attack, in each arm) we asked authors for further information.

Dealing with missing data

As the outcomes of our review were often not the planned outcomes of relevant trials (many studies with relevant methods, participants, intervention, control and duration had other primary and secondary outcomes, so mortality and morbidity were reported in many studies only as reasons for dropout, or not reported at all), we tried to contact the authors of all identified studies that were appropriate for inclusion on the basis of participants, intervention, comparison and methodology, to ask about mortality and morbidity, the review's primary and secondary outcomes. This allowed inclusion of many studies that would otherwise have had to be omitted. Studies which were otherwise relevant but where presence or absence of primary outcomes could not be established were retained in the section of studies awaiting classification.

It was often unclear where data on primary or secondary outcome events may still have been missing, and so data were not imputed for this review.

Assessment of heterogeneity

Heterogeneity was examined using the I^2 test, and considered important where > 50% (Higgins 2003; Higgins 2011).

Assessment of reporting biases

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

Data synthesis

The data within the original review were in the form of rates. Treatment effect was measured as a rate ratio and meta-analysis performed as a weighted average of (ln) rate ratios (as described by Hasselblad 1995). For trials with a zero in one arm of the data a small number (0.5) was added to the number of events in both groups.Meta-analysis was performed using random effects methodology (DerSimonian 1986) within S-PLUS (Higgins 1999). For the update of the review we checked that using event data gave similar results to rate data as described above - using the same studies the outcomes of the meta-analysis using Mantel-Haenszel random effects methods were almost identical (presence or absence of statistical significance was never different, and scale of effect size was always similar). For this reason, within the update, numbers of events in each study arm, and total number of participants randomised, were extracted, and Mantel-Haenszel random effects meta-analysis carried out in Review Manager software. Event and continuous outcome data were extracted for the latest time point available within the trial (and always at least six months from inception).

Trials where it was known that there were no events in either intervention group were included in the review for completeness, but were not included in the meta-analysis (where it was stated that no events of particular type occurred this was detailed in Characteristics of included studies). These studies inclusion or otherwise would not influence the results of the review. Where trials ran one control group and more than one included intervention group, data from the intervention group providing the comparison that best assessed the effect of altering dietary fat was used. Where the intervention groups appeared equal in this respect the intervention groups were merged (simply added for dichotomous data, and using the techniques described in the Higgins 2011 for continuous data). It was planned that if trials randomized by cluster were identified the patient numbers would be reduced to an "effective sample size" (as described by Hauck 1991), however none were identified that were both included and had cardiovascular events or deaths.

Subgroup analysis and investigation of heterogeneity

For this update dietary interventions were classified as low fat, modified fat or combined low and modified fat diets. Pre-specified analyses included:

Effects of low, modified, and combined low and modified fat diets compared with usual or standard diet on the following outcomes:

- total mortality
- cardiovascular mortality
- combined cardiovascular events

Pre-specified subgroups for primary outcomes included:

- mean follow-up time of up to and including, or over, 2 years
- initial level of cardiovascular risk (low, medium, high)
- mode of intervention (advice, supplementation or provision of diet).

Further subgroups, added into the updating of the systematic review, included:

- control group total fat intake,
- control group saturated fat intake,
- year of first publication of results
- gender, and
- setting (workplace, community, outpatient), at the request of the Cochrane Occupational Health Field.

We explored the effects of different levels of dietary fats achieved in trials (all difference between the intervention and control groups, as a percentage of energy) using meta-regression on total mortality, cardiovascular mortality and total cardiovascular events by:

- total fat intake
- saturated fat intake
- monounsaturated fat intake
- polyunsaturated fat intake
- trans fat intake
- body weight
- LDL cholesterol

The effects of low fat, modified fat and low and modified fat diets (all compared with control or usual diet), and low fat vs modified fat diets on secondary and tertiary outcomes were assessed.

Random effects meta-regression (Berkley 1995) was performed using the STATA command metareg (Sharp 1998, Sterne, Bradburn and Egger 2001, Sterne 2009).

Sensitivity analysis

Sensitivity analyses were carried out for primary outcomes, sub-grouping by type of dietary fat intervention (reduced fat, modified fat or both) assessing the effect of

- running Mantel-Haenszel fixed effects relative risk meta-analyses (rather than random effects), as events could be considered to be rare (percentages of participants experiencing events was 6% for mortality, 2% for cardiovascular mortality and 7% for cardiovascular events) (Higgins 2011),
- running Peto fixed effects odds ratio meta-analysis, which may be more useful than Mantel-Haenszel when events are rare but works better when studies have similar numbers of participants in each arm (not the case with several included studies such as WHI)
- excluding the largest study (WHI with CVD 2006, WHI without CVD 2006),
- excluding studies which were not free of systematic difference in care (or unclear)
- excluding studies that were not free of dietary differences other than fat (or unclear).

RESULTS

Description of studies

Results of the search

The initial search strategy resulted in 16,821 potential titles and abstracts, which were scanned for relevant studies. The 2010 update search found an additional 5,191 titles and abstracts to assess for inclusion, making 22,012 titles and abstracts screened in total. Two hundred and seventy six papers were collected as full text in the first review, and a further 254 were collected in the review

update, and all 530 were assessed for inclusion in duplicate. The papers were then amalgamated into studies. Of these a total of 48 randomised controlled trials were included in the review. For all included studies we searched for additional publications to ensure that we did not miss any relevant methodology or outcome data from that dataset. This full set of published papers (along with any additional information provided by authors) was data extracted (along with assessment of validity) in duplicate for each included trial. A further 15 studies (17 papers) were allocated to Studies awaiting classification as it could not be established whether they had collected data on mortality or morbidity, the outcomes of this review (Characteristics of studies awaiting classification).

Included studies

Forty eight studies were included in the review (Included studies) and were described in Characteristics of included studies. Some included studies included several comparison arms (e.g. the Kuopio study includes four comparisons: Sarkkinen Fat Mod 1995; Sarkkinen Red & Mod 1995; Sarkkinen Red Fat 1995; Sarkkinen Red vs Mod1995 and the Monounsaturated fat Obesity study includes three comparisons: Due Low fat 2008; Due Mod fat 2008; Due Low vs Mod 2008); and some studies were reported in several sections for ease of analysing subgroup data (e.g. the Minnesota Coronary Study was reported separately for men (Minnesota Coron men 1989) and women (Minnesota Coron women1989); the National Diet-Heart Study was reported in its various sub-studies (NDHS Faribault 1968; NDHS Open 1st L&M 1968; NDHS Open 1st mod 1968, NDHS Open 2nd L&M 1968, NDHS Open 2nd Mod 1968); and the Women's Health Initiative was reported by cardiovascular risk (WHI with CVD 2006, WHI without CVD 2006). In total there were 60 comparisons included in the review.

The main study papers ranged in publication date from 1965 to 2009, and the comparisons were conducted in North America (30), Europe (26), Australia/ New Zealand (3) and the Middle East (1). Ten of the comparisons included only people at high risk of cardiovascular disease, 17 at moderate risk, and 33 at low risk. Sixteen comparisons included only men, 14 only women, and 30 both men and women.

Dietary interventions varied from trials which provided dietary advice (in varying degrees of intensity and duration, 35 studies), provided advice plus some dietary supplementation (such as oils or margarines, nine studies), to studies that provided most food eaten by participants (via institutional provision, meals provided for those living independently or study shops, 16 studies). The setting for most studies was the community (in that participants were living in the community - the actual setting for provision of advice, group work etc was usually unclear, although interventional advice was occasionally clearly in a home or community setting, and occasionally in a primary or secondary healthcare setting), but three studies took place in institutions (Minnesota Coron men 1989; Minnesota Coron women1989; NDHS Faribault 1968; Veterans Admin 1969), and no studies appeared to have been carried out in occupational settings.

Twenty five comparisons, including 61,958 participants and first published between 1965 and 2007, compared a reduced fat diet with usual or control diet (Ley 2004; BDIT Pilot Studies 1996; BRIDGES 2001; CARMEN 2000; CARMEN MS sub-study 2002; DO IT 2006; Seppelt 1996; Lean 1997; Anderson 1990; Sarkkinen Red Fat 1995; Ball 1965; Boyd 1988; Moy 2001; MSFAT 1997; Due Low fat 2008; Nutrition & Breast Health; Ole Study 2002; Polyp Prevention 1996; Simon 1997; McKeown-Eyssen 1994; Black 1994; WHEL 2007; WHI with CVD 2006; WHI without CVD 2006; WINS 2006).

Fifteen comparisons, including 13,004 participants and published between 1965 and 2007, compared a modified fat diet with control or usual diet (Frenkiel 1986, Houtsmuller 1979, Sarkkinen Fat Mod 1995, Dullaart 1992, Rose 1965, Minnesota Coron men 1989, Minnesota Coron women1989, MRC 1968, Due Mod fat 2008, NDHS Faribault 1968, NDHS Open 1st mod 1968, NDHS Open 2nd Mod 1968, Oslo Diet-Heart 1966, Sydney Diet-Heart 1978, Veterans Admin 1969). Ten interventions, including 4,931 participants and published between 1968 and 2006, compared a reduced and modified fat diet with usual or control diet (beFIT 1997; DART 1989; Sarkkinen Red & Mod 1995; MeDiet 2002; NDHS Open 1st L&M 1968; NDHS Open 2nd L&M 1968; Oxford Retinopathy 1978; PREMIER 2003; Sondergaard 2003; STARS 1992). Nine interventions, including 1,290 participants and published between 1994 and 2009, compared a low fat diet with a modified fat diet (Sarkkinen Red vs Mod1995; Due Low vs Mod 2008; McAuley 2005; Rivellese 1994; Azadbakht 2007; THIS DIET 2008; Sacks high protein 2009; Sacks low protein 2009; Strychar 2009). One intervention (144 participants) was not classifiable (Curzio 1989).

Of these comparisons 12 stated that an intended outcome was to assess mortality or cardiovascular morbidity of some sort (DART 1989; DO IT 2006; Rose 1965; Ball 1965; Minnesota Coron men 1989; Minnesota Coron women1989; MRC 1968; Oslo Diet-Heart 1966; Sydney Diet-Heart 1978; THIS DIET 2008; Veterans Admin 1969; WHEL 2007). A further 36 intended to monitor lipids, blood pressure, weight or other cardiovascular risk factor outcomes, seven aimed to assess effects on cancers or cancer related outcomes such as polyps, two the feasibility of dietary intake, and the remaining three studies aimed to assess bile acid kinetics or diabetic retinopathy. Of the 48 included studies, nine recruited participants with cardiovascular disease (were secondary prevention studies), 12 recruited those at increased risk of CVD (including those recruited on the basis of raised lipids, blood pressure or weight), and 25 recruited people from the general population or without specific CVD risk (primary prevention). A further two studies recruited a mix of participants (at high and lower CVD risk).

Of the 51 comparisons of a modified and/or low fat diet with a control or usual diet, four measured the total fat intake in the control arm as less than 30% of energy (30%E), 18 30% - 34.9%E, 19 35% - 39.9%E, six had a control arm with at least 40%E, and it was unclear what the total fat intake in the control arm was in the remaining four comparisons. Three of the included comparisons had a saturated fat intake in the control group of less than 10% of energy (10%E), 19 10% - 14.9%E, 14 15% - 19.9%E and one comparison 20+%E, while saturated fat intake in the control group was unclear in a further 14 comparisons.

Of the 60 intervention arms only 21 provided data on mortality (including 71,790 participants and 4292 deaths), 16 on cardiovascular mortality (65,978 participants and 1407 cardiovascular deaths), and 23 on combined cardiovascular events (65,508 participants and 4887 events). In 25 of the included arms none of the participants experienced any deaths or cardiovascular events, and in three further studies it was clear that events had occurred, but it was not clear in which arm(s) the events had

occurred (BDIT Pilot Studies 1996; Oxford Retinopathy 1978; Simon 1997), so that data could not be included in the meta-analyses.

Excluded studies

Two hundred and eighty eight trials have been excluded (Excluded studies, the full texts assessed in duplicate for inclusion), and the reasons for these exclusions were described in Characteristics of excluded studies.

One more trial was ongoing (Ongoing studies) and described in Characteristics of ongoing studies.

Risk of bias in included studies

To understand the risk of bias in the individual included studies in a visual way, see Figure 1, and the summary of studies included in the review, see Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

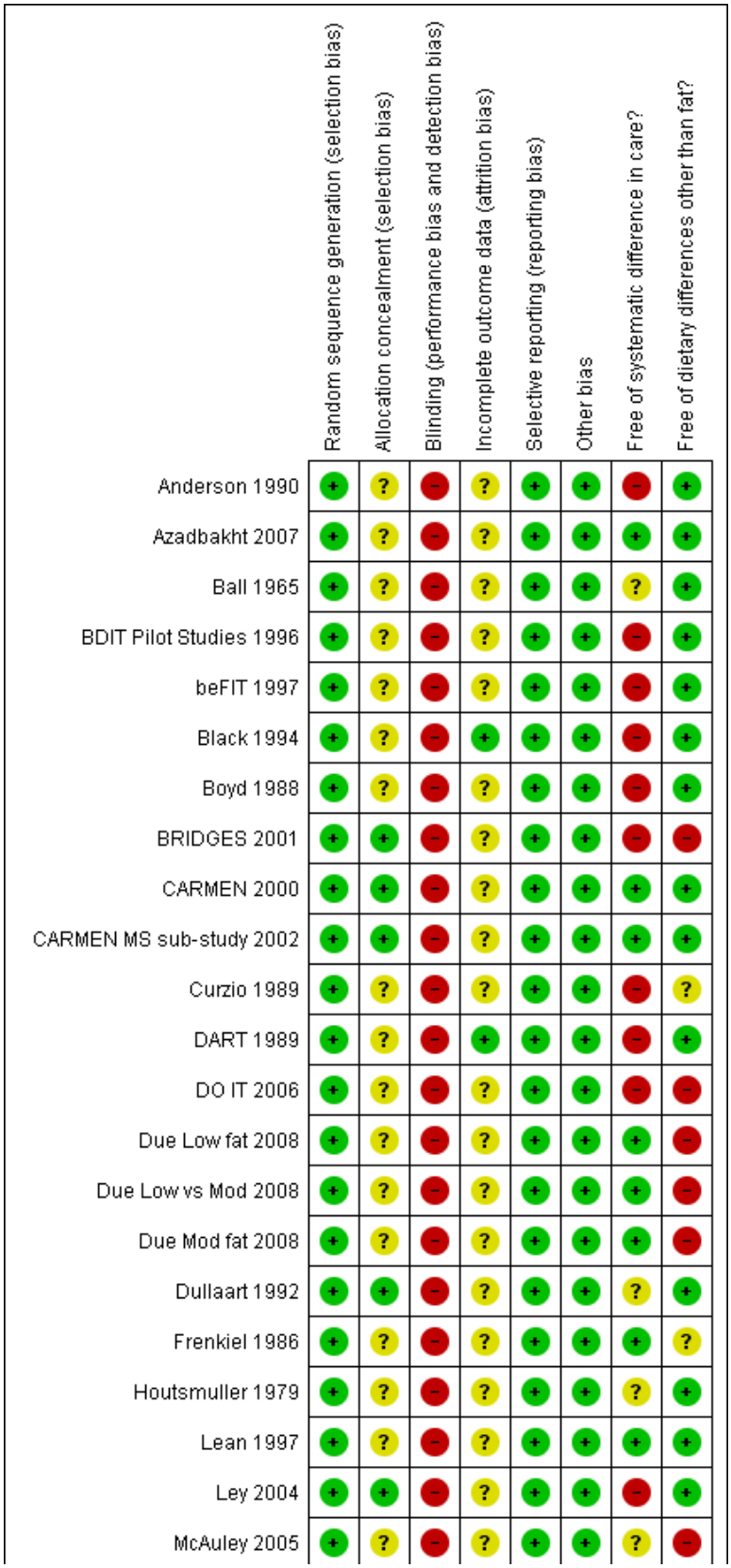


Figure 1. (Continued)

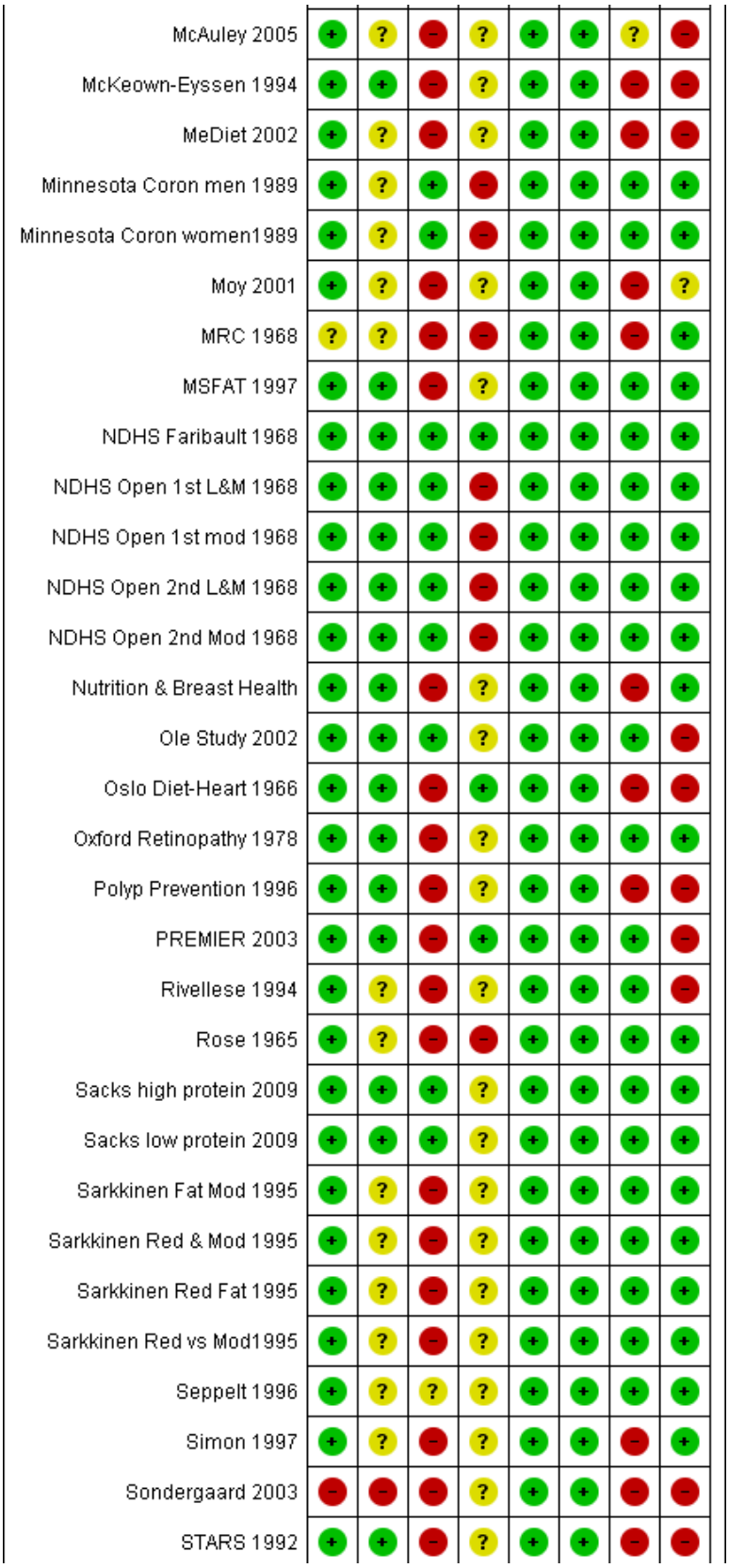


Figure 1. (Continued)

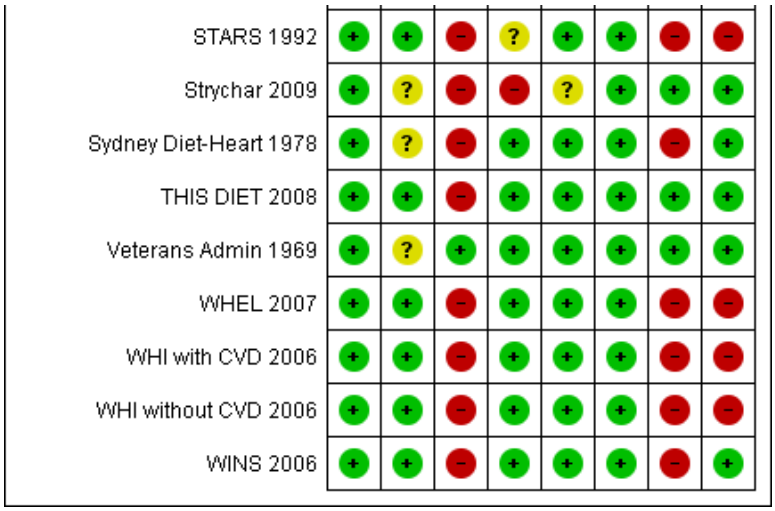
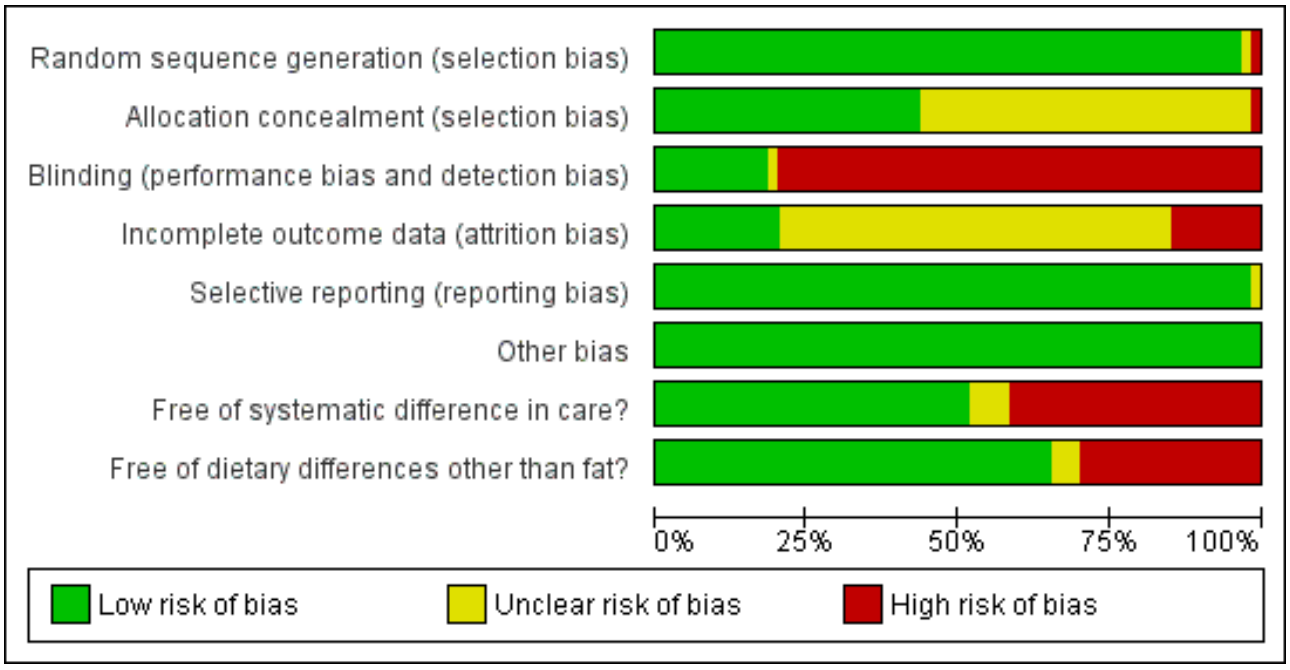


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

All trials included were randomised controlled trials, those with detected pseudo random allocation (for example where participants are randomised according to birth date or alphabetically from their name) were excluded. Allocation concealment was judged well done in 26 comparisons (Ley 2004; BRIDGES 2001; CARMEN 2000; CARMEN MS sub-study 2002; Dullaart 1992; MSFAT 1997; NDHS Faribault 1968; NDHS Open 1st L&M 1968; NDHS Open 1st mod 1968; NDHS Open 2nd L&M 1968; NDHS Open 2nd Mod 1968; Nutrition & Breast Health; Ole Study 2002; Oslo Diet-Heart 1966; Oxford Retinopathy 1978; Polyp Prevention 1996; PREMIER 2003; Sacks low protein 2009; Sacks high protein 2009; STARS 1992; THIS DIET 2008; McKeown-Eyssen 1994; WHEL 2007; WHI with CVD 2006; WHI without CVD 2006; WINS 2006), not done in one (Sondergaard 2003) and unclear in the remainder.

Blinding

Blinding of participants is not easy in dietary studies, as the participants usually have to follow instructions to attain the specific dietary goals. However, it is feasible in some circumstances, including when food is provided via an institutional setting, or meals provided at a central setting and remaining meals packed to take away, through use of a trial shop, where very specific food-based dietary advice is provided for all participants, or where the

same dietary advice is provided to both groups but a different supplement (e.g. dietary advice to reduce fats, then provision of different oils or fats) is provided. Where participants are not blinded it is difficult to ensure that study staff, health care providers and outcome assessors are blinded. The 11 comparisons that appear to have had adequate participant and study personnel blinding were Minnesota Coron men 1989, Minnesota Coron women1989, NDHS Faribault 1968, NDHS Open 1st L&M 1968, NDHS Open 1st mod 1968, half the participants in NDHS Open 2nd L&M 1968, half the participants in NDHS Open 2nd Mod 1968, Sacks low protein 2009, Sacks high protein 2009, the Ole Study 2002 and Veterans Admin 1969), and blinding was inadequate or unclear in the remaining studies.

Incomplete outcome data

Assessing whether incomplete outcome data have been addressed was difficult as the primary outcomes for this review were often seen as dropouts and exclusions from the original studies. When mortality and/or cardiovascular events 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, in some cases studies checked medical records or death registers to ensure that such events were all collected (these 10 studies included DART 1989, NDHS Faribault 1968, Oslo Diet-Heart 1966, PREMIER 2003, Sydney Diet-Heart 1978, THIS DIET 2008, Veterans Admin 1969, Black 1994, WHEL 2007, WINS 2006). In the other studies it is not possible to know whether additional deaths or cardiovascular events occurred, that were not counted or ascertained within this review.

Selective reporting

Assessment of selective reporting is difficult when the outcome of interest is simply 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, published their outcome data or have provided the data they did possess. For this reason all the included studies have been graded as 'Free of selective reporting'.

Other potential sources of bias

The studies were assessed for risk of bias in relation to 'systematic difference in care' and 'dietary differences other than fat'. The 29 comparisons free of systematic differences in care between the study arms included CARMEN 2000, CARMEN MS sub-study 2002, Frenkiel 1986, Seppelt 1996, Lean 1997, Sarkkinen Fat Mod 1995, Sarkkinen Red Fat 1995, Sarkkinen Red & Mod 1995, Sarkkinen Red vs Mod1995 Rose 1965, Minnesota Coron men 1989, Minnesota Coron women1989, MSFAT 1997, Due Low fat 2008, NDHS Faribault 1968, NDHS Open 1st L&M 1968, NDHS Open 1st mod 1968, NDHS Open 2nd L&M 1968, NDHS Open 2nd Mod 1968, Ole Study 2002, Oxford Retinopathy 1978, PREMIER 2003, Rivellese 1994, Sacks low protein 2009, Sacks high protein 2009, Strychar 2009, Azadbakht 2007, THIS DIET 2008, Veterans Admin 1969), while 27 comparisons clearly did have differences in care (such as differential time provided for those on the intervention to learn a new diet, and/or differential medical follow-up), and four were unclear.

Some comparisons were partially confounded by dietary changes other than those directly related to dietary fat intakes (for example, some studies encouraged intervention participants to make changes to their fat intake as well as changes to fruit and vegetable or fibre or salt intakes). The 39 comparisons that appeared free of such differences included Ley 2004, BDIT Pilot Studies 1996, beFIT 1997, CARMEN 2000, CARMEN MS sub-study 2002, DART 1989, Houtsmuller 1979, Seppelt 1996, Lean 1997, Anderson 1990, Sarkkinen Fat Mod 1995, Sarkkinen Red Fat 1995, Sarkkinen Red & Mod 1995, Sarkkinen Red vs Mod1995, Dullaart 1992, Rose 1965, Ball 1965, Boyd 1988, Minnesota Coron men 1989, Minnesota Coron women1989, MRC 1968, MSFAT 1997, NDHS Faribault 1968, NDHS Open 1st L&M 1968, NDHS Open 1st mod 1968, NDHS Open 2nd L&M 1968, NDHS Open 2nd Mod 1968, Nutrition & Breast Health, Oxford Retinopathy 1978, Sacks low protein 2009, Sacks high protein 2009, Simon 1997, Strychar 2009, Sydney Diet-Heart 1978, Azadbakht 2007, THIS DIET 2008, Veterans Admin 1969, Black 1994, WINS 2006. A further three comparisons were unclear, and the remainder, 18 comparisons, were confounded as to the effects of changes in fat.

Effects of interventions

Reduced, modified or reduced and modified dietary fat vs. usual or control diet

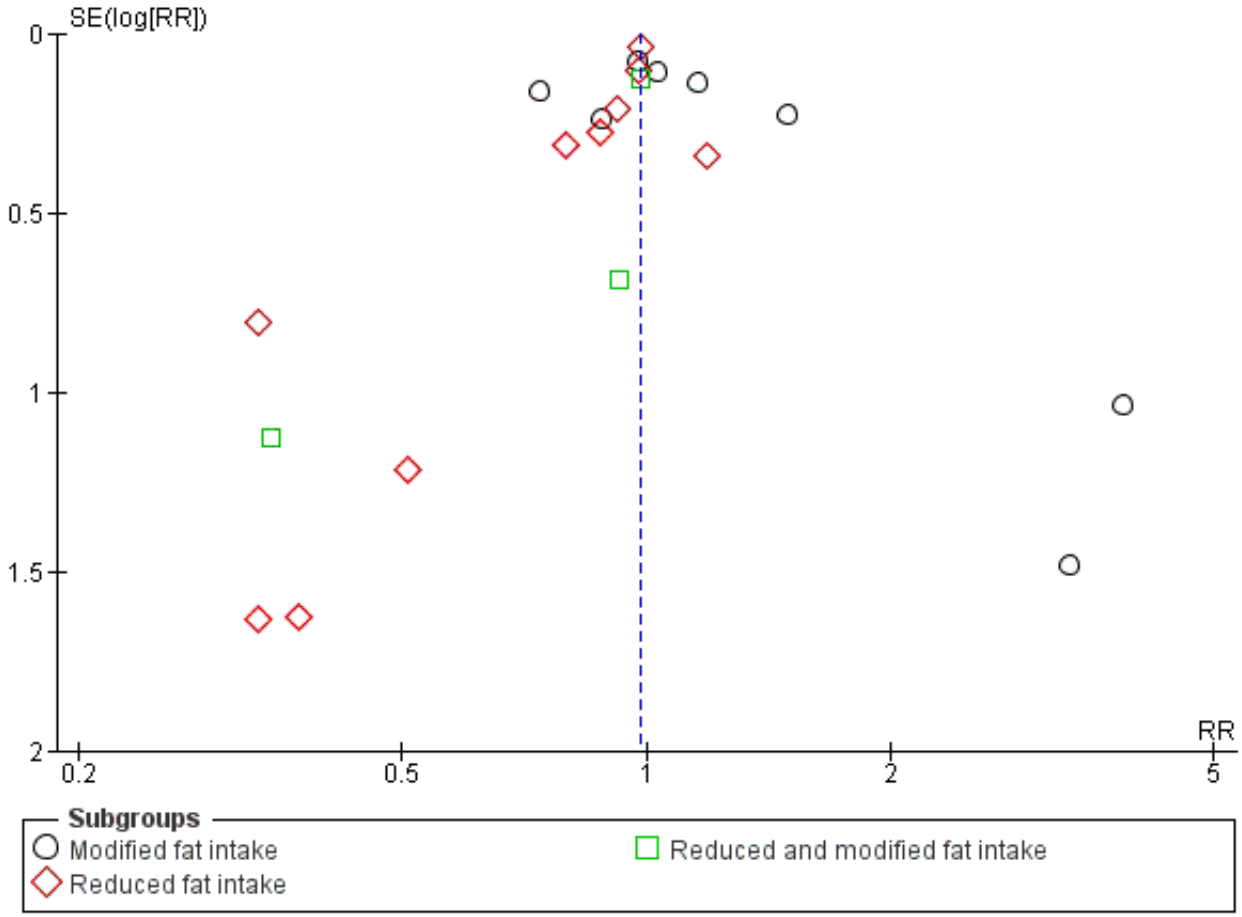
Primary outcomes

Total mortality

There was no clear effect of any dietary fat intervention compared to usual or control diet on mortality (RR 0.98, 95% CI 0.93 to 1.04, I^2 0%, 71,790 participants, 4292 deaths, p_{effect} 0.53, Analysis 1.1). Similarly there was no effect of modified fat vs usual diet (RR 1.02, 95% CI 0.88 to 1.18, I^2 34%, 11,441 participants, 1120 deaths, p_{effect} 0.81), reduced fat vs usual diet (RR 0.97, 95% CI 0.90 to 1.04, I^2 0%, 58,130 participants, 2936 deaths, p_{effect} 0.42), or reduced and modified fat vs usual diet (RR 0.97, 95% CI 0.76 to 1.23, I^2 0%, 2219 participants, 236 deaths, p_{effect} 0.78).

Sensitivity analyses (using Mantel-Haenszel fixed effects relative risk meta-analysis, Peto odds ratio (fixed effects), removing the largest single study (WHI), removing studies with a systematic difference in care between the intervention and control arms, and removing studies with dietary differences between arms other than in dietary fat intake) did not alter the lack of statistically significant effect overall or for modified fat intake, reduced fat intake or reduced and modified fat intake compared with usual or control diet (Table 1). The funnel plot does not suggest severe small study bias, although there may be some smaller studies missing suggesting increased total mortality in the intervention group (so addition of any such studies would further lessen the likelihood of a protective effect of dietary fat modification or reduction on mortality). The funnel plot is shown in Figure 3.

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



No important effects of reduced and/or modified fat diets compared to usual or control diets on mortality were seen when studies were subgrouped by duration (mean duration up to two years or over two years), cardiovascular risk (low, moderate or high cardiovascular risk), mode of intervention (dietary advice, advice plus supplementation or diet provided), total fat in the control group (less than 30% of energy from fat, 30% - 34.9%E, 35% - 39.9%E or 40%E and over from fat), saturated fat in the control group (less than 10% of energy from saturated fat, 10% - 14.9%E or 15% - 19.9%E from saturated fat), by gender (studies of men, of women and of men and women combined), by setting (community or residential institution, no studies of workplaces were identified) or by year of first publication of results (Table 2).

We explored the effects of dietary fats on total mortality, by using meta-regression of the difference between the control and intervention of duration, total fat intake, saturated fat intake, monounsaturated fat intake, polyunsaturated fat intake, trans fat intake (all by percentage of energy), weight (in kg) and serum LDL cholesterol (in mmol/L) achieved in trials. The results of all meta-regressions are shown in Table 3. As only two trials reported trans fat intakes achieved by study arm meta-regression on trans fats could not be carried out, and with only six of the studies reporting serum LDL cholesterol levels achieved the power of this analysis to suggest a result was limited. Because so few studies reported LDL cholesterol, we also ran a post-hoc meta-regression by total serum cholesterol (as a surrogate for LDL cholesterol) achieved in each arm. We did not observe any clear relationships between treatment-control group differences in dietary or serum characteristics and mortality, but power for this analysis was limited.

Cardiovascular mortality

There was no clear effect of any dietary fat intervention compared to usual diet on cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04, I^2 0%, 65,978 participants, 1407 cardiovascular deaths, p_{effect} 0.23), Analysis 1.2. Again, there was no effect within any dietary fat subgroup: modified fat diet vs usual diet RR 0.92 (95% CI 0.73 to 1.15, I^2 45%, 10,788 participants, 593 cardiovascular deaths, p_{effect} 0.46); reduced fat vs usual diet RR 0.96 (95% CI 0.82 to 1.13, I^2 0%, 52,971 participants, 602 cardiovascular deaths, p_{effect} 0.65); or reduced and modified fat vs usual diet RR 0.98 (95% CI 0.76 to 1.27, I^2 0%, 2219 participants, 212 cardiovascular deaths, p_{effect} 0.88), Analysis 1.2. Sensitivity analyses did not alter the lack of clear effects of modified fat intake, reduced fat intake, reduced and modified fat intake or all combined compared to usual or control diets on cardiovascular mortality (Table 1).

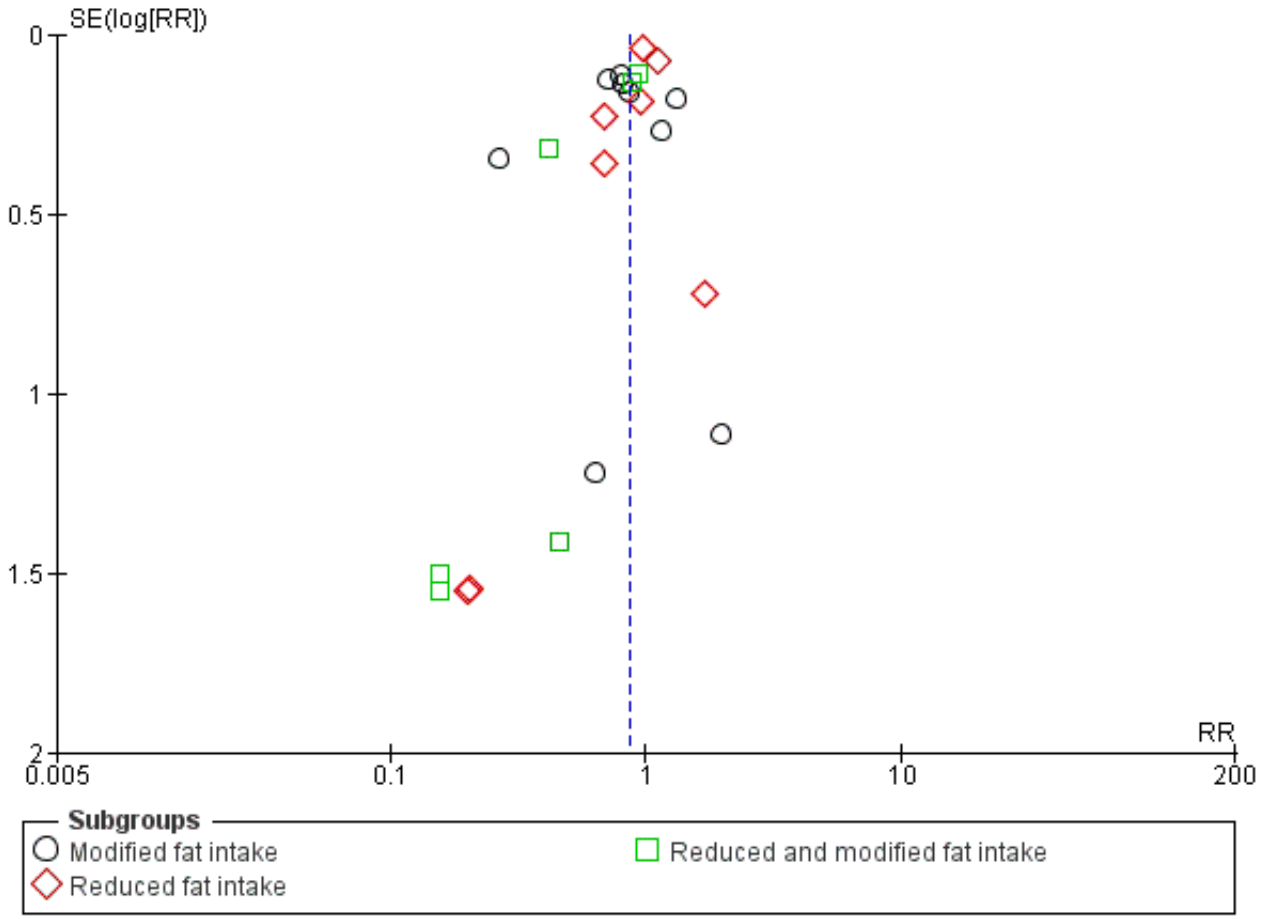
Subgrouping (as above) did not suggest important effects of reduced and/or modified fat diets on cardiovascular mortality (Table 2).

We explored the effects of dietary fats on cardiovascular mortality in meta-regression (Table 3). There were insufficient studies to explore the effects of trans fats. As only six of the studies reported serum LDL cholesterol levels achieved, we also ran a post-hoc meta-regression by total serum cholesterol (as a surrogate for LDL cholesterol) achieved in each arm. We did not observe any clear relationships between duration, weight, any dietary or serum characteristics and mortality, but power for this analysis was limited.

Cardiovascular events

There was a reduction in cardiovascular events for any dietary fat intervention compared with usual diet (RR 0.86, 95% CI 0.77 to 0.96, I^2 50%, 65,508 participants, 4887 people with cardiovascular events, p_{effect} 0.007) Analysis 1.3. Sensitivity analyses, using Mantel-Haenszel fixed effects meta-analysis, Peto fixed effects odds ratio, and removing the largest study comparisons (WHI with CVD 2006, WHI without CVD 2006) maintained this clear effect of the intervention, while removing studies with a systematic difference in care between the intervention and control arms, or removing studies with dietary differences other than dietary fat differences both removed the statistical significance of the effect (Table 1). A funnel plot did not suggest severe small study (or publication) bias, but it is likely that a few small studies with more cardiovascular events in the intervention groups may be missing from the review (Figure 4).

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



None of the subgroups of types of dietary fat change showed a clear effect of dietary fat change compared with usual diet in its own right, but the effects in both groups that included modification of fat were of marginal significance: modified fat vs usual fat RR 0.82 (95% CI 0.66 to 1.02, I^2 61%, 11,660 participants, 855 people with CVD events, p_{effect} 0.07); reduced and modified fat vs usual diet RR 0.77 (95% CI 0.57 to 1.03, I^2 40%, 3193 participants, 400 people with events, p_{effect} 0.08). There was no suggestion of an effect on cardiovascular events in studies that compared reduced fat vs usual intake (RR 0.97, 95% CI 0.87 to 1.08, I^2 17%, 50,655 participants, 3632 people with CVD events, p_{effect} 0.55).

Sensitivity analyses of the modified fat studies, using Mantel-Haenszel fixed effects relative risk meta-analysis suggested a strong and statistically significant effect of modified fat on cardiovascular events (RR 0.83, 95% CI 0.73 to 0.93, I^2 61%, 11,660 participants, 855 events, p_{effect} 0.002), as did the Peto odds ratio, and using fixed effects meta-analysis on the reduced and modified fat subgroup suggested risk reduction of 16% and of marginal statistical significance (RR 0.84, 95% CI 0.71 to 1.00, I^2 40%, 3193 participants, 400 events, p_{effect} 0.05, also reiterated by the Peto odds ratio analysis). Removing studies with systematic differences in care between intervention and control groups, or other dietary

differences, both removed statistical significance. No sensitivity analyses of the reduced fat intake compared with control or usual diet suggested important or statistically significant effects (Table 1).

As multiple analyses were run for sub-grouping, only those subgroups statistically significant to P < 0.01 are reported here (and in Table 2) as being statistically significant. Subgrouping by duration suggested no important effect in studies with duration of two years or less, but a clear and statistically significant effect in studies of more than two years duration. There was little suggestion of different effects of fat modification and/or reduction in those at low, moderate or high cardiovascular risk. Subgrouping suggested a strong effect of dietary advice plus supplementation, only marginal effect in those given dietary advice (without supplementation, but often with high levels of support and encouragement), and no effect in those provided with their food (via shops or group eating). There was no clear effect of baseline total fat intake on cardiovascular events. Many studies did not report saturated fat intakes, and sub-grouping by saturated fat intake in the control group did not result in important effects. Dietary fat intervention reduced cardiovascular events in men, but not in women or in combined studies of men and women, and studies in community settings reduced events, but those in residential institutions did not. Studies published in the 1960s, and in the 1990s, reduced cardiovascular events significantly, but not studies published in other decades (Table 2).

We explored the effects of dietary fats on cardiovascular events, by using meta-regression of the difference between the control and intervention of total fat intake, saturated fat intake, monounsaturated fat intake, polyunsaturated fat intake, trans fat intake (all by percentage of energy), weight (in kg) and serum LDL cholesterol (in mmol/L) achieved in trials (Table 3). Meta-regression of trans fats was not feasible due to lack of trials. As only seven studies reported LDL cholesterol, we also ran a post-hoc meta-regression by total serum cholesterol (as a surrogate for LDL cholesterol) achieved in each arm. As studies of shorter duration appeared to have less effect on events than longer interventions, we also performed a second post-hoc analysis, in which we carried out the meta-regression on duration alongside each dietary or serum factor. We did not observe any clear relationships between any dietary or serum characteristic and cardiovascular events (with or without co-regression on duration), but power for these analyses were limited.

Secondary outcomes

Total myocardial infarction

There was no clear effect of altering dietary fat intakes (compared to usual diet) on myocardial infarction (RR 0.93, 95% CI 0.84 to 1.02, I^2 6%, 64,891 participants, 2068 people with fatal or non-fatal myocardial infarcts, p_{effect} 0.13) (Analysis 2.1). Neither was there any effect of any of the distinct dietary fat changes: modified fat intake RR 0.91 (95% CI 0.72 to 1.16, I^2 45%, 11,831 participants, 579 people with at least one myocardial infarct, p_{effect} 0.46); reduced fat vs usual fat intake RR 0.97 (95% CI 0.86 to 1.08, I^2 0%, 50,522 participants, 1203 people having a myocardial infarct, p_{effect} 0.54); and reduced and modified fat vs usual intake RR 0.90 (95% CI 0.72 to 1.11, I^2 0%, 2538 participants, 286 people with myocardial infarcts, p_{effect} 0.32).

Stroke

There was no evidence of an effect of general dietary fat advice (RR 0.99, 95% CI 0.89 to 1.11, I^2 0%, 59,853 participants, 1140 people with at least one fatal or non-fatal stroke, p_{effect} 0.87), or modified, reduced or both vs usual diet on stroke (Analysis 2.2). As 95% of the weight of this analysis was due to inclusion of the WHI trial (WHI with CVD 2006, WHI without CVD 2006), we also checked the effect of dietary fat advice on stroke excluding both parts of this study, and there was the suggestion of an effect of dietary change on stroke (RR 0.61, 95% CI 0.37 to 1.02, I^2 0%, 11,018 participants, 64 people with a stroke, p_{effect} 0.06).

Cancer deaths

There was no effect of altering dietary fat intakes on cancer deaths (RR 0.98, 95% CI 0.91 to 1.06, I^2 0%, 65724 participants, 2818 cancer deaths, p_{effect} 0.66), or of any specific type of fat changes, although there was a marginally significant effect of modified fat intake increasing cancer deaths, although this included only 91 cancer deaths (Analysis 2.3).

Cancer diagnoses

There was no evidence of an effect of altered dietary fat intake on cancer diagnoses (RR 0.96, 95% CI 0.91 to 1.01, I^2 1%, 59,082 participants, 6115 people with at least one cancer diagnosis, p_{effect} 0.11) (Analysis 2.4). Almost all the evidence on cancer diagnoses come from studies that reduced dietary fat, and only 138 diagnoses were made in studies where modified fat or reduced and modified fat interventions had been undertaken.

Diabetes diagnoses

Most data on diabetes diagnoses came from the WHI study, and neither the study itself, or the combined data set suggested that the intervention reduced the risk of diabetes being diagnosed (RR 0.96, 95% CI 0.90 to 1.02, I^2 0%, 49,859 participants, 3367 diabetic diagnoses, p_{effect} 0.20) (Analysis 2.5).

Non-fatal myocardial infarction

There was no evidence of an effect of reduced and/or modified dietary fat vs usual fat diet on people diagnosed with at least one non-fatal MI, overall or within any subgroup of fat change (overall RR 0.95, 95% CI 0.81 to 1.12, I^2 21%, 54,883 participants, 1403 people with at least one infarct, p_{effect} 0.55 (Analysis 2.6).

Quality of life

Few studies considered quality of life. The Women's Health Initiative assessed quality of life at baseline using the SF-36 tool, but we were unable to find whether quality of life was compared between dietary intervention and control groups during the study. The Ole Study 2002 did not use a formal quality of life tool, but asked participants about their feelings about the diet they were on. They provided a scale of 1 (dislike extremely) to 7 (like extremely). Of the 13 control participants (eating meals 5 days per week in the study centre, with other meals in takeout containers) 6 participants were neutral about the diet (neither like nor dislike, 4 on the scale), and the remaining control participants were a little mor positive, choosing number 5 or 6. Results were very similar in the low fat group, with 5 being neutral, 8 choosing 5 or 6 on the scale, and one choosing 3 (a little on the negative side of neutral).

Tertiary outcomes

Note that the effects of dietary fat changes on tertiary outcomes discussed below represent a subset of all trials - we have only included assessment of effect of dietary interventions on these outcomes presented in studies that reported on occurrence of deaths and/or cardiovascular events (the review's primary or secondary outcomes). These outcomes are reported here as providing information on the potential mechanisms of any effects of dietary fat changes and also on whether participants adhered appropriately to their allocated interventions.

Weight and Body Mass Index (BMI)

Only two studies, including 99 participants, assessed the effects of modified fat intake compared to usual diet on weight, and did not find any clear effect (Analysis 3.1). One of these studies, and an additional study (116 participants in total) assessed the effect of a modified fat diet on BMI, again finding no clear effect (Analysis 3.2).

Sixteen studies (11,058 participants) compared reduced fat diets with usual diets and assessed effects on weight, finding a significant reduction in weight in those on low fat diets compared to usual diets (MD -0.83kg, 95% CI -1.37 to -0.30, I^2 54%, p_{effect} 0.002). Similarly, the ten comparisons of reduced fat with usual intake found a reduction in BMI in those on the reduced fat diets (MD -0.47kg/m^2, 95% CI -0.72 to -0.23, I^2 51%, p_{effect} 0.0002).

No studies assessed the impact of reduced and modified fat intakes compared to usual diets on weight, and only two studies (111 participants) assessed impact on BMI, finding no clear effect (MD -0.20kg/m^2, 95% CI -1.30 to 0.91, I^2 0%, p_{effect} 0.73).

In understanding the causative pathway between dietary advice or provision and mortality or morbidity it is useful to understand whether intermediate outcomes are being modified. Within this review this is complicated by the problem that some studies experienced outcomes, but did not report intermediate markers, and other studies experienced no events, but reported intermediate outcomes. For this reason we carried out a post-hoc analysis of the intermediate markers (tertiary outcomes) only for the studies that reported the primary outcomes. These are reported briefly below for weight and BMI, confirming clear and statistically significant reductions in both weight and BMI for those on reduced fat diets compared with control, but with no studies reporting these outcomes for modified or reduced and modified fat diets:

- Total mortality, modified fat intake: no studies reported weight or BMI
- Total mortality, reduced fat intake: 7 studies reported weight (MD -0.92kg, 95%CI -1.41 to -0.43, no heterogeneity), 3 studies reported BMI (MD -0.48kg/m^2, 95%CI -0.65 to -0.31, no heterogeneity)
- Total mortality, reduced and modified fat intake: no studies reported weight or BMI
- Cardiovascular mortality, modified fat intake: no studies reported weight or BMI
- Cardiovascular mortality, reduced fat intake: 3 studies reported weight (MD -0.55kg, 95%CI -1.70 to 0.61, no heterogeneity), 2 studies reported BMI (MD -0.44kg/m^2, 95%CI -0.60 to -0.29, no heterogeneity)
- Cardiovascular mortality, reduced and modified fat intake: no studies reported weight or BMI
- Cardiovascular events, modified fat intake: no studies reported weight or BMI
- Cardiovascular events, reduced fat intake: 3 studies reported weight (MD -1.00kg, 95%CI -1.60 to -0.40, no heterogeneity), 3 studies reported BMI (MD -0.43kg/m^2, 95%CI -0.57 to -0.28, no heterogeneity)
- Cardiovascular events, reduced and modified fat intake: no studies reported weight or BMI

Low density lipoprotein (LDL) cholesterol

Two studies (116 participants) assessed the effect of a modified fat intake compared to usual or control diet on LDL cholesterol, finding no significant effect (MD -0.20mmol/L, 95% CI -0.47 to 0.07, I^2 0%, p_{effect} 0.14). The 14 comparisons (6971 participants) that assessed the effect of a low fat diet compared to usual diet on LDL cholesterol found a significant reduction in LDL on a low fat diet (MD -0.10mmol/L, 95% CI -0.14 to -0.05, I^2 0%, p_{effect} <0.0001). A reduced and modified fat intake also appeared to reduce LDL cholesterol in comparison to a usual diet (MD -0.21mmol/L, 95% CI -0.35 to -0.08, 4 comparisons, 627 participants, I^2 0%, p_{effect} 0.002), see Analysis 3.3.

Post-hoc analysis of LDL cholesterol only for the studies that reported the primary outcomes confirmed clear reductions in LDL in the reduced fat subgroup, non-statistically significant reductions in the reduced and modified fat subgroup, and no relevant studies for the modified fat subgroup:

- Total mortality, modified fat intake: no studies reported LDL
- Total mortality, reduced fat intake: four studies reported LDL (MD -0.09mmol/L, 95%CI -0.14 to -0.03, no heterogeneity)
- Total mortality, reduced and modified fat intake: two studies reported LDL (MD -0.25mmol/L, 95%CI -0.63 to 0.12, I^2 56%)
- Cardiovascular mortality, modified fat intake: no studies reported LDL
- Cardiovascular mortality, reduced fat intake: four studies reported LDL (MD -0.09mmol/L, 95%CI -0.14 to -0.03, no heterogeneity)
- Cardiovascular mortality, reduced and modified fat intake: two studies reported LDL (MD -0.25mmol/L, 95%CI -0.63 to 0.12, I^2 56%)
- Cardiovascular events, modified fat intake: no studies reported LDL
- Cardiovascular events, reduced fat intake: four studies reported LDL (MD -0.10mmol/L, 95%CI -0.15 to -0.04, no heterogeneity)
- Cardiovascular events, reduced and modified fat intake: two studies reported LDL (MD -0.25mmol/L, 95%CI -0.63 to 0.12, I^2 56%)

High density lipoprotein (HDL) cholesterol

None of the interventions appeared to alter HDL cholesterol: modified fat intake MD -0.04mmol/L (95% CI -0.18 to 0.09, 3 comparisons, 152 participants, I^2 0%, p_{effect} 0.54); reduced fat intake MD -0.01mmol/L (95% CI -0.02 to 0.01, 15 comparisons, 7082 participants, I^2 0%, p_{effect} 0.30); and reduced and modified fat intake MD -0.01mmol/L (95% CI -0.04 to 0.01, four comparisons, 2073 participants, I^2 0%, p_{effect} 0.36), see Analysis 3.4.

Post-hoc analysis of HDL cholesterol only for the studies that reported the primary outcomes confirmed a lack of effects on HDL cholesterol in any group (with no studies reporting HDL in the modified fat subgroup):

- Total mortality, modified fat intake: no studies reported HDL
- Total mortality, reduced fat intake: four studies reported HDL (MD 0.00mmol/L, 95%CI -0.03 to 0.04, no heterogeneity)
- Total mortality, reduced and modified fat intake: three studies reported HDL (MD -0.01mmol/L, 95%CI -0.04 to 0.02, no heterogeneity)
- Cardiovascular mortality, modified fat intake: no studies reported HDL
- Cardiovascular mortality, reduced fat intake: four studies reported HDL (MD 0.00mmol/L, 95%CI -0.03 to 0.04, no heterogeneity)
- Cardiovascular mortality, reduced and modified fat intake: three studies reported HDL (MD -0.01mmol/L, 95%CI -0.04 to 0.02, no heterogeneity)
- Cardiovascular events, modified fat intake: no studies reported HDL
- Cardiovascular events, reduced fat intake: four studies reported LDL (MD 0.10mmol/L, 95%CI -0.03 to 0.04, no heterogeneity)
- Cardiovascular events, reduced and modified fat intake: three studies reported HDL (MD -0.01mmol/L, 95%CI -0.04 to 0.02, no heterogeneity)

Total cholesterol

More studies reported total than LDL or HDL cholesterol, and all three dietary fat interventions found significant reductions in total cholesterol: modified fat intake MD -0.44mmol/L (95% CI -0.60 to -0.28, 8 comparisons, 2280 participants, I^2 59%, p_{effect} <0.00001); reduced fat intake MD -0.10mmol/L (95% CI -0.14 to -0.05, 15 comparisons, 7602 participants, I^2 0%, p_{effect} <0.0001); reduced and modified fat intake MD -0.26mmol/L (95% CI -0.47 to -0.04, 5 comparisons, 2131 participants, I^2 51%, p_{effect} 0.02).

Post-hoc analysis of total cholesterol only for the studies that reported the primary outcomes confirmed clear total cholesterol reductions for most comparisons:

- Total mortality, modified fat intake: four studies reported total cholesterol (MD -0.47mmol/L, 95%CI -0.85 to -0.10, no heterogeneity)
- Total mortality, reduced fat intake: five studies reported total cholesterol (MD -0.08mmol/L, 95%CI -0.13 to -0.03, no heterogeneity)
- Total mortality, reduced and modified fat intake: three studies reported total cholesterol (MD -0.33mmol/L, 95%CI -0.61 to -0.06, I^2 65%)
- Cardiovascular mortality, modified fat intake: two studies reported total cholesterol (MD -0.32mmol/L, 95%CI -0.67 to 0.04, no heterogeneity)
- Cardiovascular mortality, reduced fat intake: four studies reported total cholesterol (MD -0.08mmol/L, 95%CI -0.14 to -0.02, no heterogeneity)
- Cardiovascular mortality, reduced and modified fat intake: three studies reported total cholesterol (MD -0.33mmol/L, 95%CI -0.61 to -0.06, I^2 65%)
- Cardiovascular events, modified fat intake: four studies reported total cholesterol (MD -0.44mmol/L, 95%CI -0.54 to -0.35, no heterogeneity)
- Cardiovascular events, reduced fat intake: three studies reported total cholesterol (MD -0.08mmol/L, 95%CI -0.14 to -0.02, no heterogeneity)
- Cardiovascular events, reduced and modified fat intake: three studies reported total cholesterol (MD -0.33mmol/L, 95%CI -0.61 to -0.06, I^2 65%)

Triglycerides

Modified fat intake and reduced and modified fat intake studies both reduced fasting triglycerides (modified fat intake MD -0.11mmol/L, 95% CI -0.22 to -0.00, 5 comparisons, 706 participants, I^2 0%, p_{effect} 0.04; reduced and modified fat intake MD -0.27mmol/L, 95% CI -0.53 to -0.00, 3 comparisons, 218 participants, I^2 0%, p_{effect} 0.05), see Analysis 3.6. However, studies that reduced total fat intake compared to usual diet did not have any effect on fasting triglycerides (MD -0.00mmol/L, 95% CI -0.00 to 0.00, 13 comparisons, 6875 participants, I^2 0%, p_{effect} 1.00).

Post-hoc analysis of the triglycerides for the studies that reported the primary outcomes only confirmed that diets both reducing and modifying dietary fats appeared to reduce triglycerides, while there were insufficient studies to tell for modified fat and reduced fat diets:

- Total mortality, modified fat intake: one study reported triglycerides (MD -0.10mol/L, 95%CI -0.26 to 0.06)
- Total mortality, reduced fat intake: four studies reported triglycerides (MD -0.02mmol/L, 95%CI -0.13 to 0.08, no heterogeneity)
- Total mortality, reduced and modified fat intake: two studies reported triglycerides (MD -0.31mmol/L, 95%CI -0.62 to -0.01, no heterogeneity)
- Cardiovascular mortality, modified fat intake: no studies reported triglycerides
- Cardiovascular mortality, reduced fat intake: four studies reported triglycerides (MD -0.02mmol/L, 95%CI -0.13 to 0.08, no heterogeneity)
- Cardiovascular mortality, reduced and modified fat intake: two studies reported triglycerides (MD -0.31mmol/L, 95%CI -0.62 to -0.01, no heterogeneity)
- Cardiovascular events, modified fat intake: one study reported triglycerides (MD -0.26mol/L, 95%CI -0.50 to -0.02)
- Cardiovascular events, reduced fat intake: four studies reported triglycerides (MD -0.50mmol/L, 95%CI -1.05 to 0.05, I^2 52%)
- Cardiovascular events, reduced and modified fat intake: two studies reported triglycerides (MD -0.31mmol/L, 95%CI -0.62 to -0.01, no heterogeneity)

Systolic and diastolic blood pressure (BP)

No studies reported the effects of modified fat intake on systolic or diastolic BP, and only one reported (non-significant) effects of reduced and modified fat on systolic and diastolic BP. Six included comparisons reported effects of reduced fat diets on blood pressure, but again pooled results did not suggest clear effects (systolic BP MD -0.56mmHg, 95% CI -11.22 to 1.06, 6 comparisons, 3981 participants, I^2 0%, p_{effect} 0.25; diastolic BP MD

-0.35mmHg, 95% CI -0.96 to 0.26, 6 comparisons, 3543 participants, I^2 0%, p_{effect} 0.26). See Analysis 3.7 and Analysis 3.8 for blood pressure analyses.

Post-hoc analysis of the systolic and diastolic blood pressure only for the studies that reported the primary outcomes confirmed that few studies reported blood pressure and there was no clear effect on blood pressure in those studies that did:

- Total mortality, reduced fat intake: four studies reported sBP (MD -0.55mmHg, 95%CI -1.54 to 0.43, no heterogeneity)
- Total mortality, reduced fat intake: three studies reported dBP (MD -0.32mmHg, 95%CI -0.94 to 0.30, no heterogeneity)
- Total mortality, reduced and modified fat intake: no studies reported systolic or diastolic BP
- Cardiovascular mortality, reduced fat intake: three studies reported sBP (MD -0.67mmHg, 95%CI -2.23 to 0.89, no heterogeneity)
- Cardiovascular mortality, reduced fat intake: two studies reported dBP (MD -0.43mmHg, 95%CI -6.20 to 1.58, no heterogeneity)
- Cardiovascular mortality, reduced and modified fat intake: no studies reported systolic or diastolic BP
- Cardiovascular events, reduced fat intake: four studies reported sBP (MD -0.55mmHg, 95%CI -11.22 to 1.06, no heterogeneity)
- Cardiovascular events, reduced fat intake: three studies reported dBP (MD -0.32mmHg, 95%CI -0.94 to 0.30, no heterogeneity)
- Cardiovascular events, reduced and modified fat intake: no studies reported systolic or diastolic BP

Reduced fat vs. modified fat diet

Primary outcomes

There were no included studies comparing reduced with modified fat diets that reported total or cardiovascular mortality. Three studies (with 912 participants) reported 28 cardiovascular events, and not suggesting any difference in the effects of a reduced or modified fat diet (RR 1.13, 95% CI 0.41 to 3.06, Analysis 4.3).

Secondary outcomes

No studies compared reduced with modified fat diets and provided data on diabetes diagnoses. One small study provided data on myocardial infarction, stroke and non-fatal MI, and there were no clear effects for any outcome. A further study with two comparisons found no cancer deaths and there was no difference between low and modified fat in terms of cancer diagnoses (with only 4 diagnoses). See Analysis 5.1, Analysis 5.2, Analysis 5.3, Analysis 5.4, Analysis 5.5 and Analysis 5.6 for further details.

Tertiary outcomes

Several small studies comparing reduced with modified fat diets reported tertiary outcomes. There were no clear differences between reduced and modified fat diets for weight, BMI, total, LDL or HDL cholesterol, triglycerides, systolic or diastolic blood pressure. See Analysis 6.1, Analysis 6.2, Analysis 6.3, Analysis 6.4, Analysis 6.5, Analysis 6.6, Analysis 6.7 and Analysis 6.8 for further details.

There were insufficient studies in this section of the review to carry out sensitivity analyses or sub-grouping. One study directly addressed the acceptability of modified compared to reduced fat diets finding little difference between low and modified fat diets in terms of craving, fullness, hunger, desire to eat, wellness, distaste, cost, personal inconvenience, family inconvenience or feelings of deprivation. This study also assessed quality of life for all four arms using the SF-36, but data have not yet been reported (Sacks low protein 2009, Sacks high protein 2009). A further study reported that the modified fat diet advised was 'monotonous' in comparison to the low fat diet, although it was not clear why this was (Rivellese 1994).

In the nine studies that directly compared reduced with modified fat diets there was little difference in numbers of dropouts in those on modified fat diets (RR of dropping out 0.84, 95%CI 0.58 to 1.22 in reduced compared to modified fat diets, P=0.36, 1353 participants, 237 dropouts, I^2 44%), Analysis 6.9.

DISCUSSION

Addressing the specific questions

Does reducing saturated fat intake, by reducing and/or modifying dietary fat, in the longer term (at least 6 months) reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?

- This review suggested that dietary saturated fat reduction (through reduction and/or modification of dietary fat) may be protective of cardiovascular events overall, reducing them by 14% (RR 0.86, 95% CI 0.77 to 0.96, 24 comparisons, 65,614 participants, with marginal I^2 of 50%, Analysis 1.3). This was moderate GRADE evidence (See summary of findings, Figure 5).
- Despite the reduction in total cardiovascular events, there was no clear evidence of reductions in any individual outcome (total or non-fatal myocardial infarction, stroke, cancer deaths or diagnoses, diabetes diagnoses).
- Despite a large number of participants involved in randomised controlled trials of at least six months duration there were no clear effects of dietary fat changes on total mortality (RR 0.98, 95% CI 0.93 to 1.04, 21 comparisons, 71,795 participants, without important heterogeneity, Analysis 1.1) or cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04, 16 comparisons, 65,983 participants, without important heterogeneity, Analysis 1.2).

Figure 5. Summary of findings, for reduced or modified fat diets vs usual diet (primary outcomes).

fat modification or reduction compared to usual diet for preventing cardiovascular disease

Patient or population: patients with preventing cardiovascular disease
Settings:
Intervention: fat modification or reduction
Comparison: usual diet

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk usual diet	Corresponding risk fat modification or reduction				
Total mortality Follow-up: 0.5 to 11 years	**Study population**		RR 0.98 (0.93 to 1.04)	71790 (21 studies)	⊟⊟⊟⊟ **high**[1]	
	59 per 1000	58 per 1000 (55 to 61)				
	Medium risk population					
	68 per 1000	67 per 1000 (63 to 71)				
Cardiovascular mortality Follow-up: 0.5 to 11 years	**Study population**		RR 0.94 (0.85 to 1.04)	65978 (16 studies)	⊟⊟⊟⊟ **high**[1]	
	20 per 1000	19 per 1000 (17 to 21)				
	Medium risk population					
	45 per 1000	42 per 1000 (38 to 47)				
Combined cardiovascular events Follow-up: 0.5 to 8.1 years	**Study population**		RR 0.86 (0.77 to 0.96)	65609 (24 studies)	⊟⊟⊟⊟ **moderate**[1,2,3]	
	77 per 1000	66 per 1000 (59 to 74)				
	Medium risk population					
	152 per 1000	131 per 1000 (117 to 146)				
Combined cardiovascular events - Modified fat intake Follow-up: 0.5 to 6 years	**Study population**		RR 0.83 (0.67 to 1.02)	11761 (10 studies)	⊟⊟⊟⊟ **low**[1,4]	
	81 per 1000	67 per 1000 (54 to 83)				
	Medium risk population					
	225 per 1000	187 per 1000 (151 to 229)				
Combined cardiovascular events - Reduced fat intake Follow-up: 0.5 to 8.1 years	**Study population**		RR 0.97 (0.87 to 1.08)	50655 (8 studies)	⊟⊟⊟⊟ **high**[1]	
	73 per 1000	71 per 1000 (64 to 79)				
	Medium risk population					
	115 per 1000	112 per 1000 (100 to 124)				
Combined cardiovascular events - Reduced and modified fat intake Follow-up: 0.6 to 4.3 years	**Study population**		RR 0.77 (0.57 to 1.03)	3193 (6 studies)	⊟⊟⊟⊟ **low**[1,5]	
	146 per 1000	112 per 1000 (83 to 150)				
	Medium risk population					
	100 per 1000	77 per 1000 (57 to 103)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

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] Problems in this set of dietary trials include a large proportion of comparisons were not blinded, and most have differential levels of attention and support to the intervention groups, as well as dietary advice or changes additional to the fat intervention. It is also difficult to ascertain the true dietary changes achieved (as most rely on self-reported dietary assessment or records). Despite this the data set is very large and the data are remarkably consistent. As these biases tend to favour the intervention over the control arm, but the data do not show evidence of a benefit of the intervention, the risk of bias in the results is reduced. For this reason we have chosen to state that there are no limitations in design, which allows the GRADE evidence not to suggest that further trials should be conducted.

[2] Problems in this set of dietary trials include that a large proportion of comparisons were not blinded, and most have differential levels of attention and support to the intervention groups, as well as dietary advice or changes additional to the fat intervention. It is also difficult to ascertain the true dietary changes achieved (as most rely on self-reported dietary assessment or records). These limitations would tend to favour a positive effect in the intervention group over the control group.

[3] There is evidence of heterogeneity in the studies, so the inconsistency has been explored below in subgroups.

[4] Fewer than 1000 events in total, so limited power to estimate true effect. Using fixed effects meta-analysis (both Mantel-Haenszel and Peto) alters the statistical significance of this outcome, suggesting that there is an important and statistically significant effect of a modified fat diet on cardiovascular events. While p for heterogeneity was 0.009, and I squared 61% (both suggesting important heterogeneity), there is evidence that the fixed effects analysis may deal better with studies with a low risk of events. For this reason it is unclear whether fixed or random effects methodology provides the best estimate of effect. The outcome has been

Figure 5. (Continued)

significance of this outcome, suggesting that there is an important and statistically significant effect of a modified fat diet on cardiovascular events. While p for heterogeneity was 0.009, and I squared 61% (both suggesting important heterogeneity), there is evidence that the fixed effects analysis may deal better with studies with a low risk of events. For this reason it is unclear whether fixed or random effects methodology provides the best estimate of effect. The outcome has been downgraded on inconsistency, but not on precision.

[5] Fewer than 1000 events in total, so limited power to estimate true effect.

Does a long term reduced fat diet, compared with usual diet, reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?

- There were no clear effects of reduced fat diets on any of these outcomes despite the inclusion of almost 62000 participants in studies of over 6 months. This was despite clear and statistically significant reductions in weight, BMI and total and LDL cholesterol in reduced fat vs. usual diet studies.

Does a long term reduced fat diet alter classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?

- The studies included in this review represent a subset of all relevant studies assessing the effect of reduced fat diets on classic cardiovascular risk factors, so should be treated with caution. However, they do represent a good set of data from which to assess the longer term effects of such interventions in people living in the community.
- There was evidence that reduced fat diets resulted in modestly lower weight (MD -0.83kg, 95%CI -1.37 to -0.30, 11,058 participants, I^2 54%) and body mass index (MD -0.47kgm^{-2}, 95%CI -0.72 to -0.23, 5972 participants, I^2 51%). Similary modest improvements were seen in LDL cholesterol (MD -0.10mmol/L, 95%CI -0.14 to -0.05, 5971 participants, I^2 0%) and total cholesterol (MD -0.10mmol/L, 95%CI -0.14 to -0.05, 7602 participants, I^2 0%), compared with those on usual or control diets.
- Other risk factors (HDL cholesterol, triglycerides, systolic and diastolic blood pressure) did not appear to alter with reduced fat diets.

Does a long term modified fat diet, compared with usual diet, reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?

- There were no clear effects of modified fat diets on total or cardiovascular mortality, despite the inclusion of over 13000 participants in studies of over six months.
- There was a suggestion (but without statistical significance) that modified fat diets reduced cardiovascular events by 18% (RR 0.82, 95%CI 0.66 to 1.02, p_{effect} 0.07, 11,660 participants, I^2 61%).
- There were no suggestions of effects on individual health outcomes (with no data found on diabetes diagnosis), except for a suggestion that modified fat diets increased the risk of cancer deaths (RR 1.46, 95%CI 0.96 to 2.21, p_{effect} 0.08, 9903 participants, I^2 0%).

Does a long term modified fat diet alter classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?

- The studies included in this review represent a subset of all relevant studies assessing the effect of modified fat diets on classic cardiovascular risk factors, so should be treated with caution. However, they do represent a good set of data from which to assess the longer term effects of such interventions in people living in the community.
- A modified fat diet appeared to reduce serum total cholesterol by around 7% (MD -0.44mmol/L, 95%CI -0.60 to -0.28, 2280 participants, I^2 59%) and modestly reduce fasting serum triglycerides (MD -0.11mmol/L, 95%CI -0.22 to -0.00, 701 participants, I^2 0%).
- There were no clear effects on serum LDL or HDL cholesterol, weight or BMI, although the numbers of participants in these comparisons were low (99 to 150 only). We found no data assessing the effect of modified fat diets on systolic or diastolic blood pressure.
- Few of the studies that compared a modified fat diet with a usual diet and experienced deaths or cardiovascular events reported intermediate outcomes.

Does reducing and modifying dietary fat (as a combined intervention) in the longer term reduce mortality, cardiovascular mortality or cardiovascular morbidity (or individual health events such as myocardial infarction, stroke, diabetes or cancer)?

- There were no clear effects of reduced and modified fat diets on total or cardiovascular mortality, despite the inclusion of almost 5000 participants in studies of over 6 months.
- There was a suggestion (with marginal statistical significance), that reduced and modified fat diets reduced cardiovascular events by 23% (RR 0.77, 95%CI 0.57 to 1.03, p_{effect} 0.08, 3193 participants, I^2 40%).
- There were no suggestions of effects on individual health outcomes (with no data found on diabetes diagnosis and few events for most outcomes).

Does a long term reduced and modified fat diet (as a combined intervention) alter classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?

- The studies included in this review represent a subset of all relevant studies assessing the effect of reduced and modified fat diets on classic cardiovascular risk factors, so should be treated with caution. However, they do represent a good set of data from which to assess the longer term effects of such interventions in people living in the community.

- A reduced and modified fat diet appeared to modestly reduce serum total cholesterol (MD -0.26mmol/L, 95%CI -0.47 to -0.04, 2131 participants, I^2 51%), serum LDL cholesterol (MD -0.21mmol/L, 95%CI -0.35 to -0.08, 627 participants, I^2 0%) and fasting serum triglycerides (MD -0.27mmol/L, 95%CI -0.53 to -0.00, 218 participants, I^2 0%).
- There were no clear effects on serum HDL cholesterol or BMI.
- Few of the studies that compared a reduced and modified fat diet with a usual diet and experienced deaths or cardiovascular events reported intermediate outcomes.
- We located only one study that assessed effects on systolic and diastolic blood pressure, and no studies reported weight.

Are effects on mortality, cardiovascular mortality or cardiovascular morbidity moderated by differences in baseline cardiovascular risk, mode of intervention, control group total fat intake, control group saturated fat intake, gender, setting or decade of publication, or changes in total fat intake, saturated fat intake, polyunsaturated fat intake, monounsaturated fat intake, trans fat intake, dietary cholesterol, weight, serum LDL cholesterol, or study duration?

- Lack of effects of reduced and/or modified dietary fat on total and cardiovascular mortality did not alter with any sub-grouping, and no meta-regression suggested relationships with these outcomes and any continuous factor tested.
- Subgrouping suggested that effects on cardiovascular events of reduced and/or modified fat diets were due to studies with duration greater than two years (not those of two years or less), those given dietary advice plus a supplement (not diet alone or diet provided), studies of men (not of women), those in a community rather than residential setting (no studies in workplace locations were identified). There was no suggestion that baseline CVD risk or baseline total fat intakes altered the effects of dietary fat changes on cardiovascular events. There was a suggestion of an effect in studies published in the 1960s and 1990s. Overall, the data suggest that modified or modified and reduced fat diets (but not reduced fat diets), help to reduce cardiovascular events in longer studies of men.
- Meta-regression suggested no clear effects of the amount of difference between intervention and control arms in total fat intake, saturated fat intake, polyunsaturated fat intake, monounsaturated fat intake or total cholesterol on cardiovascular events. Nor were there clear effects of duration.
- There were insufficient data to assess the associations of trans fats or LDL cholesterol with cardiovascular mortality or events.

Is a long term reduced fat diet or a modified fat diet more effective in reducing mortality, cardiovascular mortality or cardiovascular morbidity (or individual effects such as myocardial infarction, stroke or cancer diagnoses)?

- There were no studies that provided data to assess the differences between reduced and modified fat diets on total or cardiovascular mortality. Only three studies assessed the comparative effects of reduced compared to modified fat diets on cardiovascular events (28 events in total).
- One study provided some data on myocardial infarction and stroke, and two comparisons provided information on cancer diagnoses.

Is a long term reduced fat diet or a modified fat diet more acceptable to people trying to adhere to these diets?

- One study (two comparisons) directly addressed the acceptability of modified compared to reduced fat diets - no clear differences were identified and the quality of life data have not yet been reported (Sacks high protein 2009; Sacks low protein 2009). One further study reported that the modified fat diet advised was 'monotonous' in comparison to the low fat diet (Rivellese 1994).
- In the eight studies that directly compared reduced with modified fat diets there was no difference in numbers of dropouts in either arm.

Is a long term reduced fat diet or a modified fat diet more effective in altering classic cardiovascular risk factors (weight, body mass index, systolic or diastolic blood pressure, serum total, LDL or HDL cholesterol and triglyceride)?

- Several small studies provided outcome data comparing the effects of reduced and modified fat diets on these risk factors. There were no clear differences.
- When (indirectly) comparing effects on risk factors in studies that compared reduced fat with usual diets with those in studies that compared modified fat with usual diets, effects in reducing risk factors in the modified fat studies were greater than those in the reduced fat trials for total and LDL cholesterol, and triglycerides (with similarly little effect on HDL cholesterol). Data for weight, BMI and blood pressure were scarce for modified fat trials, so data were not comparable.
- The stronger effect of modified fat diets over reduced fat diets in reducing serum lipids may relate to the apparently stronger effect of modified fat diets than reduced fat diets on cardiovascular events. It is not clear from the included studies whether this is due to the greater intrinsic effect of modified fat diets on cardiovascular events, or that modified fat diets are easier to comply with than reduced fat diets.

Summary of main results

This review suggested that dietary fat manipulation (reduction and/or modification) may be protective of cardiovascular events, reducing them by 14% (RR 0.86, 95% CI 0.77 to 0.96, 24 comparisons, 65,614 participants, with marginal heterogeneity, Analysis 1.3). This was moderate GRADE evidence (See summary of findings, Figure 5). Subgrouping suggested that this reduction in cardiovascular events was due to studies of fat modification, or fat modification and reduction (not studies of fat reduction alone), seen in studies of at least two years duration, in studies of men (and not those of women), and in those with moderate or high cardiovascular risk at baseline (not general population groups).

Despite a large number of participants involved in randomised controlled trials of at least six months duration there were no clear effects of dietary fat changes on total mortality (RR 0.98, 95% CI 0.93 to 1.04, 21 comparisons, 71,795 participants, without important heterogeneity, Analysis 1.1) or cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04, 16 comparisons, 65,983 participants, without important heterogeneity, Analysis 1.2). This did not alter with sub-grouping or sensitivity analysis, and was moderate GRADE evidence (Figure 5).

Few studies directly compared reduced fat diets with modified fat diets, and only three trials reported on cardiovascular events, so direct comparison of these two diets in randomised controlled trials was not possible (Figure 6).

Figure 6. Summary of findings, reduced fat vs modified fat diets, cardiovascular events.

fat reduction compared to fat modification for preventing cardiovascular disease

Patient or population: patients with preventing cardiovascular disease
Settings:
Intervention: fat reduction
Comparison: fat modification

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk fat modification	Corresponding risk fat reduction				
Combined cardiovascular events Follow-up: mean 2.0 years	**Study population**		RR 1.02 (0.42 to 2.51)	101 (1 study)	□□□□ **low**[1,2]	
	157 per 1000	160 per 1000 (66 to 394)				
	Medium risk population					
	157 per 1000	160 per 1000 (66 to 394)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

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] This was a high quality trial, with adequate allocation concealment, free of systematic diffferences in care and of dietary interventions other than fat. However, it was not participant-blinded.
[2] Fewer than 100 events, so very limited power to estimate true effect. This was a small 2 year trial, with 101 participants of whom 16 experienced cardiovascular events.

The stronger effect of modified fat diets over reduced fat diets in reducing serum lipids may relate to the apparently stronger effect of modified fat diets than reduced fat diets on cardiovascular events. It is not clear from the included studies whether this is due to the greater intrinsic effect of modified fat diets on cardiovascular events, or that modified fat diets are easier to comply with than reduced fat diets.

Meta-regression did not suggest any clear effects of changes in any dietary fat component (total fat, saturated fat, polyunsaturated fats, monounsaturated fats) or serum lipids (LDL or total cholesterol) on mortality, cardiovascular mortality or cardiovascular events (data on trans fats were not available, and those on LDL cholesterol were very limited, Table 3).

No effects of dietary fat manipulation overall, or modifying or reducing dietary fat intake, were seen on risk of myocardial infarction, stroke or cancer diagnosis (GRADE moderate evidence, see Figure 7), nor non-fatal myocardial infarction, diabetes diagnosis or cancer deaths, and little information on the effect of diet on quality of life was found. However, reduced fat diets caused significant reductions in weight, body mass index, LDL and total cholesterol, with no change in HDL cholesterol, triglycerides, or blood pressure. Fat modified diets appeared to reduce total cholesterol and triglycerides, but there was no evidence of effects on weight, body mass index, LDL or HDL cholesterol or blood pressure (although few fat modification studies measured or reported these outcomes in ways that allowed meta-analysis). Modification of fat appeared did not alter classic CVD risk factors when directly compared to low fat diets. Studies that aimed to reduce and modify fat intake appeared to reduce total and LDL cholesterol, and triglycerides, but there was no suggestion of improvements in body mass index or HDL cholesterol and little data on blood pressure.

Figure 7. Summary of findings, reduced or modified dietary fat vs usual diet, important secondary outcomes (myocardial infarction, stroke, cancer diagnosis)

fat modification or reduction compared to usual diet for preventing cardiovascular disease

Patient or population: patients with preventing cardiovascular disease
Settings: (secondary outcomes)
Intervention: fat modification or reduction
Comparison: usual diet

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk usual diet	Corresponding risk fat modification or reduction	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Myocardial infarctions Follow-up: 0.5 to 8.1 years	**Study population**		RR 0.92 (0.84 to 1.02)	64997 (20 studies)	⊟⊟⊟⊟ **moderate**[1,2]	
	32 per 1000	29 per 1000 (27 to 33)				
	Medium risk population					
	49 per 1000	45 per 1000 (41 to 50)				
Stroke Follow-up: 0.5 to 8.1 years	**Study population**		RR 0.99 (0.89 to 1.11)	59959 (12 studies)	⊟⊟⊟⊟ **moderate**[1,3]	
	20 per 1000	20 per 1000 (18 to 22)				
	Medium risk population					
	19 per 1000	19 per 1000 (17 to 21)				
Cancer diagnoses Follow-up: 0.5 to 11 years	**Study population**		RR 0.96 (0.91 to 1.01)	58847 (12 studies)	⊟⊟⊟⊟ **moderate**[1,4]	
	106 per 1000	102 per 1000 (96 to 107)				
	Medium risk population					
	51 per 1000	49 per 1000 (46 to 52)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

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] Problems in this set of dietary trials include a large proportion of comparisons were not blinded, and most have differential levels of attention and support to the intervention groups, as well as dietary advice or changes additional to the fat intervention. It is also difficult to ascertain the true dietary changes achieved (as most rely on self-reported dietary assessment or records). Despite this the data are remarkably consistent.

[2] Fixed effects analysis produced similar results (RR 0.93, 95%CI 0.86 to 1.02). Any effects appeared to arise from modified fat (RR 0.90, 95%CI 0.71 to 1.15) and reduced and modified fat diets (RR 0.90, 95%CI 0.0.72 to 1.11), rather than reduced fat diets (RR 0.97, 95%CI 0.86 to 1.08).

[3] Fixed effects analysis produced similar results (RR 0.99, 95%CI 0.88 to 1.10). There were no clear effects in studies of reduced fat diets (RR 1.01, 95%CI 0.90 to 1.13) and there were insufficient events to understand effects of modified (RR 0.81, 95%CI 0.40 to 1.66) or reduced and modified fat diets (RR 0.40, 95%CI 0.08 to 2.03).

[4] Fixed effects analysis produced similar results (RR 0.96, 95%CI 0.91 to 1.01). Almost all data were provided by studies of reduced fat diets (RR 0.95, 95%CI 0.88 to 1.02).

Overall completeness and applicability of evidence

The review included adult participants at varying levels of risk of cardiovascular disease, men and women, in free-living and institutional settings, and across the past 50 years. Almost all the studies were conducted in industrialised countries, and almost no data were available from developing or transition countries. The effectiveness of reduced fat diets and modified fat diets have been well assessed (trials of at least 6 months included 62,000 and 13,000 participants respectively), but studies of the combined diet (reduced and modified fat) included fewer than 5000 participants. Over 4000 participants in the included trials died, 1400 died of a cardiovascular cause, and almost 5000 experienced at least one cardiovascular event.

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

Quality of the evidence

All 48 trials and 60 comparisons included were randomised controlled trials, allocation concealment was judged well done in 26 comparisons, and 11 had adequate participant and study personnel blinding (difficult and expensive in dietary trials), see Figure 1. Ten comparisons ensured compete outcome data through checking of medical records or death registers, and we attempted to contact all trialists to ascertain deaths and cardiovascular events (that were often not important outcomes for the original studies). Just under half of the included comparisons (29) were free of systematic differences in care between study arms, and 39 were free of dietary changes other than those relating to dietary fat.

The lack of blinding in most dietary trials is unlikely to alter outcome assessment when outcomes include death and cardiovascular events, but lack of blinding in the participants may have lead 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 lead 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 health care 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 and/or attainability of the fat goals.

This suggests that the evidence base for the dietary effects of changes in dietary fats on cardiovascular risk is not ideally valid, although it is large. In light of the uncertainty over allocation concealment, lack of blinding and presence of systematic differences in care and additional dietary differences between arms, the quality of evidence cannot be described as high (Figure 2). On the other hand, the scale and consistency of the evidence across studies and across decades, with very different designs and design flaws may make up for these deficits to some extent. For this reason, it is likely that the review provides robust conclusions on the effects of dietary fat modification in industrialised countries.

Complex interventions

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

For this review we have worked to define the interventions clearly (see Characteristics of studies table), 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 (for example, sub-grouping studies into those that aimed to reduce, modify or reduce and modify dietary fat) no two studies that reduced dietary fat 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 shops that sold either full or low fat versions of foods depending on the intervention or control status of the participant; to providing advice on diet alongside supplementary foods such as margarines or oils; to providing dietary advice with or without supplementary support in the way of group sessions, cooking classes, shopping tours, feedback, self-efficacy sessions and/or individual counselling. We aimed to use this variety in helping us to understand which dietary fat interventions are more useful, by using sub grouping (by reduced or modified fat aim, and by food provided or dietary advice for example) and meta-regression (on study duration and the difference between intervention and control arms in saturated or monounsaturated fat intake for example).

We addressed identifying all the relevant studies through use of a wide search strategy, that was time consuming. However, we believe that we have included most relevant trials. We also carefully defined acceptable interventions for each arm, so that decisions on inclusion were simpler, and the two independent assessors more often agreed. Data synthesis was augmented by sub-grouping 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, reducing the difference in saturated fat between the groups further and so reducing the scale of any outcome. This can be dealt with in the systematic review if we meta-regress the difference in saturated fat intake between the intervention and control group with the scale of the outcome (assuming a linear dose response), still allowing us to understand the effect of altering saturated fat intake. However, there is also a problem of measuring actual saturated fat intake achieved - some trials did not report this (whether because they did not assess it, or did assess it and were embarrassed by the results or simply didn't have space to report this relatively uninteresting outcome), and others did report the results of asking people what they are 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.

A better solution to measuring the saturated fat intake achieved individually and as a mean in each study arm may be use of a biomarker of saturated fat intake. Our understanding of the relationship between dietary saturated fat intake and serum cholesterol has been quite clear since Hegsted's work in 1965 (Hegsted 1965). Meta-analysis by Mensink and Katan provided even more specific relationships between serum HDL and LDL cholesterol and triglycerides and changes in saturated, polyunsaturated and monounsaturated fats and carbohydrate from highly controlled short term studies (Mensink 1992). Unless long term dietary fat changes differ from these short term effects, understanding the changes in serum lipids in the trials included in this systematic review should allow us to understand the dietary fat changes. However, unfortunately few studies that experienced substantial numbers of deaths or cardiovascular events also report HDL, LDL or triglycerides (most older studies do not even report the composite serum total cholesterol). This has made it very difficult to understand whether lack of effect of dietary fat changes on total and cardiovascular mortality was due to minimal differences in fat intake between the control and intervention arms, or because such changes make no difference to mortality.

Potential biases in the review process

In compiling the included studies we worked hard to locate randomised studies that altered dietary fat for at least 6 months, even when cardiovascular events were not reported in study publications, or where such events were reported incidentally as reasons for participant drop outs. We attempted to contact all

authors of potential studies to verify the presence, or not, of our outcomes. In many included studies no outcomes relevant to this review occurred within the participants, and the numbers of events occurring within single studies varied from none to over 2000 deaths, over 500 cardiovascular deaths, and over 3000 cardiovascular events (all within the WHI trial, the largest single study with almost 50,000 participants for many years). The addition of the WHI trial (WHI with CVD 2006, WHI without CVD 2006), despite its size, did not alter the results substantially from the previous review, and did not introduce heterogeneity to the review.

The number of cardiovascular deaths was relatively small, so while we can be quite confident in reporting a reduction in cardiovascular events with dietary fat intervention (especially fat modification), and a lack of effect on total mortality, the effect on cardiovascular mortality is less clear. The relative risk of 0.94 (95% CI 0.85 to 1.04) may translate into a small protective effect, however this is unclear. The lack of effect on individual cardiovascular events is harder to explain - there were over 2000 myocardial infarctions, over 1000 strokes and non-fatal MI, almost 3000 cancer deaths, over 3000 diabetes diagnoses and 6000 cancer diagnoses. Lack of clear effects on any of these outcomes is surprising given the effects on total cardiovascular events.

The funnel plots are difficult to interpret (Figure 3, Figure 4) but there is some suggestion that there may be some trials of reduced fat interventions with higher relative risks missing, and some of modified fat interventions with lower relative risks missing (there are too few studies of reduced and modified interventions to tell). If additional studies of reduced fat diets with higher relative risks were found this would not alter the lack of effect of reduced fat diets on total mortality or cardiovascular events. If further modified fat studies were found these would be unlikely to alter the lack of effect of modified fat on mortality, but may strengthen its preventive effect on cardiovascular events.

Agreements and disagreements with other studies or reviews

All of the studies included in this review, whether they reduced or modified dietary fat, aimed to reduce saturated fat intake. Overall reduction and/or modification of dietary fat had no effect on total mortality or cardiovascular mortality but did appear to reduce cardiovascular events by 14% (although effects on myocardial infarction and stroke individually were not 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 statistically significant associations between saturated fat intake and cardiovascular disease (RR 1.0, 95% CI 0.89 to 1.11). As with our review they found no relationship between saturated fat intake and coronary heart disease (RR 1.07, 95%CI 0.96 to 1.19) or stroke (RR 0.81, 95%CI 0.62 to 1.05).

In our review there was no effect of reducing total fat on total or cardiovascular mortality or cardiovascular events. This was also observed in a systematic review of observational studies. Skeaff 2009 included 28 US and European cohorts (including 6600 coronary heart disease deaths among 280000 participants) finding that total fat intake was not significantly associated with coronary heart disease mortality (RR 0.94, 95%CI 0.74 to 1.18) or coronary heart events (RR 1.02, 95%CI 0.98 to 1.05). Skeaff 2009 also partly updated the previous version of this review, adding in the Finnish Mental Hosp 1972 studies (excluded from both versions of this review as this was a cluster randomised study with only 2 clusters, and also because it carried out a crossover study, inappropriate in a progressive condition such as cardiovascular disease) and the Women's Health Initiative (WHI without CVD 2006; WHI with CVD 2006), the largest of the studies published between the versions of our review. They also found that studies reducing total fat had no effect on cardiovascular mortality or events. They also observed a marginally significant relationship between P/S (polyunsaturated / saturated fat) ratio and cardiovascular events, but no relationship with cardiovascular mortality (similar to our suggestion that modifying dietary fat reduces cardiovascular events by 18%, without an important effect on total or cardiovascular mortality).

While we found in this review that replacing saturated with unsaturated fats appeared to be beneficial in terms of cardiovascular events, it was not clear whether replacing saturated fats by polyunsaturated or monounsaturated fats, either or both, was beneficial. Meta-regression did not suggest any significant relationship between either polyunsaturated or monounsaturated fats and cardiovascular events in this review. A recent review by Mozaffarian 2010, which again included very similar studies to the last version of this review, with the Finnish Mental Hospital study and Women's Health Initiative data added, stated that their findings provided evidence that consuming polyunsaturated fat in place of saturated fat would reduce coronary heart disease. However, their evidence for this was limited and circumstantial, as they found that modifying fat reduced the risk of myocardial infarction or coronary heart disease death (combined) by 19% (similar to our result). As the mean increase in polyunsaturated fat in these studies was 9.9% of energy they infer an effect of increasing polyunsaturated fat 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 polyunsaturated fat increase and level of risk reduction.

Within the meta-regression we hoped to combine studies that effectively altered saturated fat by different degrees (so that studies that reduced saturated fat very little and studies that reduced it a great deal would all offer data points for the meta-regression against mortality and morbidity endpoints, and similarly for total fat, polyunsaturated, monounsaturated and trans fats). Unfortunately many of the included studies did not report data on assessed dietary intake during the trial, reducing the quantity of data available to understand the relationships. Another limitation in understanding effects of individual classes of fatty acids on mortality and morbidity (in both trials and observational studies) was our ability to correctly assess participant's 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 tried using 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 that LDL it was still not available for all studies. It should be noted that the meta-regression with the smallest P value (less than 0.1) was the effect of difference in serum LDL cholesterol between intervention and control arms and cardiovascular events.

Pooled results of dietary fat trials indicate that reduction or modification of dietary fat intake does significantly reduce the incidence of combined cardiovascular events. The effect is consistent with a benefit as large as a 23% reduction, or as small as a 4% reduction, with a best estimate of 14% reduction in events (the first version of this review suggested an effect of 16% with slightly wider confidence intervals). This effect is seen almost exclusively in those who continue to modify their diet over at least two years. Duration of intervention does appear to be crucial. In the 4S trial (4S 1994) 4,444 participants were followed for roughly 19,339 person-years of observation, a mean of 4.35 years each. The Kaplan-Meier curve for all-cause mortality for the 4S trial only showed a clear separation between the two randomisation groups at roughly two years. For this reason trials within the systematic review were grouped in the first version of this review into those with a mean follow-up of two years or less, and those with mean follow-up of more than two years. In our meta-analysis, studies of at least two years duration reduced the risk of cardiovascular events (by 22%) while studies shorter than 2 years did not (best estimate of effect was a reduction in risk of 5%), Analysis 7.17. The trials with follow-up times from 6 months to 2 years may be diluting the effect of the trials with more than two years follow-up in the overall meta-analysis. Despite this meta-regression of study duration vs. cardiovascular events does not suggest a statically significant relationship. This may be due to confounding effect of the diet being less rigorously adhered to over longer durations, but we have no evidence of this.

Total mortality was examined as it is an important outcome, and there is little likelihood of ascertainment or diagnostic bias which may occur with cause-specific event outcomes. The data follow a similar trend, with no effect in the shorter trials and a suggestion of benefit in the trials of more than two years, but here the trend is not significant (the rate ratio for total mortality was 0.98 overall in the 2000 version of this review, and the relative risk is 0.98 in this version), with a relative risk of 1.05 in trials with mean follow-up of two years or less, 0.97 in trials with a mean follow-up of more than two years). This pattern suggests that the effects of dietary fat modification will take time to manifest themselves, and there is little evidence of immediate effects of fat reduction and/or modification on factors such as thrombosis. The main effects of dietary fat reduction and modification are likely to be on the scale and type of atherosclerotic plaque, but other mechanisms may be operating.

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 Intervention trial (WHI with CVD 2006; WHI without CVD 2006) we now have data on more cardiovascular events in people at low risk of cardiovascular disease (3408 events) than in people with moderate (143 events) or high risk (1336 events). The same is true for cardiovascular deaths (879, 23 and 505 respectively) and total mortality (3717, 47, and 528 deaths respectively). Given reasonable sized data sets for those at both high and low risk of cardiovascular disease, a similar level of risk reduction of combined cardiovascular events was seen in high and low risk groups (a 7% reduction in risk, or RR 0.93), but this effect only reaches statistical significance in the high risk participants. The reason for this is unclear.

When endpoints such as total mortality are used the situation becomes more difficult as in low risk groups the proportion of deaths which are unrelated to cardiovascular disease (and perhaps unlikely to be influenced by dietary fat changes) rises, again diluting any differences in the numbers of deaths between intervention and control groups. It is more likely that significant changes in cardiovascular deaths will be seen than in total mortality. The trend is certainly in this direction (pooled relative risk for total mortality 0.98, 95%CI 0.93 to 1.04, for cardiovascular mortality 0.94, 95%CI 0.85 to 1.04). Our best estimate is that dietary fat reduction and modification result in a reduction of 6% in deaths due to cardiovascular disease, and a reduction of 2% in total deaths, but the confidence intervals are wide.

The high risk participants in the dietary fat trials all show evidence of cardiovascular disease at baseline. Under current guidelines most high risk participants with raised lipid levels should be on lipid lowering medication (ACC/AHA 2008; Fraker 2007; NICE 2006). This raises the question of whether there is any additional advantage of adherence to a low or modified fat 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 modified fat 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 this group from cardiovascular events, with a reduction of roughly 7% of events, by dietary fat modification (even though this does not reach statistical significance, but taking into account our best estimate) would appear to merit continued public health action.

Low fat or modified fat diets

An individuals dietary intake is a complex mixture of foods, each of which is a complex mixture of nutrients. Altering one dietary component leads to unintentional alterations in many others, each of which may have positive or negative effects on several risk factors and, eventually, health.

The fat interventions included in this review were low fat diets (where total fat is reduced, and energy is usually replaced by increasing carbohydrate intake), modified fat diets (where a proportion of saturated fat is replaced by unsaturated fats, and total fat intakes do not alter) and combinations of the two (with some fat reduction and some replacement with unsaturates). Modified fat diets appear to have rather better effects on major cardiovascular risk factors than reduced fat diets in indirect comparison, but not in direct comparisons (where the numbers of studies and participants are small). The indirect comparison data fits with data from Mensink 1992, suggesting that low fat, high carbohydrate diets are likely to result in higher triglyceride and lower HDL cholesterol levels than diets where saturated fats are wholly replaced by unsaturated fats, but direct comparisons will be important in confirming this.

It is important that individuals and populations are receiving clear, evidence-based advice about the types of dietary fat changes which are most effective in reducing cardiovascular risk, as well as ways to achieve those changes. Further research comparing low fat and modified fat changes on cardiovascular disease risk factors would be feasible and helpful.

This review suggests that modified fat intake, or modified and reduced fat intake combined (but not reduced fat intake alone) are protective against combined cardiovascular events. No clear effects of these interventions on total or cardiovascular mortality were seen.

AUTHORS' CONCLUSIONS

Implications for practice

Dietary change to reduce saturated fat and partly replace it with unsaturated fats appears to reduce the incidence of cardiovascular events, but replacing the saturated fat with carbohydrate (creating a low fat diet) was not clearly protective of cardiovascular events (despite small improvements in weight, body mass index, total and LDL cholesterol). The protective effect was seen almost exclusively in those who continue to modify their diet over at least two years, and in studies of men (not those of women). Dietary advice to those at high risk of cardiovascular disease (particularly where lipid lowering medication may not be available), and probably also to lower risk population groups, should continue to include dietary fat modification, possibly as part of a Mediterranean dietary pattern, and it should be stressed that this is a permanent pattern of eating.

Effects on total and cardiovascular mortality are much less clear. No evidence was found on the long term health effects of altering trans fat intake.

Implications for research

Long term research to help us understand what types of unsaturated fats are most useful in the diet when replacing saturated fats (monounsaturated fats, polyunsaturated fats and the relevant specific fatty acids) are urgently needed.

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 dietary 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 additional benefit of modifying dietary fat in those at high risk of cardiovascular disease who are on lipid lowering medication. Further research to examine the need for maintenance of dietary fat modification whilst on lipid lowering medication would be useful, but not as useful as understanding specific dietary fat replacements for saturated fat.

No trials assessing the long term health implications of reducing trans fat intake were found, and most trials did not report trans fat intake in intervention and control arms, so the evidence on long term impact of trans fat alteration rests on intermediate outcomes only. Long term trials of reductions in trans fats would be helpful to clarify effects on cardiovascular health and mortality.

ACKNOWLEDGEMENTS

The help of the following investigators in providing information about their own and others trials is gratefully acknowledged: H Arnesen (Ullevål University Hospital), AV Astrup (University of Copenhagen), K Aziz (NICVD, Karachi), F Azizi (Research Institute for Endocrine Sciences, Tehran), SAA Beresford (University of Washington), HS Black (Baylor College of Medicine), BPM Bloemberg (National Institute of Public Health and Environmental Protection, Netherlands), DJ Bowen (Fred Hutchinson Cancer Research Center, Seattle), NF Boyd (University of Toronto), GA Bray (Pennington Biomedical Research Center, Baton Rouge), ML Burr (University of Wales), G Carruba (University of Palermo), L Castagnetta (University of Palermo), JL Curzio (University of Glasgow), RF DeBusk (Stanford University), C Defoort (Méditerranée University), Z Djuric (Wayne State University), A Due (University of Copenhagen), S Druker (University of Massachusetts), RPF Dullaart (University Hospital, Groningen), GE Eyssen (University of Toronto), TM Hayes (University Hospital of Wales, Cardiff), JA Heady (retired, formerly of MRC Social Medicine Research Unit), J Hebert (University of South Carolina), RJ Heine (Free University Hospital, Amsterdam), M-L Hellenius (Karolinska Institute), RF Heller (University of Newcastle), TDR Hockaday (retired, formerly Radcliffe Infirmary), L-E Holm (Swedish Radiation Protection Institute), DJ Hyman (Baylor College of Medicine, Houston), AFM Kardinaal (University of Wageningen), F Khan (Ninewells Hospital and Medical School, Dundee), RH Knopp (University of Washington), D Lairon (Méditerranée University), MEJ Lean (University of Glasgow), B Leelarthaepin (University of Sydney), P Leren (University of Oslo), A Lindman (University of Oslo), S Mackey (Stanford University), R MacLennan (retired, formerly of Queensland Institute of Medical Research), F Macrae (Royal Melbourne Hospital), JI Mann (University of Otago), J Marniemi (Social Insurance Institute), K McManus (Harvard Medical School), RP Mensink (Maastricht University), PA Metcalf (University of Aukland), A Michalsen (University Duisburg-Essen), TF Moy (Johns Hopkins University), AR Ness (University of Bristol), I Okene (University of Massachusetts), GS Oostenbrug (Maastricht University), J Pierce (University of California, San Diego), SD Poppitt (University of Aukland), RJ Reber (University of Illinois), JE Reseland (University of Oslo), BM Retzlaff (University of Washington), AA Rivellese (Federico II University, Naples), P Roderick (University of Southampton), DP Rose (American Health Foundation), FM Sacks (Harvard School of Public Health), WHM Saris (University of Maastricht), ES Sarkkinen (University of Kuopio), A Schatzkin (National Cancer Institute), B Seppelt (German Institute of Human Nutrition), MS Simon (Wayne State University), B Smith (University of Kentucky), E Søndergaard (Svendborg Hospital, Svendborg), AS St. Leger (University of Manchester), VJ Stevens (Kaiser Permanente Centre for Health Research), A Stoddard (University of Massachusetts), LP Svetkey (Duke University Medical Center), LC Tapsell (University of Wollongong), BC Tilley (Medical University of South Carolina), H van den Berg (TNO Nutrition and Food Research Institute), W van Herpen (Unilever), K van het Hof (Unilever, Rotterdam), MW Verheijden

(Wageningen University), GF Watts (University Hospital of Perth), AS Wierzbichi (St. Thomas's Hospital, London), PT Williams (Stanford University), RR Wing (University of Pittsburgh), PD Wood (Stanford University), I Zazpe (University of Navarra), PL Zock (Wageningen Centre for Food Studies).

The expertise and help of the following is also gratefully acknowledged: S Adams (Royal Free Hospital, London), B Anagnostelis (Royal Free Hospital, London), M Brand (Cochrane Hypertension Group), R Clarke (Universtiy of Oxford), D Darrah-Morgan (Russian translation), A Donner (University of Western Ontario), D Fagard (University of East Anglia for duplication of inclusion and data extraction), Shweta Gidwani (University of Manchester), G Gubitz (Cochrane Stroke Group), M Haugh (Cochrane Renal Group), IU Haq (Northern General Hospital, Sheffield), J Hooper (Danish, Swedish and Norwegian translation), BK Hurley (Italian translation), L Jones (Systematic Reviews Training Unit, London), SPH Keen (Cochrane Diabetes Group), S Logan (Systematic Reviews Training Unit, London), LI Mennen (INSERM), T Moore (Cochrane Heart Group), J Muscroft (German and French translation), HL Newmark (Rutgers), E Royle (Cochrane Peripheral Vascular Diseases Group), I Tumur (Pfizer Ltd), AS Truswell (University of Sydney), M Turner (Chinese translation), JM Walsh (University of California), A Wierzbicki (St. Thomas' Hospital, London), WC Willett (Harvard School of Public Health), AF Winder (University of London).

Many thanks to those people who were co-authors of the first version of this review: Julian PT Higgins, Shah Ebrahim, Rudolph Riemersma, Nigel E Capps and Gillian Clements, and to those reviewers who worked on study inclusion, data extraction and/or assessment of validity for the update but who are not authors (Indra Tumur and Dorotheé Fagard).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anderson 1990

Methods	RCT
Participants	Moderately hypercholesterolaemic, non-obese Caucasian men and women aged 30-50 (USA) CVD risk: moderate Control: randomised 62, analysed 51 Intervention: randomised 56, analysed 47

Anderson 1990 *(Continued)*

	Mean years in trial: control 0.91, intervention 0.92 % male: control 61, intervention 66 Age: mean control 40.3 (sd 5.4), intervention 40.7 (sd 5.2) (all 30-50)
Interventions	Reduced fat diet vs usual diet Control aims: no diet intervention Intervention aims: 25%E from fats, 20%E from protein, 55%E from CHO, <200mg chol /day (Also an intervention arm with similar aims plus increased fibre intake) Control methods: no intervention Intervention methods: seminars and individual eating patterns taught, 10 weeks teaching and 40 weeks maintenance Total fat intake (at 1 year): low fat 30 (sd 7.5), cont 31 (sd 5.7)%E Saturated fat intake (at 1 year): low fat 9 (sd 2.7), cont 10 (sd 2.9)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: diet composition, lipids Data available on total mortality? yes (none) Cardiovascular mortality? yes (none) Events available for combined cardiovascular events: cardiovascular deaths, fatal and non-fatal MI, stroke (none) Secondary outcomes: total and non-fatal MI, stroke Tertiary outcomes: total, LDL and HDL cholesterol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"matched on age, gender & cholesterol level, randomly assigned to intervention group using systematic random procedure"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of their dietary advice, researchers were not
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Deaths, cancer and CV events are drop-outs, trialists asked for data
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies

Anderson 1990 *(Continued)*

Free of dietary differences other than fat?	Low risk	(As the high fibre arm has not been used in the data set). See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Azadbakht 2007

Methods	RCT
Participants	Overweight and obese people (Iran) CVD risk: low Modified fat diet: 50 randomised, 45 analysed Low fat diet: 50 randomised, 44 analysed Mean years in trial: both groups 1.1 % male: modified fat diet 32%, low fat diet 25% Age: mean modified fat 45 (sd 5), low fat diet 46 (sd 6)
Interventions	Reduced fat diet vs modified fat diet Modified fat aims: 30%E from fat, SFA 5%E, MUFA 15%E, PUFA 10%E, protein 15%E, CHO 55%E, cholesterol <200mg/d, fibre 25g/d, 500kcal below energy needs Low fat aims: 20%E from fat, SFA 5-6%E, MUFA 7%E, PUFA 7%E, protein 15%E, CHO 65%E, cholesterol <200mg/d, fibre 25g/d, 500kcal below energy needs Modified fat methods: monthly appointments, oral and written information on healthy food choices, individual programmes Low fat methods: monthly appointments, oral and written information on healthy food choices, individual programmes Total fat intake (at 14 months): low fat 20 (sd 10)%E, mod fat 30 (sd 7.2)%E Saturated fat intake (at 14 months): low fat 6.8 (sd 4.2)%E, mod fat 7.0 (sd 3.6)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: weight, metabolic risk Data available on total mortality? yes (none) Cardiovascular mortality? yes (none) Events available for combined cardiovascular events: MI, stroke (no events) Secondary outcomes: total MI, stroke, cancer diagnoses, cancer deaths (no events) Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Program generated by a random number table (?)
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described

Azadbakht 2007 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Participants and nutritionist were not blinded, lab staff were
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Both groups given equivalent intervention intensity and duration. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	Focus on fat and types of fat. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Ball 1965

Methods	RCT
Participants	Men who have recently recovered from their first MI (UK) CVD risk: high Control: unclear how many randomised, 129 analysed Intervention: unclear how many randomised, 123 analysed Mean years in trial: 3.0 % male: 100 Age: unclear (all <65)
Interventions	Reduced fat intake vs. usual diet Control aims: usual diet, overweight subjects given weight reduction advice (mainly CHO reduction) Intervention aims: reduce fat intake to 40g daily, overweight subjects given weight reducing advice Control methods: continued with normal diet, unclear if follow up for control group was as for intervention group. Intervention methods: unclear who gave dietary advice or how often, patient and wife saw doctor and dietitian 2 weeks after hospital discharge, then every 2 weeks for 3 months, every 3 months for two years and six-monthly thereafter. Diet diaries checked by dietitian at each visit and problems discussed. Total fat intake (at 4 years): low fat 21.8 (sd unclear), cont 44.3 (sd unclear)%E Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: reinfarction, death Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI

Ball 1965 *(Continued)*

	Secondary outcomes: total MI Tertiary outcomes: none (weight and total cholesterol reported but no variance info)
Notes	At 3 years weight: control -3.6kg n=67, intervention -5.4kg n=68 total cholesterol: control -0.85mmol/L n=52, intervention -1.14mmol/L n=54

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"allocated at random to one of two groups at each hospital"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, the researcher who assessed outcomes was blinded to treatment arm
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if any lost to follow up
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Unclear risk	See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

BDIT Pilot Studies 1996

Methods	RCT
Participants	Women with mammographic dysplasia (Canada) CVD risk: low Control: 147 randomised, 110 analysed at over 8 years Intervention: 148 randomised, 104 analysed at over 8 years Mean years in trial: control 7.5, intervention 6.8 % male: 0 Age: mean control 45, intervention 44 (all >30)
Interventions	Reduced fat intake vs usual diet Control aims: healthy diet advice, no alteration in dietary fat advised, aim to maintain weight Intervention aims: total fat 15%E, replace fat by complex CHO, aim to maintain weight Control methods: seen for advice once every 4 months for 12 months Intervention methods: seen for advice once a month for 12 months

BDIT Pilot Studies 1996 *(Continued)*

	Total fat intake (at 9.2 years): low fat 31.7 (sd 7.3)%E, cont 35.3 (sd 5.6)%E Saturated fat intake (at 9.2 years): low fat 10.6 (sd 4.6), cont 12.3 (sd 4.6)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary fat, serum cholesterol Data available on total mortality? yes, but not clear from which groups Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: weight, BMI, total and HDL cholesterol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Randomisation not described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded, but outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Minor, women in intervention group seen more frequently. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

beFIT 1997

Methods	RCT
Participants	Women and men with mild hypercholesterolemia (USA) CVD risk: moderate Control: unclear how many randomised, 192 analysed Intervention: unclear how many randomised, 217 analysed Mean years in trial: unclear (max duration 0.5 years)

beFIT 1997 *(Continued)*

	% male: 52 (not divided by intervention group) Age: mean 43.2 (not divided by intervention group) (all >30)
Interventions	Reduced and modified fat vs usual diet Control aims:asked to delay dietary changes (provided intervention after the randomised trial) Intervention aims: total fat <30%E, SFA <7%E, dietary chol<200mg/d Control methods: usual intake Intervention methods: 8 weekly classes with nutrition info and behaviour modification with spouses, plus individual appointments at 3 and 6 months Total fat intake (at 6 months): int 25.2 (sd unclear)%E, cont unclear - no significant difference from baseline 34 (sd unclear)%E Saturated fat intake (at 6 months): int 7.6% (sd unclear)%E, cont unclear - no significant difference from baseline 12 (sd unclear)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids Data available on total mortality? yes (no events) Cardiovascular mortality? no Events available for combined cardiovascular events: unclear but authors stated that there were no CVD events Secondary outcomes: none Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs (but variance data only provided for the randomised comparison for LDL cholesterol)
Notes	Weight: control 'no change', intervention -2.7kg at 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified random sampling scheme
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants knew their allocation, unclear for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Intensive intervention for intervention group, but no intervention during the 6 months of the randomised part of the study for the control group. See Control

beFIT 1997 *(Continued)*

		and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Black 1994

Methods	RCT
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)
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 monthly clinic visits Intervention methods: 8 weekly classes, with behavioural techniques, plus 4 monthly clinic visits Total fat intake ("during study" months 4-24): low fat 20.7 (sd 5.5), cont 37.8 (sd 4.1)%E Saturated fat intake ("during study, months 4-24): low fat 6.6 (sd 1.8), cont 12.8 (sd 2.0)%E 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	At 2 years control -1.5kg n=50?, intervention -1kg n=51?

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias)	High risk	Physician blinding: adequate Participant blinding: inadequate

Black 1994 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	For mortality. Unclear for other outcomes
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
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
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Boyd 1988

Methods	RCT
Participants	Women with severe cyclical mastopathy for at least 5 years (Canada) CVD risk: low Control: randomised 10, analysed 9 Intervention: randomised 11, analysed 10 Mean years in trial: control 0.45, intervention 0.45 % male: 0% Age: mean control 36, intervention 38 (variances unclear)
Interventions	Reduced fat vs usual diet Control aims: given principles of healthy diet, not counselled to alter fat content Intervention aims: total fat 15%E, CHO 65%E Control methods: seen every 2 months to monitor symptoms, nutrition and biochemistry Intervention methods: seen monthly to monitor symptoms, nutrition and biochemistry, teaching materials included food guide, recipes, product information and advice on eating out Total fat intake (at 6 months): low fat 22.8 (sd unclear), cont 33.4 (sd unclear)%E Saturated fat intake (at 6 months): low fat 8.8 (sd unclear), cont 12.3 (sd unclear)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: mastopathy symptoms, plasma hormone and lipids Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: none Secondary outcomes: cancer deaths (none) Tertiary outcomes: total cholesterol (but variance data not provided)
Notes	Total cholesterol rose by 0.09mmol/L in control group (from 4.5 to 4.59) and fell by 0.15mmol/L in intervention group (4.84 to 4.69)

Boyd 1988 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, those assessing physical outcomes were blinded, those assessing symptoms were not
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Minor differences in follow up frequency. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

BRIDGES 2001

Methods	RCT
Participants	Women diagnosed with stage I or II breast cancer over the past 2 years (USA) CVD risk: low Control: randomised unclear (at least 56), analysed 56 Intervention: randomised unclear (at least 50), analysed 50 Mean years in trial: unclear (1 year max follow up) % male: 0 Age: mean control unclear (71% postmenopausal), intervention unclear (56% postmenopausal) (all 20-65)
Interventions	Reduced fat vs usual diet Control aims: no formal intervention Intervention diet aims: total fat 20%E, high fibre, plant based micronutrients Intervention stress: separate parallel arm, stress reduction programme (data not used here) Control methods: no formal intervention Intervention methods: nutrition intervention programme, 15 sessions (42 hours) over 15 weeks, group-based, dietitian led, 2 individual sessions using social cognitive theory and patient centred counselling to increase self efficacy and confidence Total fat intake (at 12 months): low fat 29.9 (sd unclear), cont 33.6 (sd unclear)%E Saturated fat intake: unclear

BRIDGES 2001 *(Continued)*

	Style: diet advice Setting: community
Outcomes	Stated trial outcomes: diet and BMI Data available on total mortality? yes Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: cardiovascular deaths, non fatal MI, stroke (no events) Secondary outcomes: total and non-fatal MI, stroke, cancer deaths (events only for cancer deaths) Tertiary outcomes: weight
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised", stratified by medical centre, cancer stage and age, randomised number/envelope method by project coordinator
Allocation concealment (selection bias)	Low risk	The project coordinator had contact with those from the University of Massachussets, but not those from the other 3 centres, and allocation could not be altered later
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded, unclear about researchers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	High intensity programme for intervention group, nothing for control group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Intervention also focused on fibre and plant based micronutrients. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

CARMEN 2000

Methods	RCT
Participants	Healthy overweight people, BMI 26-34 (Europe, 5 centres) CVD risk: low Control: unclear how many randomised, 77 analysed (290 randomised over all 3 arms) Intervention with simple CHO: unclear how many randomised, 76 analysed

CARMEN 2000 *(Continued)*

	Intervention with complex CHO: unclear how many randomised, 83 analysed Mean years in trial: unclear (max duration 0.5 years) % male: control 48%, simple CHO intervention 47%, complex CHO intervention 52% Age: mean control 38 (sd 9), simple CHO intervention 41 (sd 9), complex CHO intervention 38 (sd 9)
Interventions	Reduced fat vs usual diet Control aims: to attain national "normal" intake Intervention aims: total fat reduced by 10%E with increases in simple or complex CHO Control methods: trial shop provided local selection of a specific set of national "normal" intake foods Intervention methods: trial shop provided local selection of a specific set of low fat and high simple or complex CHO foods Total fat intake (at 6 months): low fat complex CHO 27.8 (sd unclear)%E, low fat simple CHO 25.5 (sd unclear)%E, cont 36.5 (sd unclear)%E Saturated fat intake (at 6 months): low fat complex CHO 9.9 (sd unclear)%E, low fat simple CHO 8.6 (sd unclear)%E, cont 12.7 (sd unclear)%E Style: food provided Setting: community
Outcomes	Stated trial outcomes: weight, body composition, lipids Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: CVD deaths, non-fatal MI, stroke, heart failure, PVD (no events) Secondary outcomes: cancer deaths and diagnoses (no events) Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation
Allocation concealment (selection bias)	Low risk	Randomisation by 3rd party, independent of research centres. Blind data were sent to him for computer randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were clear about whether they were in the control or an intervention group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	

CARMEN 2000 *(Continued)*

Free of systematic difference in care?	Low risk	Trial shop used by both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

CARMEN MS sub-study 2002

Methods	RCT (data for this study excludes the 13 participants that were included in the main CARMEN data set)
Participants	People with at least 3 risk factors for metabolic syndrome (Europe, 5 centres) CVD risk: moderate Control: 12 randomised, 8 analysed Intervention with simple CHO: 10 randomised, 9 analysed Intervention with complex CHO: 11 randomised, 9 analysed Mean years in trial: control 0.4, simple CHO 0.5, complex CHO 0.5 % male: control 0%, simple CHO 33%, complex CHO 22% Age: mean control 47.5 (sd 3.9), simple CHO intervention 44.7 (sd 4.7), complex CHO intervention 43.4 (sd 4.5)
Interventions	Reduced fat vs usual diet Control aims: to attain national "normal" intake Intervention aims: total fat reduced by 10%E with increases in simple or complex CHO Control methods: trial shop provided local selection of a specific set of national "normal" intake foods Intervention methods: trial shop provided local selection of a specific set of low fat and high simple or complex CHO foods Total fat intake (at 6 months): low fat complex CHO 27.1 (sd 4.8), low fat simple CHO 20.6 (sd 6.6), cont 30.4 (sd 2.3)%E Saturated fat intake: unclear Style: food provided Setting: community
Outcomes	Stated trial outcomes: weight, body composition, lipids Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: CVD deaths, non-fatal MI, stroke, heart failure, PVD (no events) Secondary outcomes: cancer deaths and diagnoses (no events) Tertiary outcomes: BMI, total, LDL and HDL cholesterol, TGs, diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

CARMEN MS sub-study 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer randomisation
Allocation concealment (selection bias)	Low risk	Randomisation by 3rd party, independent of research centres. Blind data were sent to him for computer randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were clear about whether they were in the control or an intervention group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Trial shop used by both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Curzio 1989

Methods	RCT
Participants	Hypertensives with cholesterol >6.5mmol/L (UK) CVD risk: moderate Control: randomised 72, analysed 63 Intervention: randomised 72, analysed 61 Mean years in trial: control 0.47, intervention 0.46 % male: control 54%, intervention 44% Age: mean control 56, intervention 57
Interventions	Unclear Control aims: no dietary advice Intervention aims: advice to reduce serum cholesterol (?) Control methods: no advice at any visit (0, 1, 3 and 6 months) Intervention methods: intensive and specific dietary advice, by dietitian at each visit (0, 1, 3 and 6 months) Total fat intake: unclear Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: blood pressure, weight, lipids Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events)

Curzio 1989 *(Continued)*

	Events available for combined cardiovascular events: cardiovascular deaths (no events) Secondary outcomes: cancer deaths (no events) Tertiary outcomes: total, HDL and LDL cholesterol, TG (not used in analysis as unclear whether reduced and/or modified fat intervention)
Notes	Changes in lipid parameters from baseline to 6 months (control n=63, intervention n=61), all mmol/L Total cholesterol control -0.3 (sd 0.7), intervention -0.3 (sd 0.6) LDL cholesterol control -0.1 (sd 0.7), intervention -0.3 (sd 0.7) HDL cholesterol control -0.0 (sd 0.1), intervention 0.2 (sd 0.2) TGs control -0.2 (sd 0.6), intervention -0.2 (sd 0.7)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"stratified by antihypertensive treatment, randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded, researchers unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Dietetic time for those on intervention only. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Unclear risk	Dietary goals unclear.

DART 1989

Methods	RCT
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%

DART 1989 *(Continued)*

	Age: mean control 56.8, intervention 56.4 (all <70)
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. Total fat intake (through study): int 31 (sd 7), cont 35 (sd 6)%E Saturated fat intake (through study): int 11 (sd 3), cont 15 (sd 3)%E Style: diet advice Setting: community
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 Tertiary outcomes: total and HDL cholesterol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomised using sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Physician blinding: yes Participant blinding: unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	GPs contacted for information on mortality and morbidity when patients did not attend
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	

DART 1989 *(Continued)*

Free of systematic difference in care?	High risk	Different levels of advice appear to have been provided. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	There were also other arms, testing fish and fibre interventions (in a factorial design). See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

DO IT 2006

Methods	RCT
Participants	Survivors of Oslo Diet Study who had hyperlipidaemia and high risk of CVD in the 1970s (Norway) CVD risk: moderate (although 25% have CVD) control: No n-3 control, 142 randomised, 117 analysed With n-3 control, 140 randomised, 124 analysed intervention: No n-3 intervention, 139 randomised, 122 analysed With n-3 intervention, 142 randomised, 124 analysed Mean years in trial: 3 % male: 100 Age: control groups median 70 years, intervention groups median 70
Interventions	Reduced fat intake vs usual diet Control aims: usual care (with n-3 capsules or corn oil capsules) Intervention aims: 27-30%E from fat, protein 15-18%, CHO 50-55%E, increase fruit, vegetables, fish, decrease meat, polyunsaturated margarine provided free (with n-3 capsules or corn oil capsules) Control methods: usual care, with either corn oil or omega-3 capsules Intervention methods: dietary advice (30-45 mins initially plus 30 mins follow up at 3 months, then 6 monthly), polyunsaturated margarines provided free, plus either corn oil or omega-3 capsules Total fat intake (at 36 months): low fat 27.6 (sd 5.5), cont 29.5 (sd 5.4)%E Saturated fat intake (at 36 months): low fat 9.2 (sd 3.6), cont 10.5 (sd 3.7)%E Style: diet advice and supplement Setting: community
Outcomes	Stated trial outcomes: CVD Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: total MI, verified cardiovascular events Secondary outcomes: cancer deaths and diagnoses, diabetes, total MI Tertiary outcomes: BMI, total, HDL, LDL cholesterol, TG, systolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

DO IT 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Not for dietary intervention.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Additional dietary appointments in the intervention groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Also fruit, veg, fish and meat advice. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Due Low fat 2008

Methods	RCT
Participants	Young overweight adults who had lost at least 8% of body weight (Denmark) CVD risk: low control: 25 randomised, 25 analysed (24 completed) Intervention low fat: 48 randomised, 48 analysed (43 completed) Mean years in trial: control 0.49, low fat 0.47 % male: control 42%, low fat 43% Age: control group 27.6 (sd 5.1), low fat 27.3 (sd 4.9)
Interventions	Reduced fat intake vs usual diet Control aims: 30-40%E from fat, SFA >15%E, MUFA 5-15%E, PUFA 0-10%E, protein 10-20%E, CHO 45-55%E, added sugars 5-15%E, alcohol <5%E, glycaemic index high, energy density high, energy intake ad libitum Low fat aims: 20-30%E from fat, SFA <10%E, MUFA 5-15%E, PUFA 5-10%E, protein 10-20%E, CHO 55-65%E, added sugars <10%E, alcohol <5%E, glycaemic index medium, energy density low, energy intake ad libitum Control and intervention methods: supermarket model, all foods provided free, personal shoppers helped participants collect appropriate foods, not allowed to leave shop until dietary composition was correct, waste and leftovers returned to shop, minimum of 2 dietetic counselling sessions over 2 months. Total fat intake (at 6 months): low fat 23.6 (sd 1.67)%E, cont 32.1 (sd 1.62)%E Saturated fat intake (at 6 months): low fat 7.9 (sd 1.17)%E, cont 15.1 (sd 1.0)%E

Due Low fat 2008 *(Continued)*

	Style: food provided Setting: community
Outcomes	Stated trial outcomes: CVD risk, diabetes risk, weight Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: total MI, stroke (no events) Secondary outcomes: cancer deaths and diagnoses, total and non-fatal MI, stroke (no events in any group) Tertiary outcomes: weight, BMI, total, HDL, LDL cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independently randomised by 2 study personnel, stratified by sex and initial BMI
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of their own allocated diet, those assessing outcomes unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for dropouts provided, ITT analysis used for continuous outcomes
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Yes, advice and shop system was the same across all groups
Free of dietary differences other than fat?	High risk	No, there were also differences in sugary foods, legumes, dietary glycaemic index etc

Due Low vs Mod 2008

Methods	RCT
Participants	Young overweight adults who had lost at least 8% of body weight (Denmark) CVD risk: low Intervention modified fat: 52 randomised, 52 analysed (39 completed) Intervention low fat: 48 randomised, 48 analysed (43 completed) Mean years in trial: moderate fat 0.44, low fat 0.47 % male: modified fat 41%, low fat 43% Age: modified fat 29.2 (sd 4.5), low fat 27.3 (sd 4.9)

Due Low vs Mod 2008 *(Continued)*

	Baseline total fat intake: int cont Baseline saturated fat intake: int cont
Interventions	Reduced fat intake vs modified fat Modified fat aims: 35-45%E from fat, SFA <10%E, MUFA >20%E, PUFA 5-10%E, protein 10-20%E, CHO 40-50%E, added sugars <10%E, alcohol <5%E, glycaemic index low, energy density high, energy intake ad libitum Low fat aims: 20-30%E from fat, SFA <10%E, MUFA 5-15%E, PUFA 5-10%E, protein 10-20%E, CHO 55-65%E, added sugars <10%E, alcohol <5%E, glycaemic index medium, energy density low, energy intake ad libitum Control and intervention methods: supermarket model, all foods provided free, personal shoppers helped participants collect appropriate foods, not allowed to leave shop until dietary composition was correct, waste and leftovers returned to shop, minimum of 2 dietetic counselling sessions over 2 months. Total fat intake (at 6 months): low fat 23.6 (sd 1.67)%E, mod fat 38.4 (sd 1.75)%E Saturated fat intake (at 6 months): low fat 7.9 (sd 1.17)%E, mod fat 7.1 (sd 0.80)%E Style: food provided Setting: community
Outcomes	Stated trial outcomes: CVD risk, diabetes risk, weight Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: total MI, stroke (no events) Secondary outcomes: cancer deaths and diagnoses, total and non-fatal MI, stroke (no events in any group) Tertiary outcomes: weight, BMI, total, HDL, LDL cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independently randomised by 2 study personnel, stratified by sex and initial BMI
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of their own allocated diet, those assessing outcomes unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for dropouts provided, ITT analysis used for continuous outcomes
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	

Due Low vs Mod 2008 *(Continued)*

Free of systematic difference in care?	Low risk	Yes, advice and shop system was the same across all groups
Free of dietary differences other than fat?	High risk	No, there were also differences in sugary foods, legumes, dietary glycaemic index etc

Due Mod fat 2008

Methods	RCT
Participants	Young overweight adults who had lost at least 8% of body weight (Denmark) CVD risk: low control: 25 randomised, 25 analysed (24 completed) Intervention modified fat: 52 randomised, 52 analysed (39 completed) Mean years in trial: control 0.49, moderate fat 0.44 % male: control 42%, modified fat 41% Age: control group 27.6 (sd 5.1), modified fat 29.2 (sd 4.5) Baseline total fat intake: int cont Baseline saturated fat intake: int cont
Interventions	Modified fat vs usual diet Control aims: 30-40%E from fat, SFA >15%E, MUFA 5-15%E, PUFA 0-10%E, protein 10-20%E, CHO 45-55%E, added sugars 5-15%E, alcohol <5%E, glycaemic index high, energy density high, energy intake ad libitum Modified fat aims: 35-45%E from fat, SFA <10%E, MUFA >20%E, PUFA 5-10%E, protein 10-20%E, CHO 40-50%E, added sugars <10%E, alcohol <5%E, glycaemic index low, energy density high, energy intake ad libitum Control and intervention methods: supermarket model, all foods provided free, personal shoppers helped participants collect appropriate foods, not allowed to leave shop until dietary composition was correct, waste and leftovers returned to shop, minimum of 2 dietetic counselling sessions over 2 months. Total fat intake (at 6 months): mod fat 38.4 (sd 1.75)%E, cont 32.1 (sd 1.62)%E Saturated fat intake (at 6 months): mod fat 7.1 (sd 0.80)%E, cont 15.1 (sd 1.0)%E Style: food provided Setting: community
Outcomes	Stated trial outcomes: CVD risk, diabetes risk, weight Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: total MI, stroke (no events) Secondary outcomes: cancer deaths and diagnoses, total and non-fatal MI, stroke (no events in any group) Tertiary outcomes: weight, BMI, total, HDL, LDL cholesterol, TG
Notes	

Risk of bias

Due Mod fat 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independently randomised by 2 study personnel, stratified by sex and initial BMI
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of their own allocated diet, those assessing outcomes unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for dropouts provided, ITT analysis used for continuous outcomes
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Yes, advice and shop system was the same across all groups
Free of dietary differences other than fat?	High risk	No, there were also differences in sugary foods, legumes, dietary glycaemic index etc

Dullaart 1992

Methods	RCT
Participants	Type I diabetics with elevated urinary albumin (Netherlands) Risk: moderate Control: randomised 20, analysed 20 Intervention: randomised 18, analysed 16 Mean years in trial: control 2.0, intervention 1.9 % male: control 75%, intervention 81% Age: mean control 41 (sd 14), intervention 44 (sd 12) (all 21-65)
Interventions	Modified fat vs usual fat Control aims: usual diet (urged not to alter fat or protein intake) Intervention aims: replace SFA by linoleic acid to achieve P/S of 1.0, total fat and protein intake to remain unchanged Control methods: unclear Intervention methods: counselling by a dietitian (unclear how often, but at least annually) Total fat intake (at 2 years):mod fat 37 (sd 4), cont 40 (sd 7)%E Saturated fat intake (at 2 years): mod fat 13 (sd 2), cont 16 (sd 3)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: albuminuria and serum lipoproteins

Dullaart 1992 *(Continued)*

	Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, stroke (no events) Secondary outcomes: stroke (no events), MI (no events), cancer deaths (no events) Tertiary outcomes: weight, total, HDL and LDL cholesterol (data read off graph as data files no longer exist, total and LDL cholesterol data not used as very different in control and intervention arms at baseline)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"stratified according to gender, randomised in blocks of 6 using opaque sealed envelopes" by independent statistical investigator with no contact with participants
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants could not be blinded, research blinding was unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Unclear risk	Probably not, appears that the intervention group had more time with dietitian. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Frenkiel 1986

Methods	RCT
Participants	People with radiolucent gallstones taking ursodeoxycholic acid, UDCA (USA) CVD risk: low Control: randomised 17, analysed 16 Intervention: randomised 19, analysed 16 Mean years in trial: control 0.6, intervention 0.6 % male: control 35%, intervention 58% Age: mean control 52.4, intervention 53.1
Interventions	Modified fat vs average diet

Frenkiel 1986 *(Continued)*

	Control aims: dietary advice for total fat 38-42%E, dietary cholesterol 500mg/day, protein 18-22%E, CHO 38-42%E, weight maintaining, low fibre Intervention aims: as above but limit dietary cholesterol to 250mg/day, weight maintaining, low fibre Control methods: dietary advice from dietitian every 3 months Intervention methods: dietary advice from dietitian every 3 months Total fat intake (at 6 or 9 months): mod fat 32.5 (sd 6.2), cont 36.0 (sd 5.1)%E Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: bile acid kinetics Data available on total mortality? yes (no events) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: none
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants knew their allocation, unclear for researchers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar level and duration of advice. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Unclear risk	Intervention unclear, aim was to maintain total fat intake in both groups but reduce cholesterol intake - so fat modification must have occurred. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Houtsmuller 1979

Methods	RCT
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: int cont Baseline saturated fat intake: int cont
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 Total fat intake: mod fat unclear, cont unclear Saturated fat intake: mod fat unclear, cont unclear 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: none Tertiary outcomes: total cholesterol, TGs (data read off graph)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants matched in pairs then randomised
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor physicians appear blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing

Houtsmuller 1979 *(Continued)*

Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Unclear risk	Level and type of intervention unclear. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	State that fibre and dietary cholesterol were similar in control and intervention. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Lean 1997

Methods	RCT
Participants	Healthy women, BMI >25 (UK) CVD risk: low Control: randomised 53, analysed 40 Intervention: randomised 57, analysed 42 Mean years in trial: control 0.42, intervention 0.43 % male: 0 Age: mean control 50, intervention 51
Interventions	Reduced fat vs usual diet Control aims: advice - total fat 35%E, CHO 34.5%E, 1200kcal per day encouraged but not prescribed Intervention aims: total fat 20%E, CHO 58%E, 1200kcal/day encouraged but not prescribed Control methods: dietary advice supported by exchanges and recipes Intervention methods: dietary advice supported by exchanges and recipes Total fat intake: unclear Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: weight loss and cardiovascular risk factors Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: cardiovascular deaths, non fatal MI, stroke (no events) Secondary outcomes: total and non-fatal MI, stroke, cancer deaths (no events) Tertiary outcomes: BMI, total, LDL and HDL cholesterol, TG, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Lean 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	"medical officer drew coloured straws from a box"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, unclear about researchers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Deaths, cancer and CV events are drop-outs, trialists asked for data
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar intervention in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Ley 2004

Methods	RCT
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)
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: reduced fat diet (no specific goal stated) Control methods: usual intake Intervention methods: monthly 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 (at 1 year): low fat 26.1 (sd 7.7), cont 33.6 (sd 7.8)%E Saturated fat intake (at 1 year): low fat 10.0 (sd 4.2), cont 13.4 (sd 4.7)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids, glucose, blood pressure Data available on total mortality? yes

Ley 2004 *(Continued)*

	Cardiovascular mortality? yes Events available for combined cardiovascular events: MI, angina, stroke, heart failure Secondary outcomes: total MI, stroke, cancer diagnoses, cancer deaths Tertiary outcomes: weight, total, LDL and HDL cholesterol, TGs, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter allocation later
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, outcome assessors were
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

McAuley 2005

Methods	RCT
Participants	Overweight and insulin-resistant women (New Zealand) CVD risk: low Low fat: randomised 32, analysed 24 (at 1 year) Modified fat: randomised 30, analysed 28 (at 1 year) Mean years in trial: low fat 0.88, modified fat 0.97 % male: 0 Age: mean low fat 45 (sd 7.5), modified fat 47 (sd 7.9)
Interventions	Reduced fat vs Modified fat diet Modified fat aims: 30%E from fat, predominantly MUFA, protein 30%E, CHO low glycaemic index 40%E, 5 meals/d, less than 5 hours between meals, ad libitum consumption, 30mins activity 5 days/week advised Low fat aims: total fat <30%E, SFA <8%, protein 15%E, CHO >55%E, advised to reduce dietary fat, salt and sugar, national healthy eating guidelines plus at least 6 servings of bread and whole-grains /d, at

McAuley 2005 *(Continued)*

	least 3 of vegetables, 2 of fruit, 2 of low fat dairy/d, ad libitum consumption, 30mins activity 5 days/ week advised (Also a high fat Atkins-type arm) Low fat methods: unclear how much dietary advice, or who delivered Modified fat methods: unclear how much dietary advice or who delivered it Total fat intake (at 6 months): low fat 28 (sd 7)%E, mod fat 35 (sd 7)%E Saturated fat intake (at 6 months): low fat 10 (sd 4)%E, mod fat 11 (sd 3)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: weight loss, lipids Data available on total mortality? yes (none) Cardiovascular mortality? yes (none) Events available for combined cardiovascular events: total MI, stroke (no CVD events) Secondary outcomes: non-fatal and total MI, stroke, cancer deaths and diagnoses (no events for any outcome) Tertiary outcomes: weight, BMI, total, LDL and HDL cholesterol, TG, systolic and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'randomised'
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants knew allocation, unclear whether researchers did also
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Unclear risk	Probably, as both groups were taught their diets. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Differences in meal frequency, salt and sugar advice.

McKeown-Eyssen 1994

Methods	RCT
Participants	People after adenomatous colorectal polypectomy (Canada) CVD risk: low Control: randomised 102, unclear how many analysed Intervention: randomised 99, unclear how many analysed Mean years in trial: 2.0 % male: control 55%, intervention 57% age: mean control 58, intervention 58 (all <85)
Interventions	Reduced fat vs usual diet Control aims: advice for nutritionally balanced diet (optional low fibre supplement with added calcium and iron) Intervention aims: total fat <20%E (or less than 50g fat/d), at least 50g fibre daily (optional fibre supplement with added calcium and iron) Control methods: 4-monthly counselling to encourage a nutritionally balanced diet Intervention methods: monthly counselling on diet to achieve fat goals Total fat intake (at 24 months): low fat men 24.3 (sd 5.2), women 24.4 (sd 8.2), cont men 31.6 (sd 5.9), women 31.3 (sd 6.5)%E Saturated fat intake: unclear Style: dietary advice & supplement (food) Setting: community
Outcomes	Stated trial outcomes: recurrence of neoplastic polyps Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: none Secondary outcomes: cancer diagnoses, cancer deaths (no deaths) Tertiary outcomes: total cholesterol (but no variance data presented and graph too small to read)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	"stratification by physician, gender, age, randomisation by research associate, centrally, using random numbers generated by computer"
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded, physicians were
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing. ITT analysis performed.

McKeown-Eyssen 1994 *(Continued)*

Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	More frequent visits for intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Dietary fibre advice also in intervention group

MeDiet 2002

Methods	RCT
Participants	Healthy postmenopausal women with above median serum testosterone (Italy) CVD risk: low Control: randomised 57, analysed at 6 months 55 Intervention: randomised 58, analysed at 6 months 51 Mean years in trial: control 4.38, intervention 4.28 % male: 0 Age: mean unclear (age range 48-69)
Interventions	Reduced and modified fat vs usual diet Control aims: advised to increase fruit and vegetable intake Intervention aims: taught Sicilian diet including reduced total, saturated and omega-6 fats, increased blue fish (high in omega 3), increased whole cereals, legumes, seeds, fruit and vegetables Control methods: advice Intervention methods: taught Sicilian diet and cooking by professional chefs, with a weekly cooking course including social dinners Total fat intake (at 6 months): low & mod fat 30.9 (sd 11.4), cont 34.0 (sd 11.8)%E Saturated fat intake (at 6 months): low & mod fat 8.4 (sd 3.0), cont 11.2 (sd 5.0)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: breast cancer, weight, lipids, wellbeing Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: cardiovascular deaths, non fatal MI, stroke, ventricular fibrillation, ventricular overload Secondary outcomes: total and non-fatal MI, stroke, cancer diagnoses and deaths (events only for stroke and cancer diagnoses) Tertiary outcomes: none
Notes	
Risk of bias	

MeDiet 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"individually randomised"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of assignment, researchers unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Intensive cookery course with social element compared with brief advice. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Both groups encouraged to increase fruit and vegetables, but intervention group also encouraged to increase fish, pulses, seeds, whole grains.

Minnesota Coron men 1989

Methods	RCT
Participants	Institutionalised men living in a mental hospital (USA) CVD risk: low Control: randomised 2196, analysed unclear Intervention: randomised 2197, analysed unclear Mean years in trial: control 1.0, intervention 1.1 % male: 100 Age: unclear, ranges from <30 to >70
Interventions	Modified fat diet vs. usual diet Control aims: usual institutional diet provided Intervention aims: institutional diet modified to total fat 45%E, PUFA 18-20%E, P/S 2.5, less than 150mg/day dietary chol Control methods: whole diet provided Intervention methods: whole diet provided Total fat intake (over 4 years): mod fat 37.8 (sd unclear)%E, cont 39.1 (sd unclear)%E Saturated fat intake (over 4 years): mod fat 9.2 (sd unclear)%E, cont 18.3 (sd unclear)%E Style: diet provided Setting: residential institution

Minnesota Coron men 1989 *(Continued)*

Outcomes	Stated trial outcomes: MI, mortality, sudden deaths Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: total MI plus sudden death plus stroke Secondary outcomes: stroke, cancer deaths, total MI Tertiary outcomes: none (data provided on total cholesterol and TGs but no variance info)
Notes	This was a 4.5 year institutional study, but as turnover of participants was very high average time in trial per participant was actually around one year. Participants were replaced as they left, and often left the institution and later returned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"stratified randomisation"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician blinding: adequate Participant blinding: adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	No, participants appear to have been lost on leaving the institution
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Whole diet provided for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Minnesota Coron women1989

Methods	
Participants	Institutionalised women living in a mental hospital (USA) CVD risk: low Control: randomised 2320, analysed unclear Intervention: randomised 2344, analysed unclear Mean years in trial: control 1.0, intervention 1.1 % male: 0 Age: unclear, ranges from <30 to >70
Interventions	Modified fat diet vs. usual diet Control aims: usual institutional diet provided

Minnesota Coron women1989 *(Continued)*

	Intervention aims: institutional diet modified to total fat 45%E, PUFA 18-20%E, P/S 2.5, less than 150mg/day dietary chol Control methods: whole diet provided Intervention methods: whole diet provided Total fat intake (over 4 years): mod fat 37.8 (sd unclear)%E, cont 39.1 (sd unclear)%E Saturated fat intake (over 4 years): mod fat 9.2 (sd unclear)%E, cont 18.3 (sd unclear)%E Style: diet provided Setting: residential institution
Outcomes	Stated trial outcomes: MI, mortality, sudden deaths Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: total MI plus sudden death plus stroke Secondary outcomes: stroke, cancer deaths, total MI Tertiary outcomes: none (data provided on total cholesterol and TGs but no variance info)
Notes	This was a 4.5 year institutional study, but as turnover of participants was very high average time in trial per participant was actually around one year. Participants were replaced as they left, and often left the institution and later returned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"stratified randomisation"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician blinding: adequate Participant blinding: adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	No, participants appear to have been lost on leaving the institution
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Whole diet provided for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Moy 2001

Methods	RCT
Participants	Middle-aged siblings of people with early CHD, with at least one 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)
Interventions	Reduced fat intake vs. usual diet Control: physician management (physicians informed on risk factor management). Intervention: nurse management, aim total fat 40g/d or less Control methods: physician management with risk factor management at 0, 1 and 2 years Intervention methods: nurse management, appointments 6-8 weekly for 2 years Total fat intake (at 2 years): low fat 34.1 (sd unclear), cont 38.0 (sd unclear)%E Saturated fat intake (at 2 years): low fat 11.5 (sd unclear), cont 14.4 (sd unclear)%E Style: diet advice 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 Tertiary outcomes: BMI, HDL and LDL cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned via computerised schema after all eligible siblings from a family had been screened
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and trialists clear about their allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data

Moy 2001 *(Continued)*

Other bias	Low risk	
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
Free of dietary differences other than fat?	Unclear risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

MRC 1968

Methods	RCT
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)
Interventions	Modified fat vs usual diet Control aims: usual diet Intervention aims: reduce dietary fat to 35g fat per day, add 84g soya oil per day Control methods: usual diet Intervention methods: unclear who gave dietary advice or how often Total fat intake (at 3.5 years): mod fat 46 (sd unclear), cont 43 (sd unclear)%E Saturated fat intake: unclear 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 Tertiary outcomes: none (data for weight, total cholesterol and BP, but no variance info)
Notes	For all, data at 4 years, control n=89, intervention n=88 Weight change: control -3kg, intervention 0kg Total cholesterol change: control -0.47mmol/L, intervention -1.11mmol/L Systolic BP change: control 0mmHg, intervention +2mmHg Diastolic BP change: control +3mmHg, intervention -1mmHg

Risk of bias

MRC 1968 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"using random numbers, by blocks within hospitals"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Physician blinding: adequate Participant blinding: inadequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Data collection was thorough, but some participants dropped out and contact was lost
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Unlikely as control group continued diet as usual, intervention group were likely to have had additional contact. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

MSFAT 1997

Methods	RCT
Participants	Healthy people aged 20-55 (Netherlands) CVD risk: low Control: randomised unclear (120?), analysed 103 Intervention: randomised unclear (120?), analysed 117 Mean years in trial: control 0.46, intervention 0.49 % male: control 50%, intervention 50% Age: mean control men 35.6 (sd 10), control women 36.0 (sd 11), intervention men 35.5 (sd 11), intervention women 36.0 (sd 12) (all 19-55)
Interventions	Reduced fat vs usual diet Control aims: advised to use products from trial shop ad lib. (usual fat products provided) Intervention aims: advised to use products from trial shop ad lib. (low fat products provided) Control methods: participants obtained foods in a study shop at least once a week Intervention methods: participants obtained foods in a study shop at least once a week Total fat intake (at 6 months): low fat 34.7 (sd unclear), cont 42.7 (sd unclear)%E Saturated fat intake (at 6 months): low fat 14.2 (sd unclear), cont 18.2 (sd unclear)%E Style: food provided Setting: community

MSFAT 1997 *(Continued)*

Outcomes	Stated trial outcomes: weight, vitamin and fatty acid intake, anti-oxidative capacity Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: MI, stroke and CVD deaths (no events) Secondary outcomes: stroke, MI, cancer diagnoses and deaths (no events for any outcome) Tertiary outcomes: weight (for subgroup), weight and lipids provided for larger group, but without variance data
Notes	Change from baseline to 6 months for whole group (control 103, intervention 117): Weight, kg: 1.1, 0.4 total cholesterol, mmol/L: 0.07, -0.09 HDL cholesterol, mmol/L: -0.03, -0.06 LDL cholesterol, mmol/L: 0.15, 0.16 TGs, mmol/L: 0.04, -0.04

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"stratified randomisation (according to sex, age, QI index and eating behaviour) by co-ordinating centre", a statistician at Unilever Research, SAS software, and allocation could not be altered later
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants aware of allocation, those analysing biochemistry were not
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Both groups used study shop. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

NDHS Faribault 1968

Methods	RCT
Participants	Men living in a mental health institute (USA)

NDHS Faribault 1968 *(Continued)*

	CVD risk: low Control: randomised 57, analysed 52 Interventions B, C, E combined: randomised 167, analysed 143 Mean years in trial: control 1.0, Interventions 0.9 % male: 100 Age: unclear (all 45-54)
Interventions	Modified fat vs. usual diet Control aims: total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4 Intervention aims: B (C, E) total fat 30%E (40%E, 40%E), SFA <9%E (<9%E, not stated), dietary chol 350-450mg/d (350-450mg/d, not stated), PUFA 15%E (18-20%E, not stated), P/S 1.5 (2.0, 4.4) Control methods: whole diet provided Intervention methods: whole diet provided Total fat intake (at 28 & 44 weeks combined): B (C, E) mod fat 29.2 (38.5, 37.1) (sds unclear)%E, cont 39.4 (sd unclear)%E Saturated fat intake (at 28 & 44 weeks combined): B (C, E) mod fat 6.6 (7.4, 4.9) (sds unclear)%E, cont 15.6 (sd unclear)%E Style: diet provided Setting: residential institution
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Data available on total mortality? yes Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: no cancer deaths or diagnoses occurred Tertiary outcomes: total cholesterol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, facilitated by provision of the whole diet
Incomplete outcome data (attrition bias) All outcomes	Low risk	Institution so able to follow up all participants through study.
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	

NDHS Faribault 1968 *(Continued)*

Free of systematic difference in care?	Low risk	Whole diet provided for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

NDHS Open 1st L&M 1968

Methods	RCT
Participants	Free living men (USA) CVD risk: low Control: randomised 382, analysed 341 Intervention B: randomised 385, analysed 332 Intervention X: randomised 54, analysed 46 Mean years in trial: control 1.0, B 0.9, C 0.9, X 0.9 % male: 100 Age: unclear (all 45-54)
Interventions	Reduced and modified fat diet vs. usual diet Control aims: total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4 Intervention B: total fat 30%E, SFA <9%E, dietary chol 350-450mg/d, PUFA 15%E, P/S 1.5 Intervention X: total fat 30%E, SFA <9%E, dietary chol 350-450mg/d, PUFA 15%E, P/S 1.5 Control methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), purchase of 'usual fat' items from a trial shop Intervention B methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), plus purchase of appropriately reduced and modified fat items from a trial shop Intervention X methods: dietary advice but no trial shop Total fat intake (through study): B 29.7 (sd unclear)%E, X 31.7 (sd unclear), cont 34.9 (sd unclear)%E Saturated fat intake (through study): B 7.1 (sd unclear)%E, X 8.9 (sd unclear), cont 11.6 (sd unclear)%E Style: B diet provided, X - diet advice Setting: community
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Data available on total mortality? no Cardiovascular mortality? yes (none occurred) Events available for combined cardiovascular events: fatal and non-fatal MI, peripheral vascular events Secondary outcomes: no cancer diagnoses, total or non-fatal MI occurred Tertiary outcomes: total cholesterol (some weight and BP data presented but no variance info)
Notes	At 52 weeks weight change in the control was not presented, weight change in B was -2.4kg. At 52 weeks diastolic BP change from baseline was -2.2 kg in control, -1.9 in B and -5.8 in X.

Risk of bias

Bias	Authors' judgement	Support for judgement

NDHS Open 1st L&M 1968 *(Continued)*

Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Intervention B: All reduced saturated fat and purchased blinded foods from a trial shop, double blind. Intervention X: No trial shop, so participants not blinded, though those analysing blood samples etc were.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts do not appear to have been followed for death or CV events. Deaths, cancer and CV events for participants otherwise still included in the study were collated as a reason for study exclusion
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Yes for intervention B (as both intervention and control received dietary advice and purchased food from trial shop). No for intervention X (as it did not include a trial shop as in the control group). See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

NDHS Open 1st mod 1968

Methods	RCT
Participants	Free living men (USA) CVD risk: low Control: randomised 382, analysed 341 Intervention C: randomised 390, analysed 348 Mean years in trial: control 1.0, C 0.9 % male: 100 Age: unclear (all 45-54)
Interventions	Modified fat diet vs. usual diet Control aims: total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4 Intervention C: total fat 40%E, SFA <9%E, dietary chol 350-450mg/d, PUFA 18-20%E, P/S 2.0 Control methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), purchase of 'usual fat' items from a trial shop Intervention C methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), plus purchase of appropriately reduced and modified fat items from a trial shop Total fat intake (through study): C 34.4 (sd unclear)%E, cont 34.9 (sd unclear)%E Saturated fat intake (through study): C 7.4 (sd unclear)%E, cont 11.6 (sd unclear)%E

NDHS Open 1st mod 1968 *(Continued)*

	Style: food provided Setting: community
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Data available on total mortality? no Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: fatal and non-fatal MI, peripheral vascular events Secondary outcomes: cancer diagnoses, total and non-fatal MI Tertiary outcomes: none (total cholesterol and BP data presented but no variance info)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	All reduced saturated fat and purchased blinded foods from a trial shop, double blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts do not appear to have been followed for death or CV events. Deaths, cancer and CV events for participants otherwise still included in the study were collated as a reason for study exclusion
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Trial shop used by both groups, plus dietary advice. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

NDHS Open 2nd L&M 1968

Methods	RCT
Participants	Free living men who had participated in NDHS 1st studies (USA) CVD risk: low Control: randomised 304, analysed 280 Intervention BC: randomised 194, analysed 179 Mean years in trial: control 0.6, intervention BC 0.6 % male: 100 Age: unclear (all 45-54)

NDHS Open 2nd L&M 1968 *(Continued)*

Interventions	Reduced and modified fat vs usual diet Control aims: total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4, X - advice to continue usual diet Intervention aims: BC total fat 30-40%E, SFA reduced, dietary chol 350-450mg/d, increased PUFA, P/S 1.5-2.0 Control methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), purchase of 'usual fat' items from a trial shop Intervention BC methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), plus purchase of appropriately reduced and modified fat items from a trial shop Total fat intake (through study): BC 32.5 (sd unclear)%E, cont 35.5 (sd unclear)%E Saturated fat intake (through study): BC 7.4 (sd unclear)%E, cont 12.0 (sd unclear)%E Style: food provided Setting: community
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Data available on total mortality? no Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: fatal and non-fatal MI, peripheral vascular events Secondary outcomes: cancer diagnoses (no events), total and non-fatal MI Tertiary outcomes: none
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Some participants continued with advice to reduce saturated fat and purchased blinded foods from a trial shop, but half of the participants were instructed in their own purchase of appropriate foods from normal shops to compile their own dietary regimen.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts do not appear to have been followed for death or CV events. Deaths, cancer and CV events for participants otherwise still included in the study were collated as a reason for study exclusion
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Trial shop used by both groups, plus dietary advice. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies

NDHS Open 2nd L&M 1968 *(Continued)*

Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

NDHS Open 2nd Mod 1968

Methods	RCT
Participants	Free living men who had participated in NDHS 1st studies (USA) CVD risk: low Control: randomised 304, analysed 280 Intervention F: randomised 127, analysed 112 Mean years in trial: control 0.6, intervention 0.6 % male: 100 Age: unclear (all 45-54)
Interventions	Modified fat vs usual diet Control aims: total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4, Intervention aims: F total fat 40%E, SFA no data, dietary chol 350-450mg/d, increased PUFA , P/S 3.0 Control methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), purchase of 'usual fat' items from a trial shop Intervention F methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow up visits with nutritionist), plus purchase of appropriately reduced and modified fat items from a trial shop Total fat intake (through study): F 35.1 (sd unclear)%E, cont 35.5 (sd unclear)%E Saturated fat intake (through study): F 7.8 (sd unclear)%E, cont 12.0 (sd unclear)%E Style: food provided Setting: community
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Data available on total mortality? no Cardiovascular mortality? yes (none) Events available for combined cardiovascular events: fatal and non-fatal MI, peripheral vascular events Secondary outcomes: cancer diagnoses (none occurred), total and non-fatal MI Tertiary outcomes: none
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Some participants continued with advice to reduce saturated fat and purchased blinded foods from a trial shop, but half of the participants were in-

NDHS Open 2nd Mod 1968 *(Continued)*

		structed in their own purchase of appropriate foods from normal shops to compile their own dietary regimen
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts do not appear to have been followed for death or CV events. Deaths, cancer and CV events for participants otherwise still included in the study were collated as a reason for study exclusion
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Trial shop used by both groups, plus dietary advice. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Nutrition & Breast Health

Methods	RCT
Participants	Pre-menopausal women at increased risk of breast cancer (USA) CVD risk: low Control: randomised 53, analysed 50 Intervention: randomised 69, analysed 47 Mean years in trial: control 1.0, intervention 0.8 % male: control 0%, intervention 0% Age: mean 38 (sd 7) - not provided by study arm (all 21-50)
Interventions	Reduced fat vs usual diet Control aims: followed usual diet, given daily food guide pyramid (half of this group randomised to 9 portions/d of fruit and vegetables advice) Intervention aims: total fat 15%E (half of this group randomised to 9 portions/d of fruit and vegetables advice) Control methods: no dietary counselling (offered this at the end of study), but those given fruit and veg advice had support as below Intervention methods: met dietitian every 2 weeks until compliant, monthly group meetings, counselling on home diets, restaurants, parties, social support, eating at work, exchange booklets, cookbook Total fat intake (at 12 months): low fat 15.7 (sd 5.1)%E, cont 32.7 (sd 6.1)%E Saturated fat intake (at 12 months): low fat 7.2 (sd unclear)%E, cont 11.6 (sd unclear)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: body weight, dietary compliance Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: total MI, stroke (no events)

Nutrition & Breast Health *(Continued)*

	Secondary outcomes: non-fatal and total MI, stroke, cancer diagnoses and deaths (no events for any outcome) Tertiary outcomes: weight, total, LDL and HDL cholesterol, TG, BMI (but variance data not provided for any but weight)
Notes	Change from baseline to 12 months for the control (n=23), control plus fruit & veg (n=25), low fat (n=24), low fat plus fruit & veg (n=23): Total cholesterol mg/dl: 9, 2, -8, 0 TGs mg/dl: -7, 1, 5, 8 HDL chol mg/dl: 0, 0, -4, 0 LDL chol mg/dl: 11, 2, -6, -2 BMI kg/m2: 0, 4, -13, 0

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The statistician made envelopes ahead of time, dietitians handed out envelopes at first visit
Allocation concealment (selection bias)	Low risk	Allocation could not be altered once made
Blinding (performance bias and detection bias) All outcomes	High risk	Paricipants were aware of allocation, researchers and those assessing lipids were not
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	High levels of intervention for those on low fat or high fruit and vegetable diets. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	Randomisation to fruit and vegetable intervention was independent of low fat allocation

Ole Study 2002

Methods	RCT
Participants	Moderately obese healthy men (USA) CVD risk: low Control: randomised 15, analysed 12 Intervention: randomised 15, analysed 13 Mean years in trial: control 0.68, intervention 0.70

Ole Study 2002 *(Continued)*

	% male: control 100%, intervention 100% Age: mean control 37.0 (SE 2.54), intervention 36.1 (SE 2.49)
Interventions	Reduced fat vs usual diet Control aims: total fat 33%E, CHO 52%E, protein 15%E Intervention aims: total fat 25%E, CHO 58%E, protein 17%E, provided with 11% less energy than controls, but were allowed to ask for more Also second intervention arm with Olestra added to Control methods: 5 meals/week eaten in centre, other meals in takeout containers, asked to return uneaten food, allowed to ask for more Intervention methods: 5 meals/week eaten in centre, other meals in takeout containers, asked to return uneaten food, allowed to ask for more Total fat intake (at 6 months): low fat 26.2 (sd 2.8)%E, cont 34.1 (sd 2.7)%E Saturated fat intake (at 6 months): low fat 6.2 (sd 0.7)%E, cont 7.6 (sd 0.9)%E Style: diet provided Setting: community
Outcomes	Stated trial outcomes: body weight, body fat, lipids, glucose, insulin Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: total MI, stroke, angina, CABG, angioplasty, peripheral vascular events (no events) Secondary outcomes: non-fatal and total MI, stroke, cancer diagnoses and deaths (no events for any outcome), Quality of Life Tertiary outcomes: weight, total, LDL and HDL cholesterol, TG, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer stratified and randomised by personnel not involved with participants
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Workers in the dietary kitchen, who provided the meals, were the only ones who knew the allocations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	

Ole Study 2002 *(Continued)*

Free of systematic difference in care?	Low risk	Most food provided for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Potential difference in energy intake, but unclear what effect this had

Oslo Diet-Heart 1966

Methods	RCT
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)
Interventions	Modified fat diet vs control Control aims: no dietary advice but direct questions answered, supplement = 1 vitamin tablet daily Intervention aims: reduce meat & dairy fats, increase fish, vegetables, supplement - 1 vitamin tablet daily, 0.5L 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: mod fat unclear, cont unclear Saturated fat intake: mod fat unclear, cont unclear Style: diet advice & 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 Tertiary outcomes: weight, total cholesterol, systolic and diastolic BP (but no variance information is provided)
Notes	Weight change from baseline was -0.5kg in the control group (n˜155), -2.5kg in the intervention group (n˜160) to 51 months Total cholesterol change from baseline was -0.46mmol/L in the control group and -1.53mmol/L in the intervention group at 51 months. Systolic BP at baseline was 153.8mmHg in control and 159.0 in intervention, and mean sBP through trial was 154.3mmHg in control and 158.2mmHg in the intervention group. Diastolic BP at baseline was 93.5mmHg in control and 97.1mmHg in intervention, through trial mean dBP was 95.5mmHg in control and 98.6mmHg in intervention participants.

Oslo Diet-Heart 1966 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"table of random numbers used", by Prof Knut Westlund
Allocation concealment (selection bias)	Low risk	Randomisation appears to have occurred before medical examination within the study
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of their allocation as was the main trialist. Outcomes were categorised by a diagnostic board, but their blinded status was unclear.
Incomplete outcome data (attrition bias) 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 asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Dietetic input level very different, although medical care appeared similar. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Differences in fruit and vegetables, fish etc. as above.

Oxford Retinopathy 1978

Methods	RCT
Participants	Newly diagnosed non-insulin dependant diabetics (UK) CVD risk: moderate Control: randomised unclear (249 split between the 2 groups, 125?), analysed for mortality unclear (all but 2 overall at 16 years) Intervention: randomised unclear (249 split between the 2 groups, 125?), analysed as above Mean years in trial: overall 9.3? % male: overall 49 Age: mean overall 47.1 (all <65)
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), 1500kcal/day Intervention aims: total fat 26%E, PUFA 16%E, protein 20%E, CHO 54%E (reducing simple sugars), 1500kcal/day Control methods: dietary advice from diabetes dietitian Intervention methods: dietary advice from diabetes dietitian Total fat intake (at 7-9 years): low & mod fat 32 (sd unclear), cont 41 (sd unclear)%E Saturated fat intake (at 7-9 years): low & mod fat 10.7 (sd unclear), cont 20.4 (sd unclear)%E

Oxford Retinopathy 1978 *(Continued)*

	Style: diet advice Setting: community (outpatients clinic)
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	

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	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded, physicians unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Dietetic advice for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Polyp Prevention 1996

Methods	RCT
Participants	People with at least one adenomatous polyp of the large bowel removed (USA) CVD risk: low Control: 1042 randomised, 947 analysed Intervention: 1037 randomised, 958 analysed Mean years in trial: control 3.05, intervention 3.05

Polyp Prevention 1996 *(Continued)*

	% male: control 64%, intervention 66% Age: mean control 61.5, intervention 61.4 (all at least 35)
Interventions	Low fat vs usual diet Control: general dietary guidelines Intervention: total fat 20%E, 18g fibre/1000kcal, 5-8 servings fruit and veg daily Control methods: leaflet, no additional information or behaviour modification Intervention methods: >50 hours of counselling over 4 years, included skill building, behaviour modification, self monitoring and nutritional materials Total fat intake (at 4 years): low fat 23.8 (sd 6.0), cont 33.9 (sd 5.9)%E Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: recurrence of polyps, prostate cancer Data available on total mortality? yes Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: cancer diagnoses Tertiary outcomes: weight, total cholesterol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned"
Allocation concealment (selection bias)	Low risk	Phone call to computer randomisation centre, stratified according to centre
Blinding (performance bias and detection bias) All outcomes	High risk	Outcome assessors blinded, participants not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	50 hours behaviour modification in intervention group, not in control. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies

Polyp Prevention 1996 *(Continued)*

Free of dietary differences other than fat?	High risk	Fibre, fruit and vegetable goals in intervention group

PREMIER 2003

Methods	RCT
Participants	Adults with above optimal BP or stage 1 hypertension (USA) CVD risk: moderate Control: 269 randomised, 269 analysed Intervention: 268 randomised, 268 analysed Mean years in trial: 1.5 % male: control 35.3%, intervention 42.8% Age, years: control 50.2 mean (sd 8.6), intervention 50.2 (sd 9.3)
Interventions	Reduced fat vs usual diet Control: 'established' goals weight loss of 6.8kg at 6months, 180 mins/week of moderate physical activity, limited sodium intake, limited alcohol. Intervention: 'established plus DASH' goals as 'established' plus saturated fat intake 7%E or less, total fat intake 25%E or less, 2-3 portions low fat dairy foods/d, 9-12 portions fruit and veg/d. Other arms: Advice only standard care arm, data not used. Control methods: 18 face to face contacts (14 group and 4 individual), food diaries, physical activity records, calorie and sodium intake records Intervention methods: 18 face to face contacts (14 group and 4 individual), food diaries, physical activity records, calorie and sodium intake records Total fat intake (at 6 months): low fat 23.8 (sd 8.6), cont 29.4 (sd 8.4)%E Saturated fat intake (at 6 months): low fat 7.7 (sd 3.2), cont 9.4 (sd 3.5)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: blood pressure Data available on total mortality? yes Cardiovascular mortality? yes, none by 18 months Events available for combined cardiovascular events: total MI, stroke. Secondary outcomes: cancer deaths (none), cancer diagnoses, diabetes, stroke, total and non-fatal MI Tertiary outcomes: weight, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out centrally by computer programme, stratified by clinic and baseline BP, blocked

PREMIER 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded to the intervention, though efforts were made to mask centre staff involved in outcome assessments to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All those randomised were included in the analysis of both events and blood pressure
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar style and duration of interventions. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Differences in fruit and vegetable advice

Rivellese 1994

Methods	RCT
Participants	Adults with primary hyperlipoproteinaemia (Italy) CVD risk: moderate Intervention reduced fat: 33 randomised, 27 analysed Intervention modified fat: 30 randomised, 17 analysed Mean years in trial: reduced fat 0.4, modified fat 0.4 % male: reduced fat 82%, modified fat 63% Age, years: reduced fat 47.4 mean (sd 10.3), modified fat 48.6 (sd 8.1)
Interventions	Reduced fat vs Modified fat diet Reduced fat aims: total fat 25%E, SFA 8%E, MUFA 15%, PUFA 2%, dietary chol <300mg/d, CHO 58%, protein 17%E, soluble fibre 41g/d Modified fat aims: total fat 38%E, SFA <10%E, MUFA 20%E, PUFA 10%E, dietary chol<300mg/d, CHO 47%E, protein 15%E, soluble fibre 19g/d Reduced fat methods:seen monthly by dietitian and doctor, feedback based on 7 day food diary each time Modified fat methods: seen monthly by dietitian and doctor, feedback based on 7 day food diary each time Total fat intake (at 5-6 months): low fat 27 (sd unclear)%E, mod fat 36 (sd unclear)%E Saturated fat intake (at 5-6 months): low fat 6 (sd unclear)%E, mod fat 7 (sd unclear)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: metabolic effects Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events)

Rivellese 1994 *(Continued)*

	Events available for combined cardiovascular events: total MI, cardiovascular deaths, stroke (no events) Secondary outcomes: stroke, total and non-fatal MI (no events for any outcomes) Tertiary outcomes: total, LDL and HDL cholesterol, TGs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Following 3 or 6 weeks compliance with control diet run-in, stratified block randomisation with tables of random numbers
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	None
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Identical follow up. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Some differences in soluble fibre intake

Rose 1965

Methods	RCT
Participants	Men (?) with angina or following MI (UK) CVD risk: high Control: randomised 26, analysed 18 Intervention - olive: randomised 28, analysed 12 Intervention - corn: randomised 26, analysed 13 Mean years in trial: control 1.7, olive 1.5, corn 1.5 % male: unclear (100%?) Age: mean control 58.8, olive 55.0, corn 52.6 (all <70)
Interventions	Modified fat vs. usual diet Control aims: usual diet Intervention aims -olive: restrict dietary fat, plus 80g/day olive oil provided Intervention aims - corn: restrict dietary fat, plus 80g/day corn oil provided

Rose 1965 *(Continued)*

	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 Total fat intake (at 18 months): corn 50.5 (sd unclear), olive 46.2 (sd unclear), cont 32.6 (sd unclear)%E Saturated fat intake: unclear Style: diet advice & 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 Tertiary outcomes: total cholesterol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"sealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Physician blinding: inadequate Participant blinding: inadequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Some lost to follow up by 2 years
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	All received conventional treatments at the discretion of the physicians, all attended a special follow up clinic. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Sacks high protein 2009

Methods	RCT
Participants	Overweight or obese adults (USA) CVD risk: low Intervention reduced fat: 202 randomised, 202 analysed Intervention modified fat: 201 randomised, 201 analysed Mean years in trial: reduced fat 1.78, modified fat 1.84 % male: reduced fat 33%, modified fat 36% Age, years: reduced fat 50 (SD 10), modified fat 51 (9)
Interventions	Reduced fat vs Modified fat diet Reduced fat aims: total fat 20%E, SFA ≤8%E, MUFA 6%, PUFA 6%, dietary chol 150mg/1000kcal, CHO 55%, protein 25%E, dietary fibre 20g/d Modified fat aims: total fat 40%E, SFA ≤8%E, MUFA 22%E, PUFA 10%E, dietary chol 150mg/1000kcal, CHO 35%E, protein 25%E, dietary fibre 20g/d Reduced fat methods: 18 group sessions in first 6 months, then 2 group sessions per month to 2 years, plus individual sessions every 8 weeks for 2 years. All sessions included behavioural counselling, daily meal plans provided, food diary and web-based self-monitoring tool provided, 90 mins/week of moderate exercise encouraged. Modified fat methods: 18 group sessions in first 6 months, then 2 group sessions per month to 2 years, plus individual sessions every 8 weeks for 2 years. All sessions included behavioural counselling, daily meal plans provided, food diary and web-based self-monitoring tool provided, 90 mins/week of moderate exercise encouraged. Total fat intake (at 2 years): low fat 28.4 (sd 8.1)%E, mod fat 35.1 (sd 7.0)%E Saturated fat intake (at 2 years): low fat 8.9 (sd 3.8)%E, mod fat 10.5 (sd 2.7)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: weight Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: unclear Secondary outcomes: cancer deaths (no events) and cancer diagnoses Tertiary outcomes: weight; total, LDL and HDL cholesterol; TGs; systolic and diastolic blood pressure, QoL (QoL outcomes not reported)
Notes	This was a factorial trial, so there were also 2 arms with lower protein intake (see Sacks low protein 2009)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization assignments to one of 4 diet groups were generated by the data manager at the coordinating center... after confirming, by computer program, that all screening activities had occurred... Diet group assignments were stratified by site with varying block sizes to ensure a balance at each site.'
Allocation concealment (selection bias)	Low risk	As above

Sacks high protein 2009 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	'Blinding was established by naming each diet with colors, and using the same foods for each diet. Blinding and equipoise were strictly maintained by emphasizing to intervention staff and participants that each diet adheres to healthy principles, and each is advocated by certain experts to be superior for long-term weight-loss. Except for interventionists ... investigators and staff were kept blind to diet assignment of the participants. The trial adhered to established procedures to maintain separation between staff that take outcome measurements and staff that deliver the intervention. Staff members who obtained outcome measurements were not informed of the diet group assignment.... All investigators, staff and participants were kept masked to outcome measurements and trial results.'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear for cardiovascular events. Yes for tertiary outcomes - intention to treat analysis, imputing zero change from baseline for missing data (except for weight which was more complex, assuming weight regain for missing data following weight loss, and zero change for those who had previously gained weight).
Selective reporting (reporting bias)	Low risk	ClinicalTrials.gov number NCT00072995. Protocol secondary outcomes (hepatic and skeletal muscle, visceral fat, and quality of life) not yet reported in full
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Identical follow up for all groups
Free of dietary differences other than fat?	Low risk	Clear dietary goal similarities across saturated fat, fibre, cholesterol etc.

Sacks low protein 2009

Methods	RCT
Participants	Overweight or obese adults (USA) CVD risk: low Intervention reduced fat: 204 randomised, 204 analysed Intervention modified fat: 204 randomised, 204 analysed Mean years in trial: reduced fat 1.83, modified fat 1.74 % male: reduced fat 38%, modified fat 39% Age, years: reduced fat 51 (SD 9), modified fat 52 (9)
Interventions	Reduced fat vs Modified fat diet Reduced fat aims: total fat 20%E, SFA ≤8%E, MUFA 6%, PUFA 6%, dietary chol 150mg/1000kcal, CHO 65%, protein 15%E, dietary fibre 20g/d Modified fat aims: total fat 40%E, SFA ≤8%E, MUFA 22%E, PUFA 10%E, dietary chol 150mg/1000kcal, CHO 45%E, protein 15%E, dietary fibre 20g/d Reduced fat methods: 18 group sessions in first 6 months, then 2 group sessions per month to 2 years, plus individual sessions every 8 weeks for 2 years. All sessions included behavioural counselling, daily meal plans provided, food diary and web-based self-monitoring tool provided, 90 mins/week of moderate exercise encouraged. Modified fat methods: 18 group sessions in first 6 months, then 2 group sessions per month to 2 years, plus individual sessions every 8 weeks for 2 years. All sessions included behavioural counselling, daily

Sacks low protein 2009 *(Continued)*

	meal plans provided, food diary and web-based self-monitoring tool provided, 90 mins/week of moderate exercise encouraged. Total fat intake (at 2 years): low fat 26.5 (sd 8.0)%E, mod fat 33.3 (sd 8.2)%E Saturated fat intake (at 2 years): low fat 8.0 (sd 3.1)%E, mod fat 9.8 (sd 3.3)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: weight Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: unclear Secondary outcomes: cancer deaths (no events) and cancer diagnoses Tertiary outcomes: weight; total, LDL and HDL cholesterol; TGs; systolic and diastolic blood pressure, QoL (QoL outcomes not reported)
Notes	This was a factorial trial, so there were also 2 arms with higher protein intake (see Sacks high protein 2009)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization assignments to one of 4 diet groups were generated by the data manager at the coordinating center... after confirming, by computer program, that all screening activities had occurred... Diet group assignments were stratified by site with varying block sizes to ensure a balance at each site.'
Allocation concealment (selection bias)	Low risk	As above.
Blinding (performance bias and detection bias) All outcomes	Low risk	'Blinding was established by naming each diet with colors, and using the same foods for each diet. Blinding and equipoise were strictly maintained by emphasizing to intervention staff and participants that each diet adheres to healthy principles, and each is advocated by certain experts to be superior for long-term weight-loss. Except for interventionists ... investigators and staff were kept blind to diet assignment of the participants. The trial adhered to established procedures to maintain separation between staff that take outcome measurements and staff that deliver the intervention. Staff members who obtained outcome measurements were not informed of the diet group assignment.... All investigators, staff and participants were kept masked to outcome measurements and trial results.'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear for cardiovascular events. Yes for tertiary outcomes - intention to treat analysis, imputing zero change from baseline for missing data (except for weight which was more complex, assuming weight regain for missing data following weight loss, and zero change for those who had previously gained weight).
Selective reporting (reporting bias)	Low risk	ClinicalTrials.gov number NCT00072995. Protocol secondary outcomes (hepatic and skeletal muscle, visceral fat, and quality of life) not yet reported in full
Other bias	Low risk	

Sacks low protein 2009 *(Continued)*

Free of systematic difference in care?	Low risk	Identical follow up for all groups
Free of dietary differences other than fat?	Low risk	Clear dietary goal similarities across saturated fat, fibre, cholesterol etc.

Sarkkinen Fat Mod 1995

Methods	RCT (the 3 Kuopio trials share a common control group)
Participants	Free-living people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L (Finland) CVD risk: moderate Control: randomised 37, analysed 37 Intervention Mono: randomised 41, analysed 41 Mean years in trial: for both groups 0.5 % male: control 46, Mono 46 Age: mean control 43.2, Mono 46.4 (all 30-60)
Interventions	Modified fat vs usual diet Control aims: advised total fat 38%E, SFA <18%E, MUFA 15%E, PUFA <5%E, rapeseed oil, butter and semi-skimmed milk provided Intervention aims Mono: total fat 38%E, SFA <14%E, MUFA 18%E, PUFA <6%E, rapeseed oil, rapeseed spread and skimmed milk provided Control and intervention methods: given written dietary instructions and a diet plan with checking and reinforcement for 3 visits, then at 2, 6, 12, 18 and 26 weeks Total fat intake (weeks 14-28): mod fat 35 (sd 5), cont 36 (sd 5)%E Saturated fat intake (weeks 14-28): mod fat 11 (sd 2), cont 15 (sd 2)%E Style: dietary advice & supplement (food) Setting: community
Outcomes	Stated trial outcomes: lipids and blood pressure Data available on total mortality? yes (no events) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: BMI, total, LDL and HDL cholesterol, TG, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation stratified for men and women, singles and couples, random number tables"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described

Sarkkinen Fat Mod 1995 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Participants and researchers knew allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar intensity and duration for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies.
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Sarkkinen Red & Mod 1995

Methods	RCT (the 3 Kuopio trials share a common control group)
Participants	Free-living people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L (Finland) CVD risk: moderate Control: randomised 37, analysed 37 Intervention AHA: randomised 41, analysed 41 Mean years in trial: for all 4 groups 0.5 % male: control 46, AHA 46 Age: mean control 43.2, AHA 47.3 (all 30-60)
Interventions	Reduced and modified fat vs usual diet Control aims: advised total fat 38%E, SFA <18%E, MUFA 15%E, PUFA <5%E, rapeseed oil, butter and semi-skimmed milk provided Intervention aims AHA: total fat 30%E, SFA <10%E, MUFA 10%E, PUFA 10%E, sunflower oil, sunflower spread and skimmed milk provided Control and intervention methods: given written dietary instructions and a diet plan with checking and reinforcement for 3 visits, then at 2, 6, 12, 18 and 26 weeks Total fat intake (weeks 14-28): low & mod fat 34 (sd 4), cont 36 (sd 5)%E Saturated fat intake (weeks 14-28): low & mod fat 11 (sd 2), cont 15 (sd 2)%E Style: dietary advice & supplement (food) Setting: community
Outcomes	Stated trial outcomes: lipids and blood pressure Data available on total mortality? yes (no events) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: BMI, total, LDL and HDL cholesterol, TG, BP

Sarkkinen Red & Mod 1995 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation stratified for men and women, singles and couples, random number tables"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and researchers knew allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar intensity and duration in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Sarkkinen Red Fat 1995

Methods	RCT (the 3 Kuopio trials share a common control group)
Participants	Free-living people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L (Finland) CVD risk: moderate Control: randomised 37, analysed 37 Intervention low fat: randomised 40, analysed 40 Mean years in trial: for both groups 0.5 % male: control 46, low fat 48 Age: mean control 43.2, low fat 45.8 (all 30-60)
Interventions	Reduced fat vs usual diet (low fat vs control) Control aims: advised total fat 38%E, SFA <18%E, MUFA 15%E, PUFA <5%E, rapeseed oil, butter and semi-skimmed milk provided Intervention aims low fat: total fat 28-30%E, SFA <14%E, MUFA 10%E, PUFA 4%E, butter and rapeseed spread and skimmed milk provided Control and intervention methods: given written dietary instructions and a diet plan with checking and reinforcement for 3 visits, then at 2, 6, 12, 18 and 26 weeks Total fat intake (weeks 14-28): low fat 31 (sd 5), cont 36 (sd 5)%E Saturated fat intake (weeks 14-28): low fat 12 (sd 2), cont 15 (sd 2)%E

Sarkkinen Red Fat 1995 *(Continued)*

	Style: dietary advice & supplement (food) Setting: community
Outcomes	Stated trial outcomes: lipids and blood pressure Data available on total mortality? yes (no events) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: BMI, total, LDL and HDL cholesterol, TG, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation stratified for men and women, singles and couples, random number tables"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and researchers knew allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar intensity and duration in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Sarkkinen Red vs Mod1995

Methods	RCT
Participants	Free-living people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L (Finland) CVD risk: moderate Intervention Mono: randomised 41, analysed 41 Intervention low fat: randomised 40, analysed 40 Mean years in trial: for both groups 0.5 % male: mono 46, low fat 48 Age: mean Mono 46.4 (all 30-60), low fat 45.8 (all 30-60)

Sarkkinen Red vs Mod1995 *(Continued)*

Interventions	Reduced fat vs modified fat (low fat vs Mono) Intervention aims Mono: total fat 38%E, SFA <14%E, MUFA 18%E, PUFA <6%E, rapeseed oil, rapeseed spread and skimmed milk provided Intervention aims low fat: total fat 28-30%E, SFA <14%E, MUFA 10%E, PUFA 4%E, butter and rapeseed spread and skimmed milk provided Both intervention methods: given written dietary instructions and a diet plan with checking and reinforcement for 3 visits, then at 2, 6, 12, 18 and 26 weeks Total fat intake (weeks 14-28): mod fat 35 (sd 5), low fat 31 (sd 5)%E Saturated fat intake (weeks 14-28): mod fat 11 (sd 2), low fat 12 (sd 2)%E Style: dietary advice & supplement (food) Setting: community
Outcomes	Stated trial outcomes: lipids and blood pressure Data available on total mortality? yes (no events) Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: BMI, total, LDL and HDL cholesterol, TG, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation stratified for men and women, singles and couples, random number tables"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and researchers knew allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar intensity and duration in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Seppelt 1996

Methods	RCT
Participants	Women with BMI 24-29 (Germany) CVD risk: low Control: randomised 35, analysed 32 Intervention: randomised 35, analysed 35 Mean years in trial: control 0.7, intervention 0.8 % male: 0 Age: mean control 46, intervention 48 (all 40-60)
Interventions	Reduced fat vs usual diet Control aims: advice to buy foods from trial shop, usual fat foods supplied Intervention aims: advice to buy foods from trial shop, low fat foods supplied Control methods: trial shop provided ad libitum usual fat foods Intervention methods: trial shop provided ad libitum low fat foods Total fat intake (at 9 months): low fat 35.1 (sd unclear), cont 35.5 (sd unclear)%E Saturated fat intake: unclear Style: food provided Setting: community
Outcomes	Stated trial outcomes: weight Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, stroke (no events) Secondary outcomes: total and non-fatal MI, stroke, cancer deaths (no events for any outcomes) Tertiary outcomes: weight, total, LDL and HDL cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"participants assigned to a random number, later numbers sorted & assigned"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding unclear for participants and researchers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing

Seppelt 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Trial shop for both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Simon 1997

Methods	RCT
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
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: total fat 15%E Control methods: continued usual diet Intervention methods: Biweekly individual dietetic appointments over 3 months followed by monthly individual or group appointments, including education, goal setting, evaluation, feedback and self-monitoring Total fat intake (at 12 months): low fat 18.0 (sd 5.6), cont 33.8 (sd 7.4)%E Saturated fat intake (at 12 months): low fat 6.0 (sd unclear), cont 11.3 (sd unclear)%E Style: diet advice Setting: community
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	

Risk of bias

Bias	Authors' judgement	Support for judgement

Simon 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	Stratified by age and randomised (block size 2)
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Participants knew their allocation, unclear whether physicians did
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Very different contact time with dietitian, but medical appointments same in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Sondergaard 2003

Methods	RCT
Participants	People with IHD plus total cholesterol at least 5mmol/L (Denmark) CVD risk: high Control: 63 randomised, 52 analysed Intervention: 68 randomised, 63 analysed Mean years in trial: 1.0 % male: control 79%, intervention 62% age: control mean 62.8 (sd 10.5), intervention mean 62.1 (sd 9.3)
Interventions	Reduced and modified fat intake vs. usual diet Control: aims unclear Intervention: aims reductions in total and saturated fat, replace fats with oils, 600g fruit and vegetables/d, fatty fish at least once a week, eat plenty of bread and cereals Control methods: booklets plus one dietetic interview, and 3 monthly clinical review Intervention methods: 1 hour nutrition interview every 3 months, plus 3 monthly clinical review Total fat intake (at 12 months): low & mod fat 26.2 (sd 5.1), cont 28.9 (sd 7.9)%E Saturated fat intake (at 12 months): unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: endothelial function

Sondergaard 2003 *(Continued)*

	Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: total MI, cardiovascular deaths, stroke, angina, heart failure, CABG, PCI and atrial fibrillation. Secondary outcomes: cancer diagnoses and deaths, stroke, total MI Tertiary outcomes: total, LDL and HDL cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"randomised in unblinded 1:1 fashion"
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants aware of allocation, unclear about others
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Additional dietetic time for intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Additional dietary advice for intervention group (fruit, vegetables, fish, cereals).

STARS 1992

Methods	RCT
Participants	Men with angina referred for angiography (UK) CVD risk: high Control: unclear 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)
Interventions	Reduced and modified fat diet vs usual diet Control aims: no diet intervention but advised to lose weight if BMI>25

STARS 1992 *(Continued)*

	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 100mg/1000kcal, advised to lose weight if BMI>25 Control methods: usual care but no formal dietetic counselling Intervention methods: Usual care plus dietetic assessment of diet and advice Total fat intake (through study): int 27 (sd unclear), cont 37 (sd unclear)%E Saturated fat intake (through study): int 9 (sd unclear), cont 17 (sd unclear)%E Style: diet advice Setting: community
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 Secondary outcomes: cancer deaths (none), stroke, total MI Tertiary outcomes: total, HDL, LDL cholesterol, TGs (weight and BP "remained similar" but were not reported)
Notes	

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	
Blinding (performance bias and detection bias) All outcomes	High risk	Physician blinding: unclear Participant blinding: inadequate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Usual care in both groups, dietetic counselling only in the intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Intervention group also encouraged to increase plant derived soluble fibre

Strychar 2009

Methods	RCT
Participants	People with well controlled type I diabetes mellitus (Canada) CVD risk: moderate Intervention reduced fat: 18 randomised, 15 analysed Intervention modified fat: 17 randomised, 15 analysed Mean years in trial: reduced fat 0.46, modified fat 0.47 % male: reduced fat unclear, modified fat unclear Age, years: 37.9 (8.1 SD) (not specified by study arm)
Interventions	Reduced fat vs Modified fat diet Reduced fat aims: total fat 27-30%E, SFA ≤10%E, MUFA 10%, CHO 54-57% Modified fat aims: total fat 37-40%E, SFA ≤10%E, MUFA 20%E, CHO 43-46%E Reduced fat methods: after initial dietary advice monitored weekly by phone by a dietitian (24 hour food recall). Glycaemia, insulin doses, CHO at meals, hypoglycaemic attacks all self-monitored daily and reported weekly. Modified fat methods: after initial dietary advice monitored weekly by phone by a dietitian (24 hour food recall). Glycaemia, insulin doses, CHO at meals, hypoglycaemic attacks all self-monitored daily and reported weekly. Total fat intake (at 6 months): not stated Saturated fat intake (at 6 months): not stated Style: diet advice Setting: community
Outcomes	Stated trial outcomes: Triglycerides and other CVD risk factors Data available on total mortality? yes (no events) Cardiovascular mortality? yes (no events) Events available for combined cardiovascular events: none Secondary outcomes: cancer deaths (no events) and cancer diagnoses (no events) Tertiary outcomes: weight; BMI; total, LDL and HDL cholesterol; TGs; systolic and diastolic blood pressure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	High risk	No details provided, but participants had to make decisions about what they ate
Incomplete outcome data (attrition bias) All outcomes	High risk	Data reported for those who completed

Strychar 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Similar intervention in both groups
Free of dietary differences other than fat?	Low risk	Focus on fat and CHO intake

Sydney Diet-Heart 1978

Methods	RCT
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)
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 <300mg/day Control methods: no specific dietary instruction (except re weight) Intervention methods: advised and tutored individually, diet assessed 3 times in first year and twice annually thereafter Total fat intake ("during follow up"): mod fat 38.3 (sd 5.9), cont 38.1 (sd 5.4)%E Saturated fat intake ("during follow up"): mod fat 9.8 (sd 2.6), cont 13.5 (sd 3.2)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: cardiovascular mortality and morbidity Data available on total mortality? yes Cardiovascular mortality? no (overall number given, but not by intervention group) Events available for combined cardiovascular events: none Secondary outcomes: none Tertiary outcomes: total cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Sydney Diet-Heart 1978 *(Continued)*

Random sequence generation (selection bias)	Low risk	"random numbers"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	High risk	Physician blinding: adequate participant blinding: inadequate
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 asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Advice and follow up in intervention group, not in control. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

THIS DIET 2008

Methods	RCT
Participants	People following a first MI (USA) CVD risk: high Intervention 1 low fat: 50 randomised, 50 analysed Intervention 2 modified fat: 51 randomised, 51 analysed Mean years in trial: 2 % male: low fat 68%, modified fat 80% Age, years: low fat 58 (sd 9), modified fat 58 (sd 10)
Interventions	Low fat vs modified fat Low fat aims: <30%E from fat, 7%E or less from SFA, 10-15%E MUFA, 200mg/d or less cholesterol, 0.3 to 0.45%E from n-3 Modified fat aims: 30-40%E from fat, 7%E or less from SFA, 20-25%E MUFA, 200mg/d or less cholesterol, >0.75%E from n-3 Control methods: 6+ classes plus individual dietetic appointments (2 in first month, then at 3, 6, 12, 18 and 24 months) Intervention methods: 6+ classes plus individual dietetic appointments (2 in first month, then at 3, 6, 12, 18 and 24 months) Total fat intake (at 12 months): low fat 27.9 (sd 7.0), mod fat 30.1 (sd 8.6)%E Saturated fat intake (at 12 months): low fat 7.5 (sd 2.7), mod fat 7.9 (sd 3.4)%E Style: diet advice

THIS DIET 2008 *(Continued)*

	Setting: community
Outcomes	Stated trial outcomes: mortality and morbidity Data available on total mortality? yes, none Cardiovascular mortality? yes, none Events available for combined cardiovascular events: MI, unstable angina, stroke Secondary outcomes: cancer deaths (none), stroke, total and non-fatal MI Tertiary outcomes: HDL and LDL cholesterol, TG, BMI, BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes, stratified by diabetes, 10 envelope blocks, selected in prepared order from locked drawer by study dietitian.
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were aware of allocation as taught the diet.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For primary outcomes
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	Same number of individual dietetic appointments and group sessions in both arms. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	Smoking cessation, weight loss and exercise encouraged in both arms.

Veterans Admin 1969

Methods	RCT
Participants	Men living at the Veterans Administration Centre (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)
Interventions	Modified fat vs. usual diet

Veterans Admin 1969 *(Continued)*

	Control aims: provided, total fat 40%E Intervention aims: total fat 40%E, 2/3 of SFA replaced by unsaturated fats, dietary chol reduced Control methods: whole diet provided Intervention methods: whole diet provided Total fat intake (during trial): mod fat 38.9 (sd unclear), cont 40 (sd unclear)%E Saturated fat intake (during trial): mod fat 8.3 (sd unclear), cont 18.5 (sd unclear)%E Style: diet provided Setting: residential institution
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, PV events Secondary outcomes: cancer deaths, cancer diagnoses, stroke, non-fatal MI, total MI Tertiary outcomes: none (some data on total cholesterol, but no variance info)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"table of random numbers used"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding (performance bias and detection bias) All outcomes	Low risk	physician blinding: adequate participant blinding: adequate
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 asked for data
Other bias	Low risk	
Free of systematic difference in care?	Low risk	All ate centre food as usual. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

WHEL 2007

Methods	RCT
Participants	Women with previously treated early breast cancer (USA) CVD risk: low Control: randomised 1561, analysed 1551 Intervention: randomised 1546, analysed 1537 Mean years in trial: unclear, 11 years max, around 11 years mean? % male: 0 Age: control mean 53.0 (sd 9.0), intervention mean 53.3 (sd 8.9)
Interventions	Reduced fat intake vs usual diet Control: aim 30%E from fat Intervention: aim 15-20%E from fat, 5veg/d, 3 fruit/d, 16oz veg juice and 30g/d fibre Control methods: given print materials only Intervention methods: telephone counselling programme (31 calls by study end), cooking classes (12 offered in first year, 4 attended on average) and monthly newsletters (48 by study end), all focused on self-efficacy, self-monitoring and barriers, retaining motivation Total fat intake (at 72 months): low fat 28.9 (sd 9.0), cont 32.4 (sd 8.0)%E Saturated fat intake (at 72 months): low fat 7.2 (sd unclear), cont 8.9 (sd unclear)%E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: mortality, invasive breast cancer Data available on total mortality? yes Cardiovascular mortality? yes Events available for combined cardiovascular events: none Secondary outcomes: cancer diagnoses and deaths Tertiary outcomes: weight, total, LDL and HDL cholesterol, TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation via computer programme
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Monitoring of national death register and medical records

WHEL 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	High intensity intervention compared with leaflets. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Fruit and veg intervention in low fat arm, not in control.

WHI with CVD 2006

Methods	RCT
Participants	Post-menopausal women aged 50-79 with CVD at baseline (USA) CVD risk: high Control: randomised 1369, analysed 1369 Intervention: randomised 908, analysed 908 Mean years in trial: control 8.1, intervention 8.1 % male: 0 Age: mean (women both with and without CVD at baseline) int 62.3 (sd 6.9), control 62.3 (sd 6.9)
Interventions	Reduced fat vs. usual diet Control: diet-related education materials Intervention: low fat diet (20% E from fat) 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 first year, quarterly maintenance sessions thereafter, focusing on diet and behaviour modification Total fat intake (at 6 years): int 28.8 (sd 8.4)%E, cont 37.0 (sd 7.3)%E Saturated fat intake (at 6 years): int 9.5 (sd 3.2)%E, cont 12.4 (sd 3.1)%E Style: dietary advice Setting: community
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, revascularization, pulmonary embolism, DVT Secondary outcomes: cancer deaths*, cancer diagnoses*, stroke, non-fatal MI Tertiary outcomes: weight, BMI, total, LDL and HDL cholesterol, TGs, systolic and diastolic BP * these are only available for the whole cohort, not split between low and high CVD risk groups
Notes	
Risk of bias	

WHI with CVD 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer algorithm
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Intervention participants received 18 group sessions with behavioural modification plus quarterly maintenance sessions thereafter, control groups received a leaflet. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Also fruit and vegetable intervention. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

WHI without CVD 2006

Methods	RCT
Participants	Post-menopausal women aged 50-79 without CVD at baseline (USA) CVD risk: low Control: randomised 29294, analysed 29294 Intervention: randomised 19541, analysed 19541 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)
Interventions	Reduced fat vs. usual diet Control: diet-related education materials Intervention: low fat diet (20% E from fat) 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 first year, quarterly maintenance sessions thereafter, focusing on diet and behaviour modification Total fat intake (at 6 years): int 28.8 (sd 8.4)%E, cont 37.0 (sd 7.3)%E Saturated fat intake (at 6 years): int 9.5 (sd 3.2)%E, cont 12.4 (sd 3.1)%E Style: dietary advice

WHI without CVD 2006 *(Continued)*

	Setting: community
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, revascularization, 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 * these are only available for the whole cohort, not split between low and high CVD risk groups
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer algorithm
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Not relevant for primary and secondary outcomes as all trialists asked for data
Other bias	Low risk	
Free of systematic difference in care?	High risk	Intervention participants received 18 group sessions with behavioural modification plus quarterly maintenance sessions thereafter. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	High risk	Also fruit and vegetable intervention. See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

WINS 2006

Methods	RCT
Participants	Women with localised re-sected breast cancer (USA) CVD risk: low Control: 1462 randomised, 1462 analysed Intervention: 975 randomised, 975 analysed

WINS 2006 *(Continued)*

	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)
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, then optional monthly group sessions, incorporating individual fat gram goals, social cognitive theory, self-monitoring, goal setting, modelling, social support and relapse prevention and management Total fat intake (at 1 year): low fat 20.3 (sd 8.1), cont 29.2 (sd 7.4)%E Saturated fat intake (at 1 year): low fat 10.4 (sd 6.7), cont 16.6 (sd 9.3)%E Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: dietary fat intake, total cholesterol, weight and waist Data available on total mortality? yes Cardiovascular mortality? no Events available for combined cardiovascular events: none Secondary outcomes: cancer diagnoses Tertiary outcomes: weight, BMI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded, not relevant for assessment of mortality by researchers
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 asked for data
Other bias	Low risk	

WINS 2006 *(Continued)*

Free of systematic difference in care?	High risk	Differences in attention - more time for those in intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies
Free of dietary differences other than fat?	Low risk	See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

Abreviations:
CHO = carbohydrates,
%E = percent of total energy intake,
P/S = polyunsaturated / saturated fat ratio,
chol = cholesterol,
CVD = cardiovascular disease,
MI = myocardial infarction

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)
Anti-Coronary C 1966	Not randomised
Aquilani 2000	No appropriate control group (and not low fat vs modified fat)
Arntzenius 1985	No appropriate control group (and not low fat vs modified fat)
Aro 1990	Intervention and randomised follow up less than 6 months
ASSIST 2001	Intervention is not dietary fat modification or low fat diet
Australian Polyp Prev 95	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
Baer 1993	Not randomised
Bakx 1997	Multifactorial intervention
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
Baumann 1982	Intervention and randomised follow up less than 6 months
Beckmann 1988	Not randomised
Beckmann 1995	Intervention is not dietary fat modification or low fat diet
Beresford 1992	Intervention and randomised follow up less than 6 months

Study	Reason for exclusion
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 one author)
Bloomgarden 1987	Multifactorial intervention
Bonnema 1995	No appropriate control group (and not low fat vs modified fat)
Bosaeus 1992	Intervention and randomised follow up less than 6 months
Boyar 1988	Not randomised
Brensike 1982	No appropriate control group (and not low fat vs modified fat)
Broekmans 2003	Intervention is not dietary fat modification or low fat diet
Brown 1984	No appropriate control group (and not low fat vs modified fat)
Bruce 1994	No appropriate control group (and not low fat vs modified fat)
Bruno 1983	Multifactorial intervention
Butcher 1990	Intervention and randomised follow up less than 6 months
Butowski 1998	Not randomised
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)
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
Chicago CPEP 1977	Not randomised
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

Study	Reason for exclusion
Cohen 1991	Intervention is not dietary fat modification or low fat diet
Cole 1988	Intervention and randomised follow up less than 6 months
Colquhoun 1990	Intervention and randomised follow up less than 6 months
Consolazio 1946	Intervention and randomised follow up less than 6 months
Cox 1996	Multifactorial intervention
Croft 1986	Intervention is not dietary fat modification or low fat diet
Crouch 1986	Not randomised
Da Qing IGT 1997	Intervention is 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
Delahanty 2001	No appropriate control group (and not low fat vs modified fat)
Delius 1969	Intervention is not dietary fat modification or low fat diet
Demark 1990	Intervention and randomised follow up less than 6 months
Dengel 1995	No appropriate control group (and not low fat vs modified fat)
Denke 1994	Intervention and randomised follow up less than 6 months
Diabetes CCT 1995	Intervention is not dietary fat modification or low fat diet
DIET 1998	Multifactorial intervention
Ding 1992	Intervention and randomised follow up less than 6 months
Dobs 1991	No appropriate control group (and not low fat vs modified fat)
Duffield 1982	Multifactorial intervention
Dullaart 1997	Not randomised
Eating Patterns 1997	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)

Study	Reason for exclusion
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)
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
Finckenor 2000	Not randomised
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
Fleming 2002	No appropriate control group (and not low fat vs modified fat)
Fortmann 1988	Intervention is not dietary fat modification or low fat diet
Foster 2003	Weight reduction in one arm but not the other
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
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

Study	Reason for exclusion
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
Haynes 1984	Intervention is not dietary fat modification or low fat diet
Heber 1991	Intervention and randomised follow up less than 6 months
Heine 1989	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
Hellenius Diet & Ex 95	The study aimed for weight loss in one arm and not in the comparison arm
Hellenius Diet 1995	The study aimed for weight loss in one arm and not in the comparison arm
Heller 1993	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one 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 one author)
Hood 1965	Not randomised
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 one author)
Iacono 1981	Not randomised, Intervention and randomised follow up less than 6 months
IMPACT 1995	Multifactorial intervention
Ishikawa 1995	Not randomised
Iso 1991	No appropriate control group (and not low fat vs modified fat)
Ives 1993	Multifactorial intervention
Jalkanen 1991	Multifactorial intervention
Jepson 1969	Not randomised
Jerusalem Nut 1992	Intervention and randomised follow up less than 6 months

Study	Reason for exclusion
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 1995a	Not randomised
Katzel 1995b	Intervention is not dietary fat modification or low fat diet
Kawamura 1993	Intervention and randomised follow up less than 6 months
Keidar 1988	Intervention and randomised follow up less than 6 months
Kempner 1948	No appropriate control group (and not low fat vs modified fat)
Keys 1952	Not randomised
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 one author)
King 2000	Intervention and randomised follow up less than 6 months
Kingsbury 1961	Intervention and randomised follow up less than 6 months
Kohler 1986	Not randomised
Koopman 1990	Intervention and randomised follow up less than 6 months
Korhonen 2003	Multifactorial intervention
Kriketos 2001	Intervention and randomised follow up less than 6 months
Kris 1994	Intervention and randomised follow up less than 6 months
Kristal 1997	Multifactorial intervention
Kromhout 1987	No appropriate control group (and not low fat vs modified fat)
Kummel 2008	Intervention is not dietary fat modification or low fat diet
Laitinen 1993	Multifactorial intervention

Study	Reason for exclusion
Laitinen 1994	Multifactorial intervention
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
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 1991	Not randomised
Little 2004	Intervention is 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 is not dietary fat modification or low fat diet
Lysikova 2003	Intervention and randomised follow up less than 6 months
Macdonald 1972	Intervention and randomised follow up less than 6 months
Mansel 1990	Intervention is not dietary fat modification or low fat diet
Marckmann 1993	Not randomised
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
McCarron 1997	Intervention and randomised follow up less than 6 months
McCarron 2001	Intervention is not dietary fat modification or low fat diet
McManus 2001	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one 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
Mensink 1987	Intervention and randomised follow up less than 6 months

Study	Reason for exclusion
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
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 one author)
Milne 1994	No appropriate control group (and not low fat vs modified fat) - the high CHO diet is neither 'usual' or 'low fat' to compare with the modified fat diet
Minnesota HHP 1990	No appropriate control group (and not low fat vs modified fat)
Mokuno 1988	Intervention and randomised follow up less than 6 months
Moreno 1994	Not randomised
Morrison 1950	Not randomised
Morrison 1951	Not randomised
Morrison 1960	Not randomised
Mortensen 1983	Intervention and randomised follow up less than 6 months
MRFIT substudy 1986	Intervention and randomised follow up less than 6 months
MSDELTA 1995	Intervention and randomised follow up less than 6 months
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
NAS 1987	Intervention and randomised follow up less than 6 months
NCEP weight 1991	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
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 one author)

Study	Reason for exclusion
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)
O'Brien 1976	Intervention and randomised follow up less than 6 months
ODES 2006	The study aimed for weight loss in one arm and not in the other arm
Oldroyd 2001	Multifactorial intervention
ORIGIN 2008	Intervention is not dietary fat modification or low fat diet
Oslo Study 2004	Multifactorial intervention
Pascale 1995	Multifactorial intervention
PEP 2001	Multifactorial intervention
PHYLLIS 1993	No appropriate control group (and not low fat vs modified fat)
Pilkington 1960	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
Pritchard 2002	The study aimed for weight loss in one 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 one 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 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 one author)
Roman CHD prev 1986	Multifactorial intervention
Rose 1987	No appropriate control group (and not low fat vs modified fat)
Sandstrom 1992	Not randomised
Sasaki 2000	Not randomised

Study	Reason for exclusion
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
Singh 1990	Not randomised
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 one arm and not in the comparison arm
Staff HHP 1994	Not randomised
Stanford NAP 1997	Intervention and randomised follow up less than 6 months
Stanford Weight 1994	The study aimed for weight loss in one 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)
Sweeney 2004	Intervention is not dietary fat modification or low fat diet
TAIM 1992	Intervention is not dietary fat modification or low fat diet
Take Heart II 1997	Not randomised
Taylor 1991	Not randomised
TOHP I 1992	Multifactorial intervention
TONE 1997	Intervention is not dietary fat modification or low fat diet
Toobert 2003	Multifactorial intervention
Towle 1994	Intervention and randomised follow up less than 6 months
TRANSFACT 2006	Intervention and randomised follow up less than 6 months

Study	Reason for exclusion
Treatwell 1992	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
Tromso Heart 1989	Multifactorial intervention
Turpeinen 1960	Not randomised
UK PDS 1996	No appropriate control group (and not low fat vs modified fat)
Urbach 1952	No appropriate control group (and not low fat vs modified fat)
Uusitupa 1993	Multifactorial intervention
Vavrikova 1958	Intervention and randomised follow up less than 6 months
Wass 1981	Intervention and randomised follow up less than 6 months
Wassertheil 1985	Intervention is not dietary fat modification or low fat diet
WATCH 1999	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
Watts 1988	Intervention and randomised follow up less than 6 months
Weintraub 1992	No appropriate control group (and not low fat vs modified fat)
Westman 2006	Intervention is not dietary fat modification or low fat diet
Weststrate 1998	Intervention and randomised follow up less than 6 months
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 one author)
Wilke 1974	Intervention and randomised follow up less than 6 months
Williams 1990	Intervention is not dietary fat modification or low fat diet
Williams 1992	Intervention is not dietary fat modification or low fat diet
Williams 1994	Intervention is not dietary fat modification or low fat diet
Wilmot 1952	No appropriate control group (and not low fat vs modified fat)
Wing 1998	No appropriate control group (and not low fat vs modified fat)
WOMAN 2007	Lifestyle intervention includes exercise and weight as well as diet
Wood 1988	Intervention is not dietary fat modification or low fat diet
Woollard 2003	Multifactorial intervention including smoking, weight, exercise and alcohol components

Study	Reason for exclusion
Working Well 1996	Multifactorial intervention
Zock 1995	Intervention and randomised follow up less than 6 months

The figure in brackets following the Study ID of each reference is a code for "reason for exclusion". The code is given in full in "Description of Studies section of the text.

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

Barsotti 1991

Methods	RCT
Participants	356 people with hyperlipidaemia
Interventions	Allocated to bezafibrate, not bezafibrate, simvastatin or low fat low cholesterol diet for 4 years
Outcomes	Plaque progression
Notes	Complex paper in Italian, unclear whether cardiovascular events occurred

Bonk 1975

Methods	Trial, unclear if randomised
Participants	300 people who have had a myocardial infarction (Germany)
Interventions	Intensive change of nutrition vs. usual diet (both with comprehensive medical care)
Outcomes	Return to work
Notes	No answer to requests to clarify the way that participants were allocated to intervention or control

Brehm 2009

Methods	RCT
Participants	124 overweight or obese people with type 2 diabetes
Interventions	Low fat vs modified fat diet
Outcomes	Weight and glycaemic control
Notes	LH has recently contacted the authors about whether any deaths or CV events occurred

Canadian DBCP 1997

Methods	RCT

Canadian DBCP 1997 *(Continued)*

Participants	4690 women with mammographic densities >50% breast area (Canada)
Interventions	Control: self-selected diet (no advice) vs intervention: total fat 15%E, protein 20%E, CHO 65%E, followed up for 10 years style: diet advice
Outcomes	Stated trial outcomes: incidence of breast cancer
Notes	No answer to requests for data on deaths or health events

DEER 1998

Methods	RCT
Participants	180 Postmenopausal women and 197 men with low HDL and raised LDL
Interventions	NCEP step 2 diet vs aerobic exercise vs diet and exercise vs no intervention, all for 1 year
Outcomes	lipids and diet
Notes	No answer to requests for data on deaths or health events

Diet & Hormone Study 2003

Methods	RCT
Participants	213 healthy women aged 20-40 years (USA)
Interventions	Low fat, high fruit, vegetable and fibre diet vs usual diet, for 1 year
Outcomes	Hormone levels
Notes	No answer to requests for data on deaths or health events

DIRECT 2009

Methods	RCT
Participants	322 moderately obese people
Interventions	Low fat restricted-calorie diet vs modified fat restricted-calorie diet, for 24 months
Outcomes	Weight and safety
Notes	LH has recently contacted the authors about whether any deaths or CV events occurred

Esposito 2004

Methods	RCT
Participants	180 men and women with metabolic syndrome (Italy)
Interventions	Mediterranean style diet vs low fat diet, for 2 years
Outcomes	Remaining metabolic syndrome, inflammatory markers
Notes	No answer to requests for data on deaths or health events

Koranyi 1963

Methods	Intervention study, unclear if randomised
Participants	Nearly 250 people with severe coronary stenosis (mostly post MI) acrued since 1957 (Hungary)
Interventions	Low fat diet (35-40g fat/d) vs Modified fat (50g edible oil but no butter, lard etc/d) vs Modified fat 2 (50g fat/d made up of both edible oil and butter, lard etc) vs control (no intervention)
Outcomes	Mortality rates (8.6% in low fat diet, 19.7% controls, other groups not reported, nor numbers of participants in each group)
Notes	

Metroville Health 2003

Methods	RCT
Participants	403 middle class urban households (Pakistan)
Interventions	Counselling on changing cooking fats and reducing salt vs. usual diet
Outcomes	Dietary intake
Notes	No answer to requests for data on deaths or health events

Mojonnier 1980

Methods	RCT
Participants	418 people with hypercholesterolaemia (USA)
Interventions	Self-teaching vs group-teaching vs individual teaching vs mixed teaching (all teaching eating with reduced and modified dietary fat) vs usual care, for 9 months
Outcomes	Dietary intake and total cholesterol
Notes	No answer to requests for data on deaths or health events

Naglak 2000

Methods	RCT
Participants	153 people within 16 primary care practices - cluster randomised by practice (USA)
Interventions	Home based healthy heart programme vs usual care
Outcomes	Dietary intake
Notes	Have written to ask whether any deaths or CV events occurred, but no reply

OLIVE 1997

Methods	RCT
Participants	180 people with CHD documented by angiography
Interventions	Mediterranean diet vs low fat diet, for 2.5 years
Outcomes	Angiographic endpoints
Notes	No answer to requests for data on deaths or health events

Tapsell 2004

Methods	RCT
Participants	86 people with type II diabetes (Australia)
Interventions	Low fat diet vs modified fat diet, for 1 year
Outcomes	Uptake of advice
Notes	No answer to questions about whether any deaths or CV events occurred.

Verheiden 2003

Methods	RCT
Participants	143 patients at risk of CVD in Dutch general practices (Netherlands)
Interventions	9 family practices were randomised to dietary advice according to stages of change vs. usual care for 12 months
Outcomes	Fat intake and lipids
Notes	No answer to requests for data on deaths or health events

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

PREDIMED 2008

Trial name or title	PREDIMED
Methods	RCT
Participants	372 people at high cardiovascular risk
Interventions	Low fat diet vs. modified fat diets (2), for 4 years
Outcomes	Various CVD risk factors
Starting date	2003
Contact information	Professor Ramon Estruch, Department of Internal Medicine, University of Barcelona
Notes	Authors replied that mortality and morbidity data will not be analysed until 2011

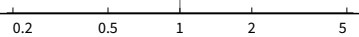
DATA AND ANALYSES

Comparison 1. fat modification or reduction vs usual diet - primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	21	71790	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
1.1 Modified fat intake	8	11441	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.88, 1.18]
1.2 Reduced fat intake	10	58130	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.04]
1.3 Reduced and modified fat intake	3	2219	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.23]
2 Cardiovascular mortality	16	65978	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
2.1 Modified fat intake	6	10788	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.15]
2.2 Reduced fat intake	7	52971	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.13]
2.3 Reduced and modified fat intake	3	2219	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.27]
3 Combined cardiovascular events	23	65508	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.77, 0.96]
3.1 Modified fat intake	9	11660	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.02]
3.2 Reduced fat intake	8	50655	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.08]
3.3 Reduced and modified fat intake	6	3193	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.57, 1.03]

Analysis 1.1. Comparison 1 fat modification or reduction vs usual diet - primary outcomes, Outcome 1 Total mortality.

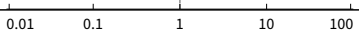
Study or subgroup	reduced or modified fat n/N	usual diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Modified fat intake					
Rose 1965	8/54	1/26		0.08%	3.85[0.51,29.2]
Veterans Admin 1969	174/424	177/422		12.73%	0.98[0.83,1.15]
Oslo Diet-Heart 1966	48/206	65/206		3.2%	0.74[0.54,1.02]
NDHS Faribault 1968	4/143	0/52		0.04%	3.31[0.18,60.49]
MRC 1968	28/199	31/194		1.47%	0.88[0.55,1.41]
Minnesota Coron women1989	111/2344	95/2320		4.54%	1.16[0.88,1.51]
Minnesota Coron men 1989	158/2197	153/2196		7.1%	1.03[0.83,1.28]
Sydney Diet-Heart 1978	39/221	28/237		1.61%	1.49[0.95,2.34]
Subtotal (95% CI)	**5788**	**5653**		**30.78%**	**1.02[0.88,1.18]**
Total events: 570 (reduced or modified fat), 550 (usual diet)					
Heterogeneity: Tau^2=0.01; Chi^2=10.53, df=7(P=0.16); I^2=33.55%					
Test for overall effect: Z=0.24(P=0.81)					
1.1.2 Reduced fat intake					
Ball 1965	20/123	24/129		1.12%	0.87[0.51,1.5]
WINS 2006	15/975	19/1462		0.72%	1.18[0.6,2.32]
Black 1994	1/66	2/67		0.06%	0.51[0.05,5.46]
Polyp Prevention 1996	42/1037	46/1042		1.95%	0.92[0.61,1.38]
Ley 2004	2/88	6/88		0.13%	0.33[0.07,1.61]
BRIDGES 2001	0/50	1/56		0.03%	0.37[0.02,8.94]
PREMIER 2003	0/269	1/268		0.03%	0.33[0.01,8.12]
DO IT 2006	17/246	21/241		0.86%	0.79[0.43,1.47]
WHI without CVD 2006	950/19541	1454/29294		51.29%	0.98[0.9,1.06]
WHEL 2007	155/1537	160/1551		7.44%	0.98[0.79,1.21]
Subtotal (95% CI)	**23932**	**34198**		**63.63%**	**0.97[0.9,1.04]**
Total events: 1202 (reduced or modified fat), 1734 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=3.86, df=9(P=0.92); I^2=0%					
Test for overall effect: Z=0.81(P=0.42)					
1.1.3 Reduced and modified fat intake					
DART 1989	111/1018	113/1015		5.34%	0.98[0.76,1.25]
STARS 1992	1/27	3/28		0.07%	0.35[0.04,3.12]
Sondergaard 2003	4/68	4/63		0.18%	0.93[0.24,3.55]
Subtotal (95% CI)	**1113**	**1106**		**5.59%**	**0.97[0.76,1.23]**
Total events: 116 (reduced or modified fat), 120 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=0.29(P=0.78)					
Total (95% CI)	**30833**	**40957**		**100%**	**0.98[0.93,1.04]**
Total events: 1888 (reduced or modified fat), 2404 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=15.52, df=20(P=0.75); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Chi^2=0.34, df=1 (P=0.85), I^2=0%					



Favours altered fat diet — Favours control

Analysis 1.2. Comparison 1 fat modification or reduction vs usual diet - primary outcomes, Outcome 2 Cardiovascular mortality.

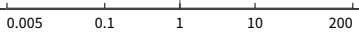
Study or subgroup	reduced or modified fat n/N	usual diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Modified fat intake					
Rose 1965	8/54	1/26		0.25%	3.85[0.51,29.2]
Veterans Admin 1969	57/424	81/422		10.79%	0.7[0.51,0.96]
Oslo Diet-Heart 1966	38/206	52/206		7.57%	0.73[0.5,1.06]
MRC 1968	27/199	25/194		4.06%	1.05[0.63,1.75]
Minnesota Coron men 1989	92/2197	94/2196		13.18%	0.98[0.74,1.3]
Minnesota Coron women1989	65/2344	53/2320		8.13%	1.21[0.85,1.74]
Subtotal (95% CI)	**5424**	**5364**		**43.97%**	**0.92[0.73,1.15]**
Total events: 287 (reduced or modified fat), 306 (usual diet)					
Heterogeneity: Tau^2=0.03; Chi^2=9.13, df=5(P=0.1); I^2=45.22%					
Test for overall effect: Z=0.74(P=0.46)					
1.2.2 Reduced fat intake					
Ball 1965	17/123	20/129		2.92%	0.89[0.49,1.62]
Black 1994	0/66	2/67		0.11%	0.2[0.01,4.15]
Ley 2004	1/88	4/88		0.22%	0.25[0.03,2.19]
DO IT 2006	8/246	10/241		1.25%	0.78[0.31,1.95]
WHI without CVD 2006	170/18633	258/27925		28.07%	0.99[0.81,1.2]
WHI with CVD 2006	43/908	62/1369		7.23%	1.05[0.72,1.53]
WHEL 2007	2/1537	5/1551		0.39%	0.4[0.08,2.08]
Subtotal (95% CI)	**21601**	**31370**		**40.19%**	**0.96[0.82,1.13]**
Total events: 241 (reduced or modified fat), 361 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=4.1, df=6(P=0.66); I^2=0%					
Test for overall effect: Z=0.46(P=0.65)					
1.2.3 Reduced and modified fat intake					
DART 1989	101/1018	100/1015		15.13%	1.01[0.77,1.31]
STARS 1992	1/27	3/28		0.22%	0.35[0.04,3.12]
Sondergaard 2003	3/68	4/63		0.49%	0.69[0.16,2.98]
Subtotal (95% CI)	**1113**	**1106**		**15.84%**	**0.98[0.76,1.27]**
Total events: 105 (reduced or modified fat), 107 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=1.12, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					
Total (95% CI)	**28138**	**37840**		**100%**	**0.94[0.85,1.04]**
Total events: 633 (reduced or modified fat), 774 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=14.72, df=15(P=0.47); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.92), I^2=0%					



Favours altered fat diet Favours control

Analysis 1.3. Comparison 1 fat modification or reduction vs usual diet - primary outcomes, Outcome 3 Combined cardiovascular events.

Study or subgroup	reduced or modified fat n/N	usual diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Modified fat intake					
Veterans Admin 1969	97/424	122/422		8.76%	0.79[0.63,1]
Rose 1965	26/54	11/26		3.39%	1.14[0.67,1.93]
Oslo Diet-Heart 1966	64/206	90/206		8.06%	0.71[0.55,0.92]
NDHS Open 1st mod 1968	4/348	1/170		0.26%	1.95[0.22,17.35]
NDHS Open 2nd Mod 1968	1/112	2/140		0.22%	0.63[0.06,6.8]
MRC 1968	62/199	74/194		7.6%	0.82[0.62,1.07]
Minnesota Coron men 1989	67/2197	78/2196		6.48%	0.86[0.62,1.18]
Minnesota Coron women1989	67/2344	51/2320		5.7%	1.3[0.91,1.86]
Houtsmuller 1979	8/51	30/51		2.28%	0.27[0.14,0.52]
Subtotal (95% CI)	**5935**	**5725**		**42.74%**	**0.82[0.66,1.02]**
Total events: 396 (reduced or modified fat), 459 (usual diet)					
Heterogeneity: Tau^2=0.06; Chi^2=20.43, df=8(P=0.01); I^2=60.85%					
Test for overall effect: Z=1.79(P=0.07)					
1.3.2 Reduced fat intake					
Ball 1965	38/123	42/129		5.64%	0.95[0.66,1.36]
Black 1994	0/66	2/67		0.14%	0.2[0.01,4.15]
Ley 2004	11/88	16/88		2.11%	0.69[0.34,1.4]
Moy 2001	5/117	3/118		0.6%	1.68[0.41,6.87]
PREMIER 2003	0/269	2/268		0.13%	0.2[0.01,4.13]
DO IT 2006	28/246	40/241		4.28%	0.69[0.44,1.07]
WHI without CVD 2006	1132/18633	1777/27925		13.18%	0.95[0.89,1.03]
WHI with CVD 2006	225/908	311/1369		11.16%	1.09[0.94,1.27]
Subtotal (95% CI)	**20450**	**30205**		**37.25%**	**0.97[0.87,1.08]**
Total events: 1439 (reduced or modified fat), 2193 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=8.44, df=7(P=0.3); I^2=17.06%					
Test for overall effect: Z=0.6(P=0.55)					
1.3.3 Reduced and modified fat intake					
NDHS Open 2nd L&M 1968	0/179	2/140		0.13%	0.16[0.01,3.24]
NDHS Open 1st L&M 1968	1/378	1/171		0.16%	0.45[0.03,7.19]
DART 1989	136/1018	147/1015		9.16%	0.92[0.74,1.15]
STARS 1992	8/27	20/28		2.59%	0.41[0.22,0.78]
Sondergaard 2003	40/68	42/63		7.82%	0.88[0.68,1.15]
MeDiet 2002	0/51	3/55		0.14%	0.15[0.01,2.91]
Subtotal (95% CI)	**1721**	**1472**		**20%**	**0.77[0.57,1.03]**
Total events: 185 (reduced or modified fat), 215 (usual diet)					
Heterogeneity: Tau^2=0.04; Chi^2=8.36, df=5(P=0.14); I^2=40.21%					
Test for overall effect: Z=1.77(P=0.08)					
Total (95% CI)	**28106**	**37402**		**100%**	**0.86[0.77,0.96]**
Total events: 2020 (reduced or modified fat), 2867 (usual diet)					
Heterogeneity: Tau^2=0.02; Chi^2=44.3, df=22(P=0); I^2=50.33%					
Test for overall effect: Z=2.71(P=0.01)					
Test for subgroup differences: Chi^2=3.51, df=1 (P=0.17), I^2=42.97%					



Favours altered fat diet — Favours control

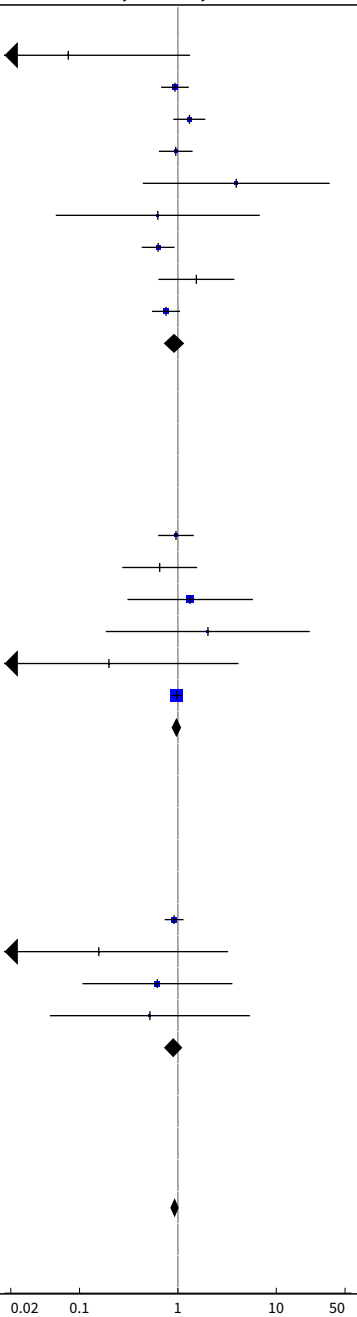
Comparison 2. fat modification or reduction vs usual diet - secondary outcomes

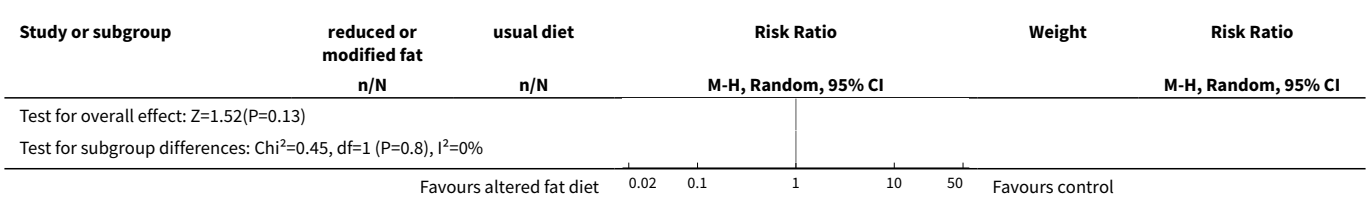
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarctions	19	64891	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.02]
1.1 Modified fat intake	9	11831	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.72, 1.16]
1.2 Reduced fat intake	6	50522	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.08]
1.3 Reduced and modified fat intake	4	2538	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.11]
2 Stroke	11	59853	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.11]
2.1 Modified fat intake	4	10315	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.36, 1.34]
2.2 Reduced fat intake	4	49246	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]
2.3 Reduced and modified fat intake	3	292	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 2.04]
3 Cancer deaths	10	64759	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.06]
3.1 Modified fat intake	3	9903	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.96, 2.21]
3.2 Reduced fat intake	5	52692	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
3.3 Reduced and modified fat intake	2	2164	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.25, 2.61]
4 Cancer diagnoses	12	58847	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.01]
4.1 Modified fat intake	2	1535	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.85, 1.60]
4.2 Reduced fat intake	8	57075	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.02]
4.3 Reduced and modified intake	2	237	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.06, 9.03]
5 Diabetes diagnoses	3	49859	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
5.1 Modified fat intake	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Reduced fat intake	3	49859	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
5.3 Reduced and modified intake	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal MI	13	54883	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.81, 1.12]
6.1 Modified fat intake	6	2672	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.16]
6.2 Reduced fat intake	5	49859	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.80, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Reduced and modified intake	2	2352	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.10]

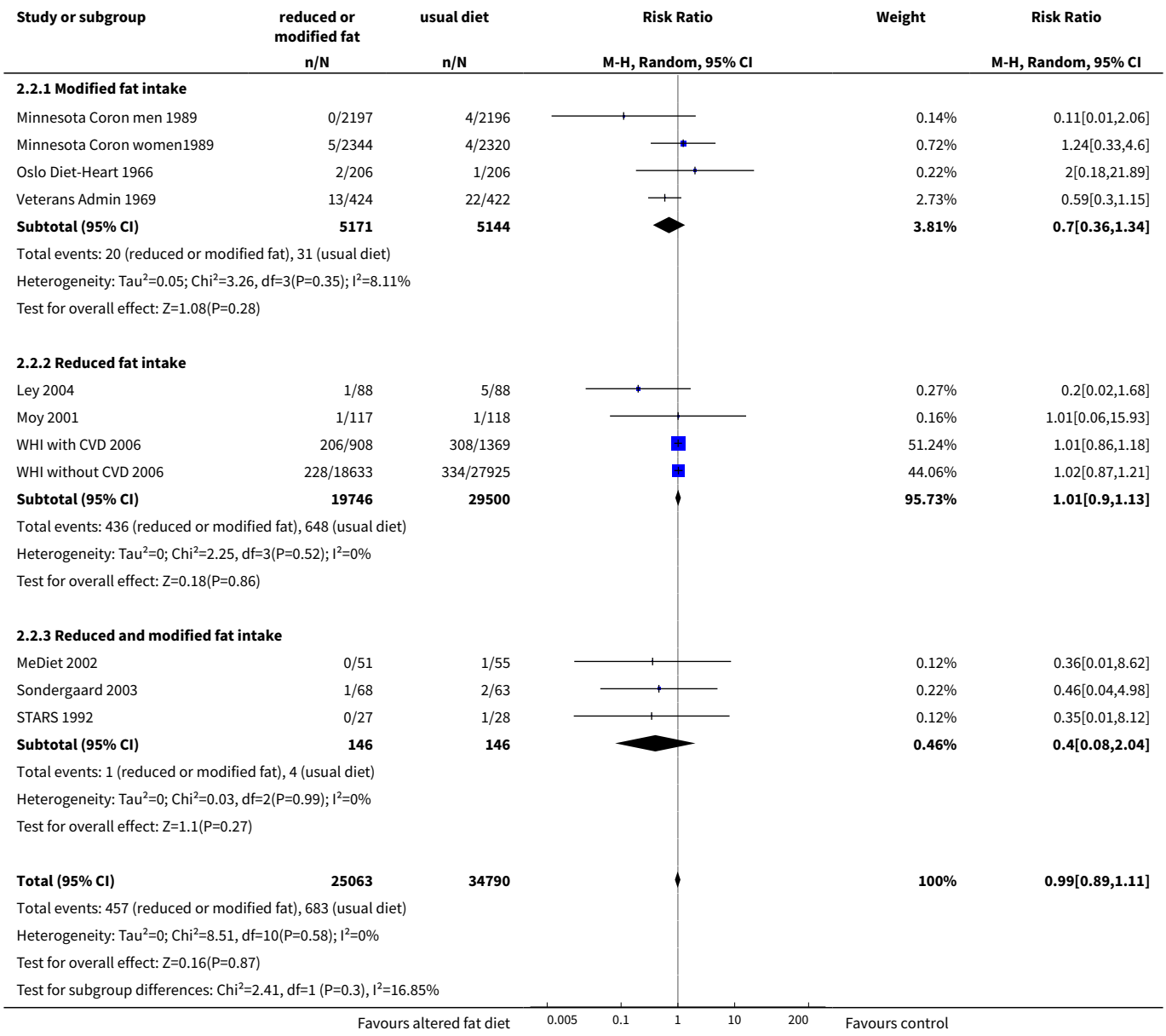
Analysis 2.1. Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 1 Myocardial infarctions.

Study or subgroup	reduced or modified fat n/N	usual diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Modified fat intake					
Houtsmuller 1979	0/51	6/51		0.12%	0.08[0,1.33]
Minnesota Coron men 1989	69/2197	74/2196		8.58%	0.93[0.68,1.29]
Minnesota Coron women1989	62/2344	47/2320		6.53%	1.31[0.9,1.9]
MRC 1968	39/199	40/194		5.95%	0.95[0.64,1.41]
NDHS Open 1st mod 1968	4/348	1/341		0.21%	3.92[0.44,34.89]
NDHS Open 2nd Mod 1968	1/112	2/140		0.17%	0.63[0.06,6.8]
Oslo Diet-Heart 1966	34/206	54/206		6.27%	0.63[0.43,0.92]
Rose 1965	16/54	5/26		1.24%	1.54[0.63,3.75]
Veterans Admin 1969	54/424	71/422		8.36%	0.76[0.55,1.05]
Subtotal (95% CI)	**5935**	**5896**		**37.44%**	**0.91[0.72,1.16]**
Total events: 279 (reduced or modified fat), 300 (usual diet)					
Heterogeneity: Tau^2=0.05; Chi^2=14.42, df=8(P=0.07); I^2=44.51%					
Test for overall effect: Z=0.73(P=0.46)					
2.1.2 Reduced fat intake					
Ball 1965	31/123	34/129		5.3%	0.96[0.63,1.45]
DO IT 2006	8/246	12/241		1.27%	0.65[0.27,1.57]
Ley 2004	4/88	3/88		0.46%	1.33[0.31,5.78]
Moy 2001	2/117	1/118		0.17%	2.02[0.19,21.94]
PREMIER 2003	0/269	2/268		0.11%	0.2[0.01,4.13]
WHI without CVD 2006	435/19541	671/29294		38.08%	0.97[0.86,1.09]
Subtotal (95% CI)	**20384**	**30138**		**45.39%**	**0.97[0.86,1.08]**
Total events: 480 (reduced or modified fat), 723 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=2.37, df=5(P=0.8); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
2.1.3 Reduced and modified fat intake					
DART 1989	132/1018	144/1015		16.55%	0.91[0.73,1.14]
NDHS Open 2nd L&M 1968	0/179	2/140		0.11%	0.16[0.01,3.24]
Sondergaard 2003	2/68	3/63		0.32%	0.62[0.11,3.58]
STARS 1992	1/27	2/28		0.18%	0.52[0.05,5.39]
Subtotal (95% CI)	**1292**	**1246**		**17.16%**	**0.9[0.72,1.11]**
Total events: 135 (reduced or modified fat), 151 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=1.69, df=3(P=0.64); I^2=0%					
Test for overall effect: Z=0.99(P=0.32)					
Total (95% CI)	**27611**	**37280**		**100%**	**0.93[0.84,1.02]**
Total events: 894 (reduced or modified fat), 1174 (usual diet)					
Heterogeneity: Tau^2=0; Chi^2=19.19, df=18(P=0.38); I^2=6.19%					



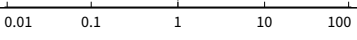


Analysis 2.2. Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 2 Stroke.



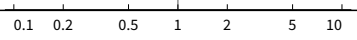
Analysis 2.3. Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 3 Cancer deaths.

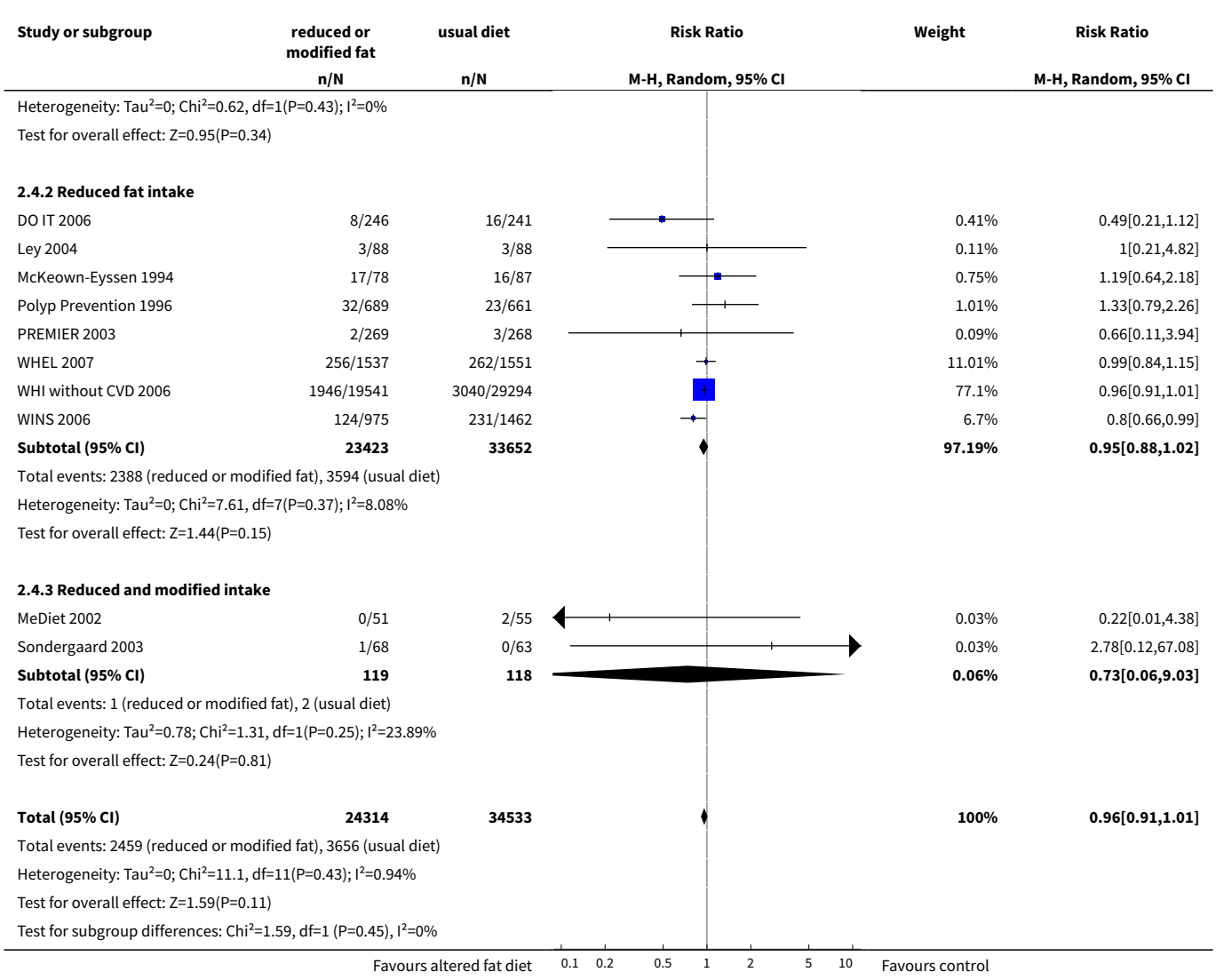
Study or subgroup	reduced or modified fat n/N	usual diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Modified fat intake					
Minnesota Coron men 1989	16/2197	12/2196		0.97%	1.33[0.63,2.81]
Minnesota Coron women1989	7/2344	8/2320		0.52%	0.87[0.31,2.38]
Veterans Admin 1969	31/424	17/422		1.62%	1.81[1.02,3.23]
Subtotal (95% CI)	**4965**	**4938**		**3.11%**	**1.46[0.96,2.21]**
Total events: 54 (reduced or modified fat), 37 (usual diet)					
Heterogeneity: Tau²=0; Chi²=1.63, df=2(P=0.44); I²=0%					
Test for overall effect: Z=1.77(P=0.08)					
2.3.2 Reduced fat intake					
BRIDGES 2001	0/50	1/56		0.05%	0.37[0.02,8.94]
DO IT 2006	9/246	10/241		0.69%	0.88[0.36,2.13]
Ley 2004	1/88	2/88		0.09%	0.5[0.05,5.41]
WHEL 2007	139/1537	150/1551		11.13%	0.94[0.75,1.16]
WHI without CVD 2006	950/19541	1454/29294		84.53%	0.98[0.9,1.06]
Subtotal (95% CI)	**21462**	**31230**		**96.5%**	**0.97[0.9,1.05]**
Total events: 1099 (reduced or modified fat), 1617 (usual diet)					
Heterogeneity: Tau²=0; Chi²=0.85, df=4(P=0.93); I²=0%					
Test for overall effect: Z=0.74(P=0.46)					
2.3.3 Reduced and modified fat intake					
DART 1989	4/1018	6/1015		0.34%	0.66[0.19,2.35]
Sondergaard 2003	1/68	0/63		0.05%	2.78[0.12,67.08]
Subtotal (95% CI)	**1086**	**1078**		**0.39%**	**0.81[0.25,2.61]**
Total events: 5 (reduced or modified fat), 6 (usual diet)					
Heterogeneity: Tau²=0; Chi²=0.67, df=1(P=0.41); I²=0%					
Test for overall effect: Z=0.36(P=0.72)					
Total (95% CI)	**27513**	**37246**		**100%**	**0.98[0.91,1.06]**
Total events: 1158 (reduced or modified fat), 1660 (usual diet)					
Heterogeneity: Tau²=0; Chi²=6.77, df=9(P=0.66); I²=0%					
Test for overall effect: Z=0.43(P=0.66)					
Test for subgroup differences: Chi²=3.62, df=1 (P=0.16), I²=44.68%					



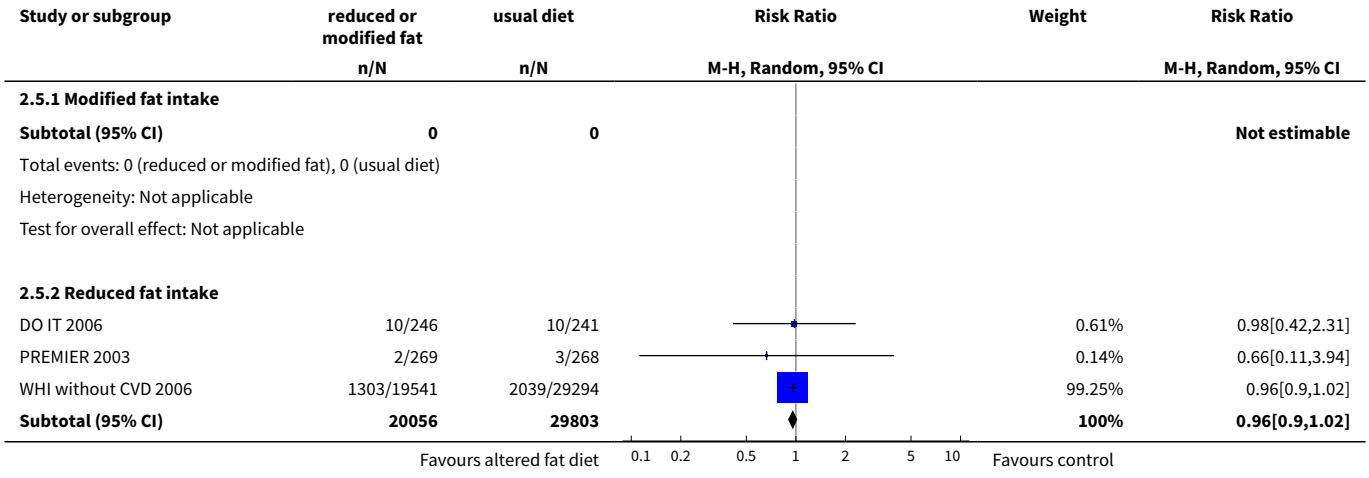
Analysis 2.4. Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 4 Cancer diagnoses.

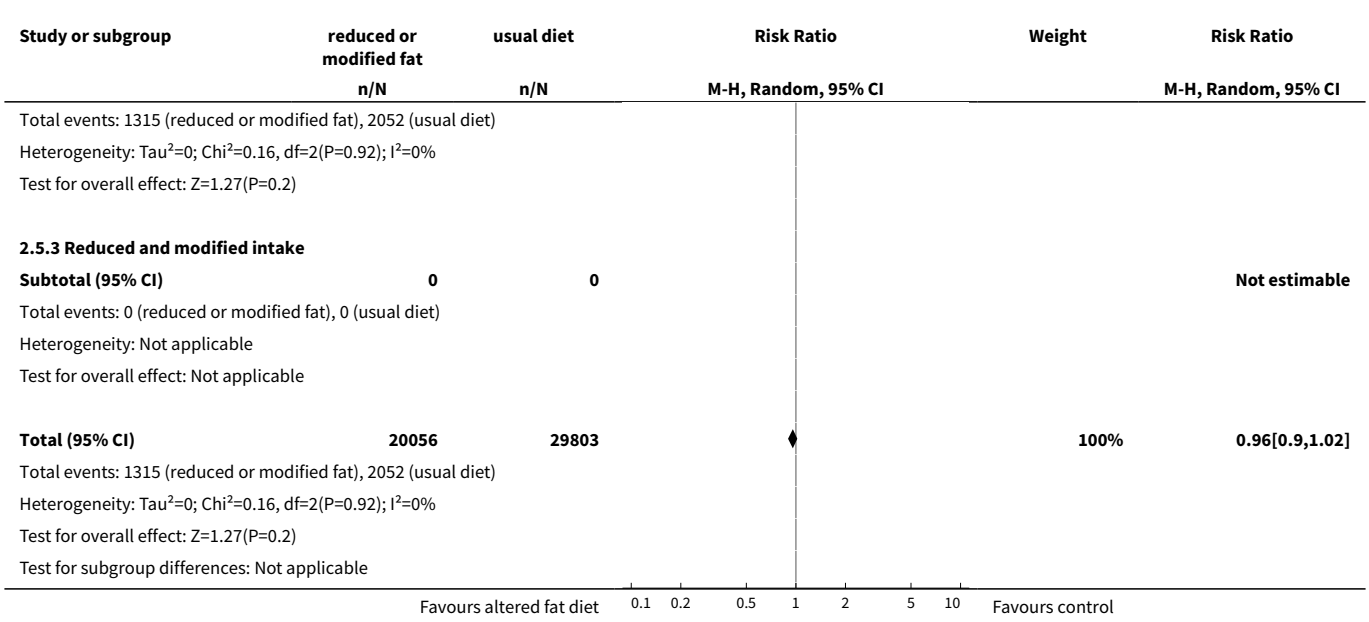
Study or subgroup	reduced or modified fat n/N	usual diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Modified fat intake					
NDHS Open 1st mod 1968	0/348	1/341		0.03%	0.33[0.01,7.99]
Veterans Admin 1969	70/424	59/422		2.73%	1.18[0.86,1.62]
Subtotal (95% CI)	**772**	**763**		**2.76%**	**1.17[0.85,1.6]**
Total events: 70 (reduced or modified fat), 60 (usual diet)					



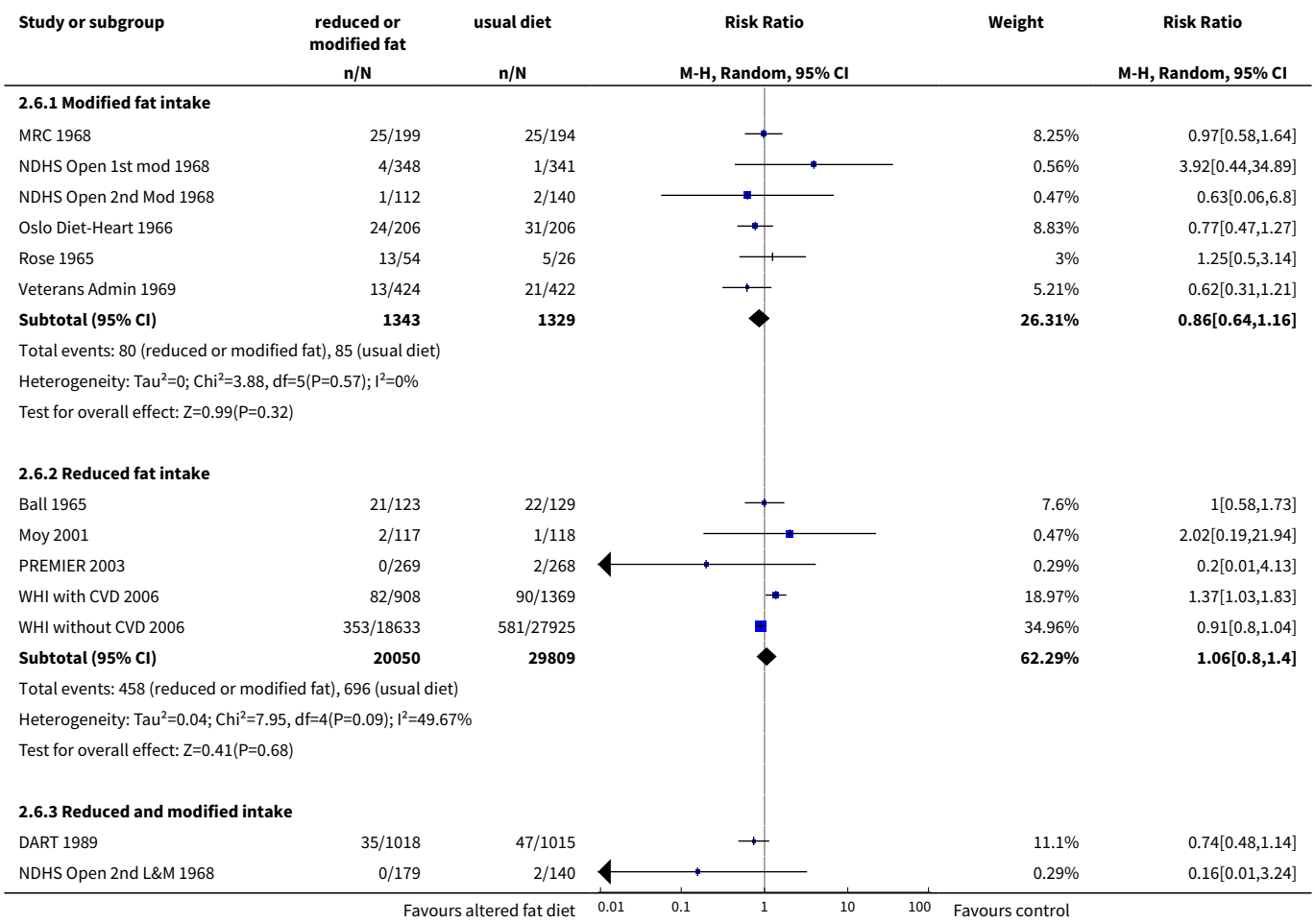


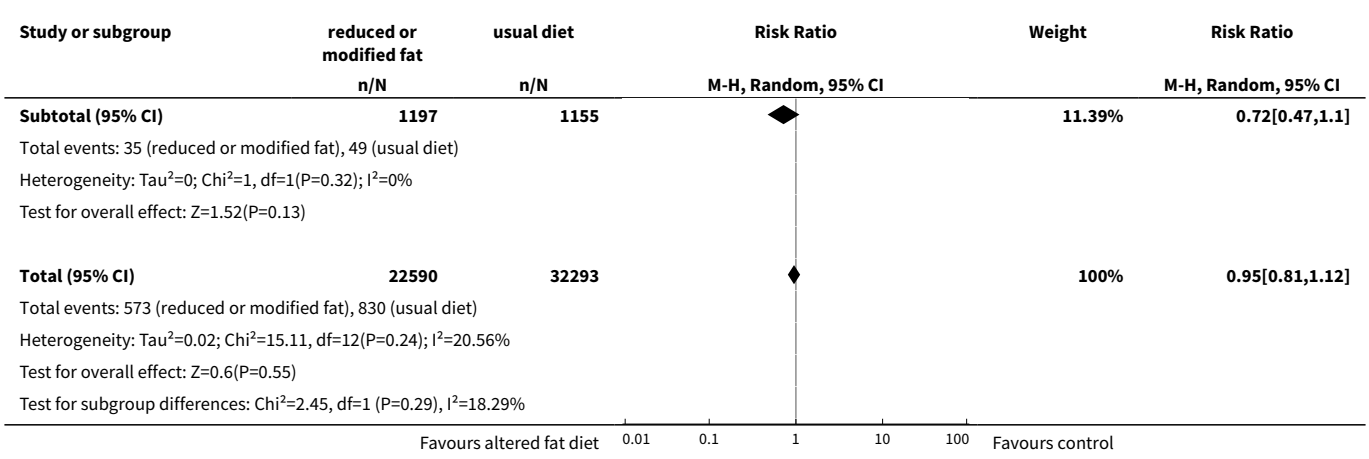
Analysis 2.5. Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 5 Diabetes diagnoses.





Analysis 2.6. Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 6 Non-fatal MI.





Comparison 3. fat modification or reduction vs usual diet - tertiary outcomes

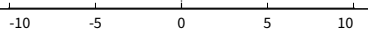
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight, kg	18		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Modified fat intake	2	99	Mean Difference (IV, Random, 95% CI)	-1.10 [-3.14, 0.93]
1.2 Reduced fat intake	16	11058	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.37, -0.30]
1.3 Reduced and modified fat intake	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 BMI, kg/m2	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Modified fat intake	2	116	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.99, 0.31]
2.2 Reduced fat intake	10	5972	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.72, -0.23]
2.3 Reduced and modified fat intake	2	111	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.30, 0.91]
3 LDL cholesterol, mmol/L	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Modified fat intake	2	116	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.47, 0.07]
3.2 Reduced fat intake	14	6971	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.14, -0.05]
3.3 Reduced and modified fat intake	4	627	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.35, -0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 HDL cholesterol, mmol/Lkg	22		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Modified fat intake	3	152	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.18, 0.09]
4.2 Reduced fat intake	15	7082	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
4.3 Reduced and modified fat intake	4	2073	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
5 Total cholesterol, mmol/L	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Modified fat intake	8	2280	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.60, -0.28]
5.2 Reduced fat intake	15	7602	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.14, -0.05]
5.3 Reduced and modified fat intake	5	2131	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.47, -0.04]
6 Triglycerides, mmol/L	21		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Modified fat intake	5	706	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.22, -0.00]
6.2 Reduced fat intake	13	6875	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.00, 0.00]
6.3 Reduced and modified fat intake	3	218	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.53, -0.00]
7 Systolic Blood Pressure, mmHg	7	4059	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.61, 0.28]
7.1 Modified fat intake	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Reduced fat intake	6	3981	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.52, 0.40]
7.3 Reduced and modified fat intake	1	78	Mean Difference (IV, Random, 95% CI)	-5.08 [-11.22, 1.06]
8 Diastolic Blood Pressure, mmHg	7	3621	Mean Difference (IV, Random, 95% CI)	-0.40 [1.00, 0.20]
8.1 Modified fat intake	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Reduced fat intake	6	3543	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.96, 0.26]
8.3 Reduced and modified fat intake	1	78	Mean Difference (IV, Random, 95% CI)	-2.31 [-6.20, 1.58]

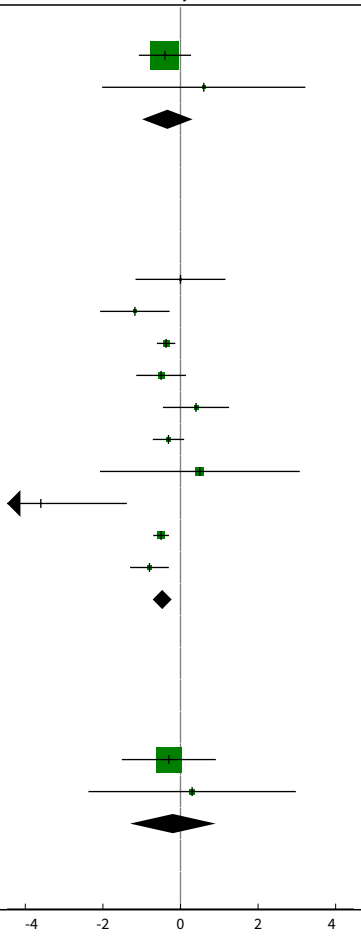
Analysis 3.1. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 1 Weight, kg.

Study or subgroup	Reduced or modified fat N	Reduced or modified fat Mean(SD)	Control or usual diet N	Control or usual diet Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 Modified fat intake							
Due Mod fat 2008	39	2.5 (4.5)	24	3.8 (4)		91.41%	-1.3[-3.43,0.83]
Dullaart 1992	16	77 (10)	20	76 (11.2)		8.59%	1[-5.94,7.94]
Subtotal ***	**55**		**44**			**100%**	**-1.1[-3.14,0.93]**
Heterogeneity: Tau^2=0; Chi^2=0.39, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=1.06(P=0.29)							
3.1.2 Reduced fat intake							
BDIT Pilot Studies 1996	76	64.9 (11.2)	81	64.1 (9.6)		2.31%	0.8[-2.47,4.07]
BRIDGES 2001	48	0.1 (4.9)	46	0.5 (4.1)		5.66%	-0.4[-2.21,1.41]
CARMEN 2000	159	-1.4 (3.4)	77	0.8 (4.1)		9.71%	-2.17[-3.23,-1.11]
Due Low fat 2008	43	2.2 (4.4)	24	3.8 (4)		4.75%	-1.6[-3.66,0.46]
Lean 1997	42	-5.6 (5)	40	-6.8 (5.2)		4.35%	1.2[-0.99,3.39]
Ley 2004	51	1.1 (4.6)	52	1.3 (4.9)		5.57%	-0.2[-2.03,1.63]
MSFAT 1997	40	-0.1 (2.4)	36	0.5 (2.2)		9.97%	-0.54[-1.56,0.48]
Nutrition & Breast Health	47	67.3 (13.8)	50	66.4 (12)		1.02%	0.9[-4.26,6.06]
Ole Study 2002	14	-2.5 (3)	14	-3.9 (3.3)		4.01%	1.36[-0.96,3.68]
Polyp Prevention 1996	943	-0.6 (5.2)	943	0.3 (5.2)		13.88%	-0.96[-1.43,-0.49]
PREMIER 2003	241	-4.3 (7.4)	235	-3.8 (6.1)		8.67%	-0.5[-1.72,0.72]
Seppelt 1996	35	70.3 (7.4)	32	71.9 (10)		1.46%	-1.6[-5.84,2.64]
Simon 1997	34	63.4 (11.1)	38	71.9 (11.7)		0.98%	-8.5[-13.77,-3.23]
WHEL 2007	1308	74.1 (19.5)	1313	73.7 (19.2)		7.14%	0.4[-1.08,1.88]
WHI without CVD 2006	1133	-0.7 (9)	1699	0.6 (9.2)		12.43%	-1.3[-1.98,-0.62]
WINS 2006	854	70.6 (14.9)	1310	72.8 (15.7)		8.09%	-2.2[-3.51,-0.89]
Subtotal ***	**5068**		**5990**			**100%**	**-0.83[-1.37,-0.3]**
Heterogeneity: Tau^2=0.49; Chi^2=32.37, df=15(P=0.01); I^2=53.66%							
Test for overall effect: Z=3.03(P=0)							
3.1.3 Reduced and modified fat intake							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



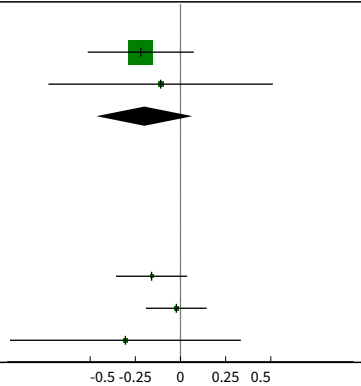
Analysis 3.2. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 2 BMI, kg/m2.

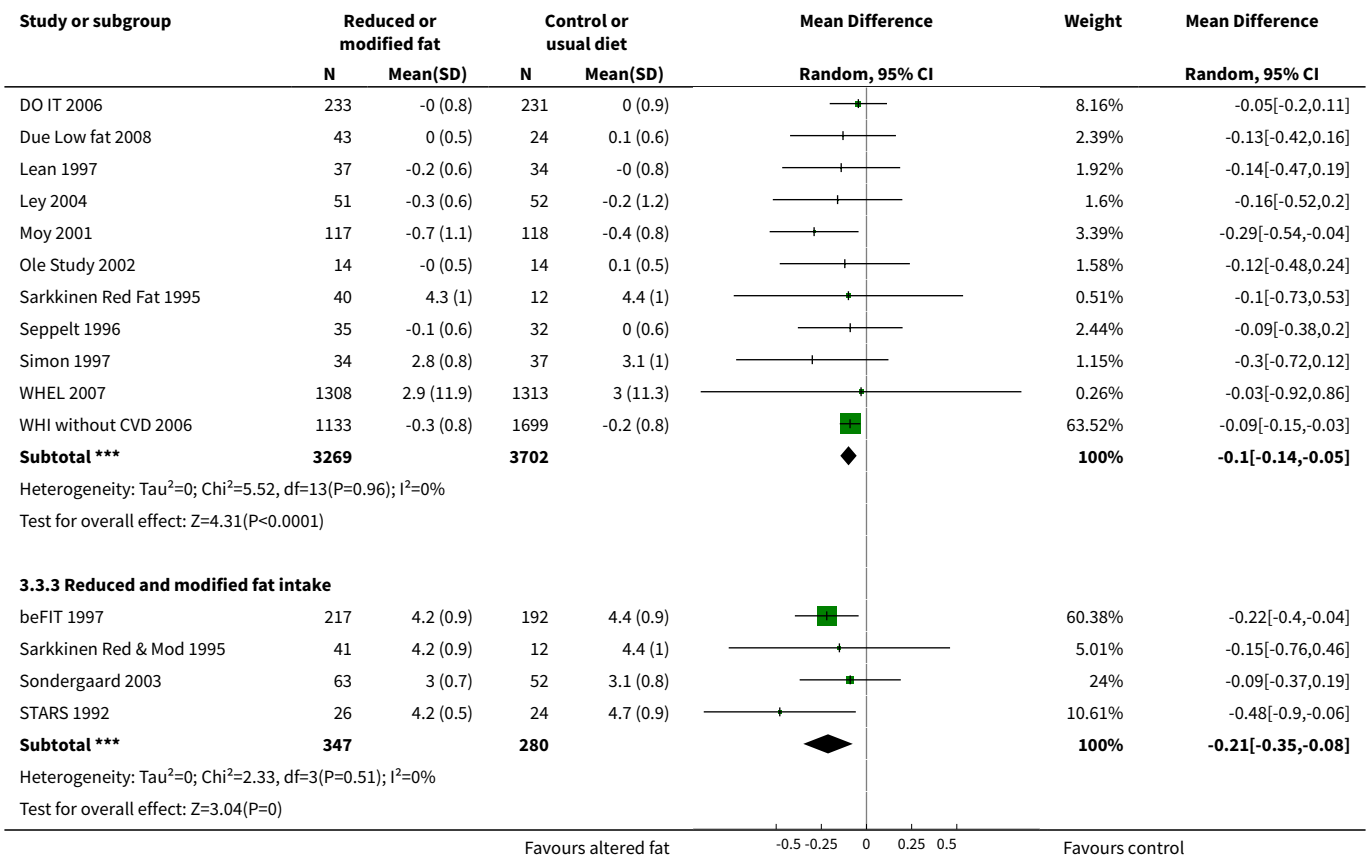
Study or subgroup	Reduced or modified fat N	Mean(SD)	Control or usual diet N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.2.1 Modified fat intake							
Due Mod fat 2008	39	0.8 (1.4)	24	1.2 (1.3)		93.83%	-0.4[-1.07,0.27]
Sarkkinen Fat Mod 1995	41	26.3 (3.6)	12	25.7 (4.2)		6.17%	0.6[-2.02,3.22]
Subtotal ***	**80**		**36**			**100%**	**-0.34[-0.99,0.31]**
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%							
Test for overall effect: Z=1.02(P=0.31)							
3.2.2 Reduced fat intake							
BDIT Pilot Studies 1996	76	24.3 (3.8)	81	24.3 (3.6)		3.81%	0[-1.16,1.16]
CARMEN MS sub-study 2002	18	-0.8 (1.4)	8	0.4 (0.9)		5.83%	-1.17[-2.07,-0.28]
DO IT 2006	233	-0.2 (1.3)	231	0.2 (1.3)		21.57%	-0.37[-0.61,-0.13]
Due Low fat 2008	43	0.7 (1.3)	24	1.2 (1.3)		9.45%	-0.5[-1.14,0.14]
Lean 1997	42	-2.2 (1.8)	40	-2.6 (2.1)		6.3%	0.4[-0.45,1.25]
Moy 2001	117	-0.1 (1)	118	0.2 (2)		15.55%	-0.31[-0.71,0.09]
Sarkkinen Red Fat 1995	40	26.2 (3.2)	12	25.7 (4.2)		0.87%	0.5[-2.07,3.07]
Simon 1997	34	23.8 (4.7)	38	27.4 (4.9)		1.16%	-3.6[-5.82,-1.38]
WHI without CVD 2006	1133	-0.2 (2.7)	1699	0.3 (2.7)		22.79%	-0.5[-0.7,-0.3]
WINS 2006	755	26.8 (5.6)	1230	27.6 (5.4)		12.67%	-0.8[-1.3,-0.3]
Subtotal ***	**2491**		**3481**			**100%**	**-0.47[-0.72,-0.23]**
Heterogeneity: Tau^2=0.06; Chi^2=18.21, df=9(P=0.03); I^2=50.59%							
Test for overall effect: Z=3.78(P=0)							
3.2.3 Reduced and modified fat intake							
Oxford Retinopathy 1978	29	-1 (2.8)	29	-0.7 (1.8)		82.96%	-0.3[-1.51,0.91]
Sarkkinen Red & Mod 1995	41	26 (4)	12	25.7 (4.2)		17.04%	0.3[-2.37,2.97]
Subtotal ***	**70**		**41**			**100%**	**-0.2[-1.3,0.91]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%							
Test for overall effect: Z=0.35(P=0.73)							



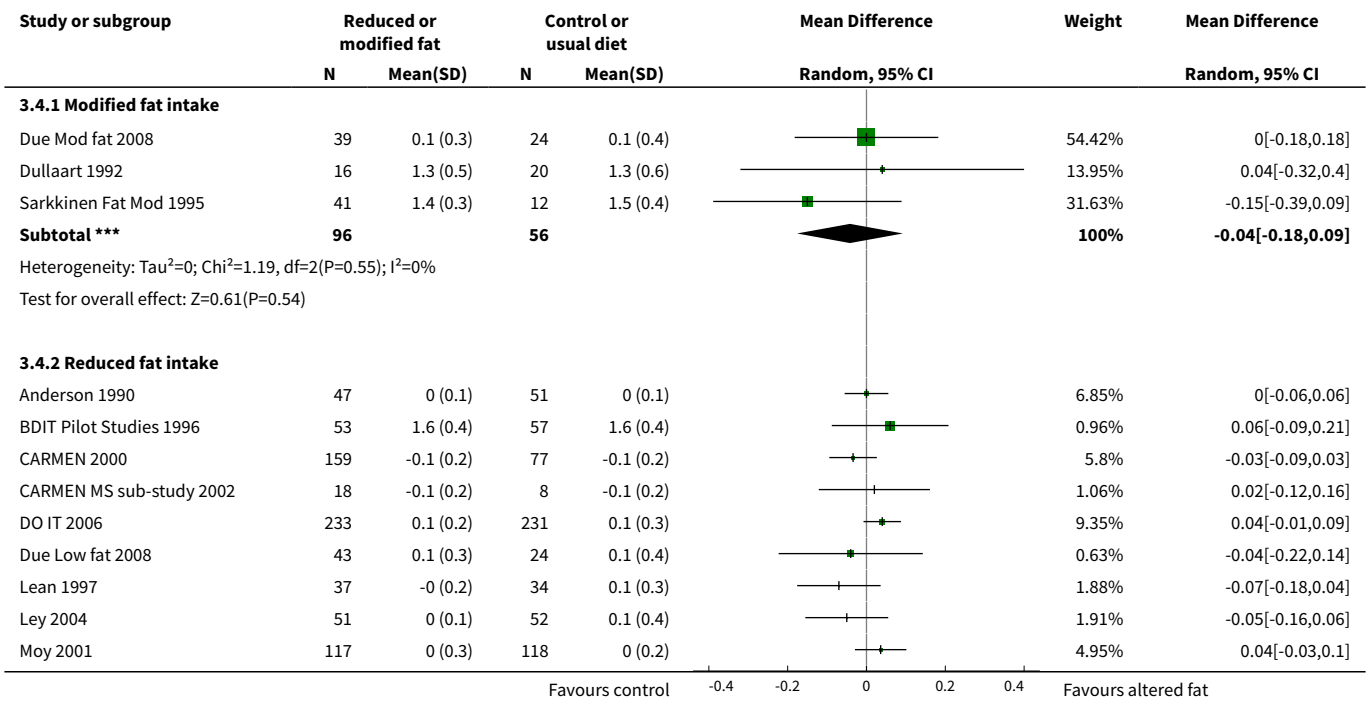
Analysis 3.3. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 3 LDL cholesterol, mmol/L.

Study or subgroup	Reduced or modified fat N	Mean(SD)	Control or usual diet N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.3.1 Modified fat intake							
Due Mod fat 2008	39	-0.1 (0.5)	24	0.1 (0.6)		81.73%	-0.22[-0.51,0.07]
Sarkkinen Fat Mod 1995	41	4.3 (1)	12	4.4 (1)		18.27%	-0.11[-0.73,0.51]
Subtotal ***	**80**		**36**			**100%**	**-0.2[-0.47,0.07]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%							
Test for overall effect: Z=1.48(P=0.14)							
3.3.2 Reduced fat intake							
Anderson 1990	47	-0.6 (0.6)	51	-0.4 (0.4)		5.31%	-0.16[-0.36,0.04]
CARMEN 2000	159	-0.1 (0.5)	77	-0 (0.7)		7.26%	-0.02[-0.19,0.15]
CARMEN MS sub-study 2002	18	-0.1 (0.5)	8	0.2 (0.9)		0.5%	-0.3[-0.94,0.33]

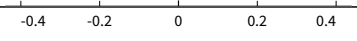




Analysis 3.4. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 4 HDL cholesterol, mmol/Lkg.

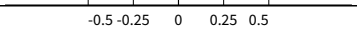


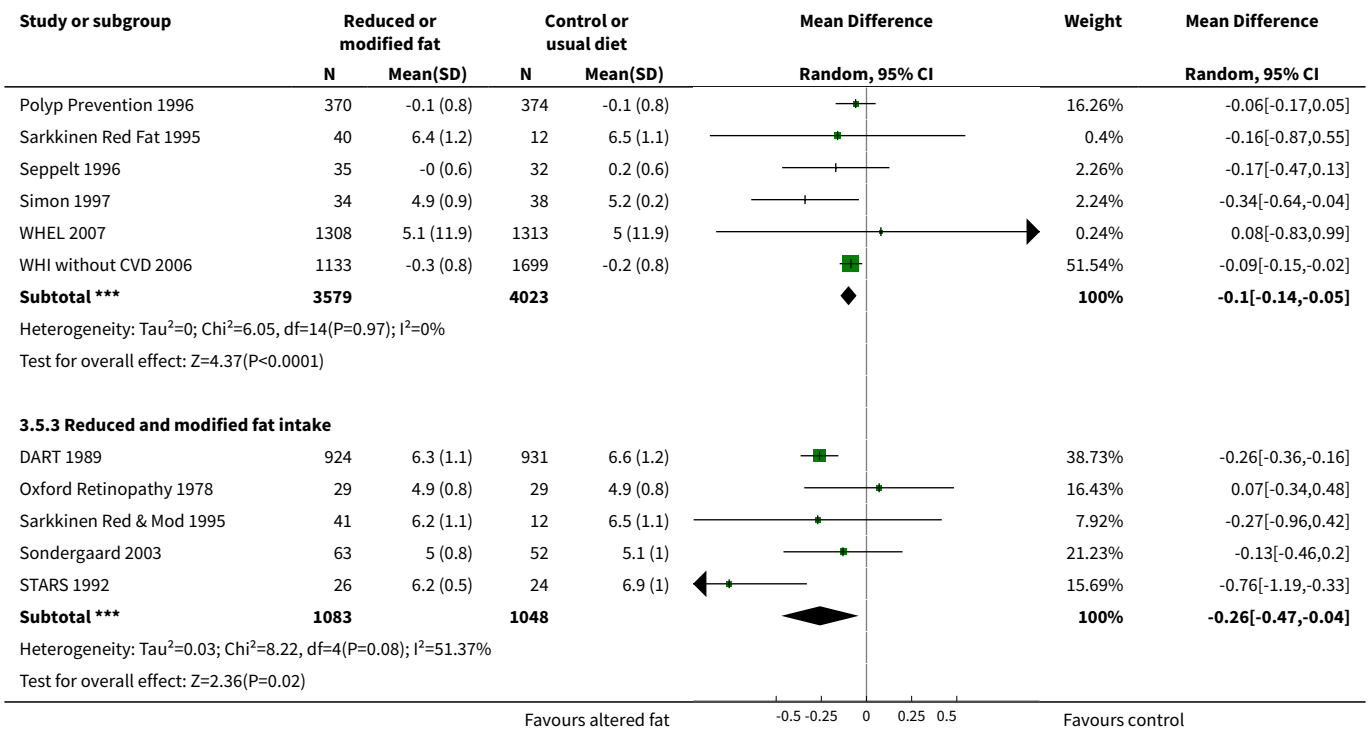
Study or subgroup	Reduced or modified fat N	Mean(SD)	Control or usual diet N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ole Study 2002	14	0 (0.1)	14	0.1 (0.1)		4.52%	-0.02[-0.09,0.05]
Sarkkinen Red Fat 1995	40	1.4 (0.3)	12	1.5 (0.4)		0.35%	-0.15[-0.39,0.09]
Seppelt 1996	35	0 (0.2)	32	0.1 (0.2)		2.35%	-0.07[-0.16,0.02]
Simon 1997	34	1.4 (0.6)	38	1.6 (0.6)		0.31%	-0.12[-0.38,0.14]
WHEL 2007	1308	1.5 (4.7)	1313	1.5 (4.3)		0.18%	-0.08[-0.43,0.27]
WHI without CVD 2006	1133	-0 (0.2)	1699	-0 (0.3)		58.91%	-0.01[-0.03,0.01]
Subtotal * **	**3322**		**3760**			**100%**	**-0.01[-0.02,0.01]**
Heterogeneity: Tau^2=0; Chi^2=13.45, df=14(P=0.49); I^2=0%							
Test for overall effect: Z=1.03(P=0.3)							
3.4.3 Reduced and modified fat intake							
DART 1989	924	1 (0.3)	931	1.1 (0.3)		90.82%	-0.01[-0.04,0.02]
Sarkkinen Red & Mod 1995	41	1.4 (0.3)	12	1.5 (0.4)		1.25%	-0.1[-0.34,0.14]
Sondergaard 2003	63	1.3 (0.4)	52	1.2 (0.4)		3.89%	0.02[-0.11,0.15]
STARS 1992	26	1.1 (0.2)	24	1.2 (0.3)		4.05%	-0.07[-0.2,0.06]
Subtotal * **	**1054**		**1019**			**100%**	**-0.01[-0.04,0.01]**
Heterogeneity: Tau^2=0; Chi^2=1.52, df=3(P=0.68); I^2=0%							
Test for overall effect: Z=0.92(P=0.36)							



Analysis 3.5. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 5 Total cholesterol, mmol/L.

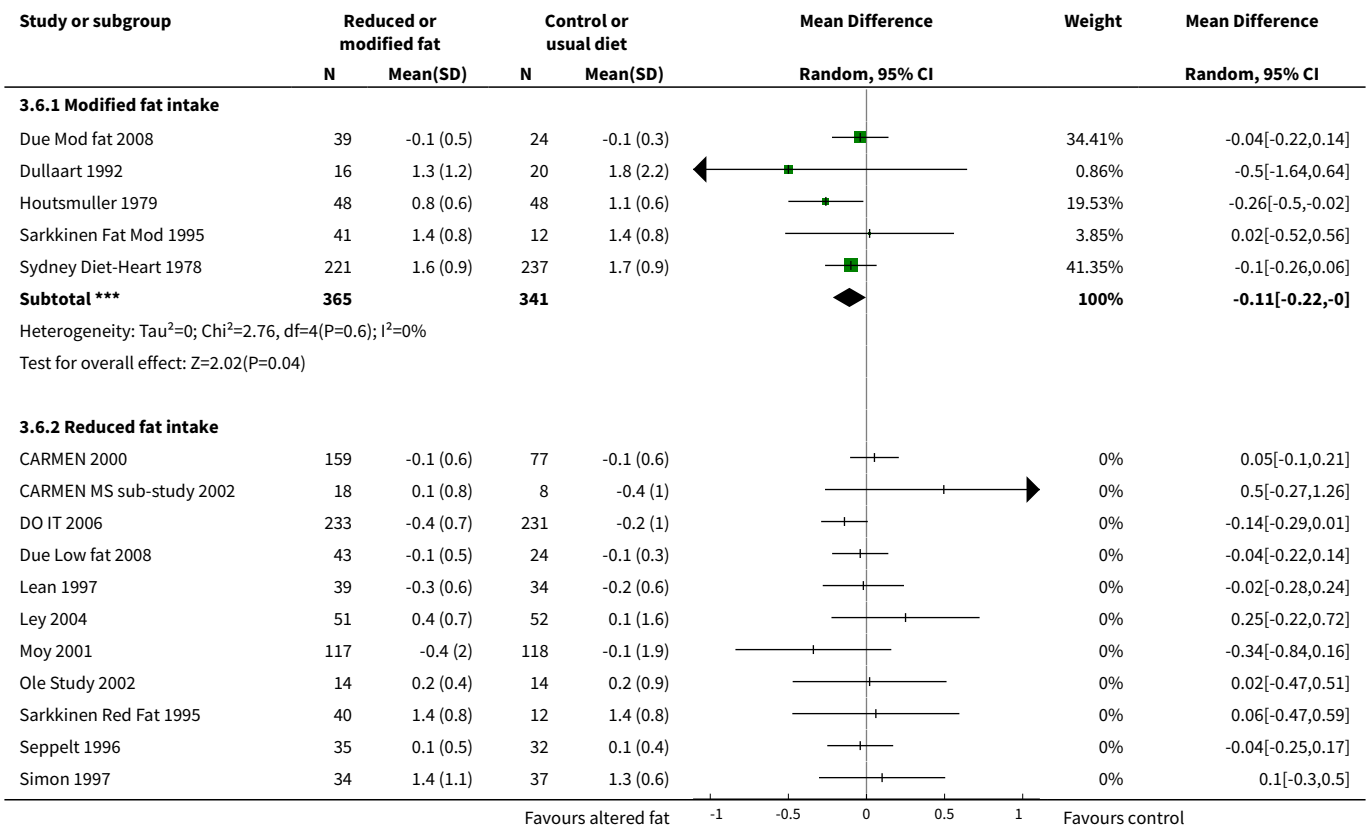
Study or subgroup	Reduced or modified fat N	Mean(SD)	Control or usual diet N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.5.1 Modified fat intake							
Due Mod fat 2008	39	-0.1 (0.8)	24	0.2 (0.6)		11.35%	-0.23[-0.59,0.13]
Houtsmuller 1979	48	6.4 (0.7)	48	6.9 (0.8)		13.83%	-0.47[-0.76,-0.18]
NDHS Faribault 1968	50	-1.1 (0.7)	51	-0.2 (0.6)		15.43%	-0.91[-1.17,-0.65]
NDHS Open 1st mod 1968	311	-0.7 (0.7)	309	-0.2 (0.6)		23.49%	-0.45[-0.55,-0.35]
Rose 1965	28	-0.3 (1.6)	18	-0.2 (1)		3.67%	-0.11[-0.88,0.66]
Sarkkinen Fat Mod 1995	41	6.3 (1.1)	12	6.5 (1.1)		4.4%	-0.21[-0.9,0.48]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		17.86%	-0.3[-0.51,-0.09]
Veterans Admin 1969	423	4.9 (3.7)	420	5.3 (1.9)		9.98%	-0.37[-0.77,0.03]
Subtotal * **	**1161**		**1119**			**100%**	**-0.44[-0.6,-0.28]**
Heterogeneity: Tau^2=0.03; Chi^2=16.88, df=7(P=0.02); I^2=58.54%							
Test for overall effect: Z=5.41(P<0.0001)							
3.5.2 Reduced fat intake							
Anderson 1990	47	-0.6 (0.6)	51	-0.4 (0.6)		3.56%	-0.17[-0.41,0.07]
BDIT Pilot Studies 1996	54	5.1 (0.8)	61	5.4 (0.8)		2.18%	-0.24[-0.54,0.06]
CARMEN 2000	159	-0.2 (0.6)	77	-0.1 (0.6)		6.75%	-0.09[-0.26,0.08]
CARMEN MS sub-study 2002	18	-0.2 (0.7)	8	-0.1 (0.8)		0.46%	-0.1[-0.76,0.56]
DO IT 2006	233	-0.1 (0.9)	231	-0 (1)		6.64%	-0.06[-0.23,0.11]
Due Low fat 2008	43	0 (0.7)	24	0.2 (0.6)		1.92%	-0.16[-0.48,0.16]
Lean 1997	40	-0.3 (0.7)	37	-0.1 (0.4)		3.24%	-0.22[-0.47,0.03]
Ley 2004	51	-0.2 (0.8)	52	-0.1 (1.3)		1.16%	-0.05[-0.46,0.36]
Ole Study 2002	14	0.1 (0.6)	14	0.2 (0.6)		1.16%	-0.08[-0.49,0.33]



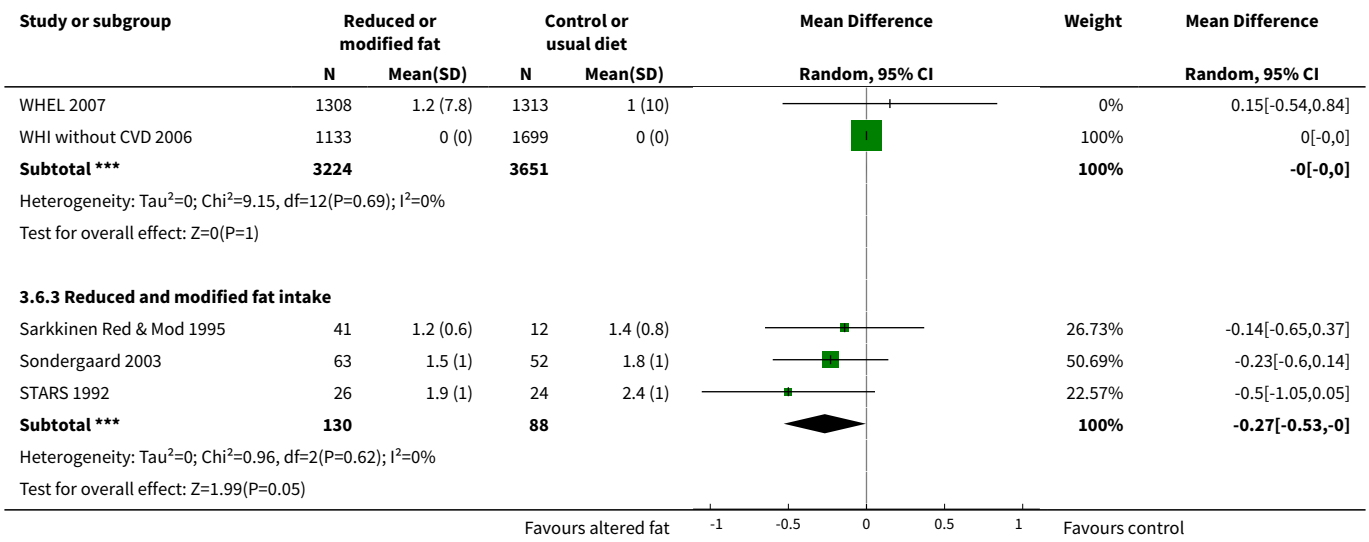


Study or subgroup	Reduced or modified fat N	Mean(SD)	Control or usual diet N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Polyp Prevention 1996	370	-0.1 (0.8)	374	-0.1 (0.8)		16.26%	-0.06[-0.17,0.05]
Sarkkinen Red Fat 1995	40	6.4 (1.2)	12	6.5 (1.1)		0.4%	-0.16[-0.87,0.55]
Seppelt 1996	35	-0 (0.6)	32	0.2 (0.6)		2.26%	-0.17[-0.47,0.13]
Simon 1997	34	4.9 (0.9)	38	5.2 (0.2)		2.24%	-0.34[-0.64,-0.04]
WHEL 2007	1308	5.1 (11.9)	1313	5 (11.9)		0.24%	0.08[-0.83,0.99]
WHI without CVD 2006	1133	-0.3 (0.8)	1699	-0.2 (0.8)		51.54%	-0.09[-0.15,-0.02]
Subtotal ***	**3579**		**4023**			**100%**	**-0.1[-0.14,-0.05]**
Heterogeneity: Tau^2=0; Chi^2=6.05, df=14(P=0.97); I^2=0%							
Test for overall effect: Z=4.37(P<0.0001)							
3.5.3 Reduced and modified fat intake							
DART 1989	924	6.3 (1.1)	931	6.6 (1.2)		38.73%	-0.26[-0.36,-0.16]
Oxford Retinopathy 1978	29	4.9 (0.8)	29	4.9 (0.8)		16.43%	0.07[-0.34,0.48]
Sarkkinen Red & Mod 1995	41	6.2 (1.1)	12	6.5 (1.1)		7.92%	-0.27[-0.96,0.42]
Sondergaard 2003	63	5 (0.8)	52	5.1 (1)		21.23%	-0.13[-0.46,0.2]
STARS 1992	26	6.2 (0.5)	24	6.9 (1)		15.69%	-0.76[-1.19,-0.33]
Subtotal ***	**1083**		**1048**			**100%**	**-0.26[-0.47,-0.04]**
Heterogeneity: Tau^2=0.03; Chi^2=8.22, df=4(P=0.08); I^2=51.37%							
Test for overall effect: Z=2.36(P=0.02)							

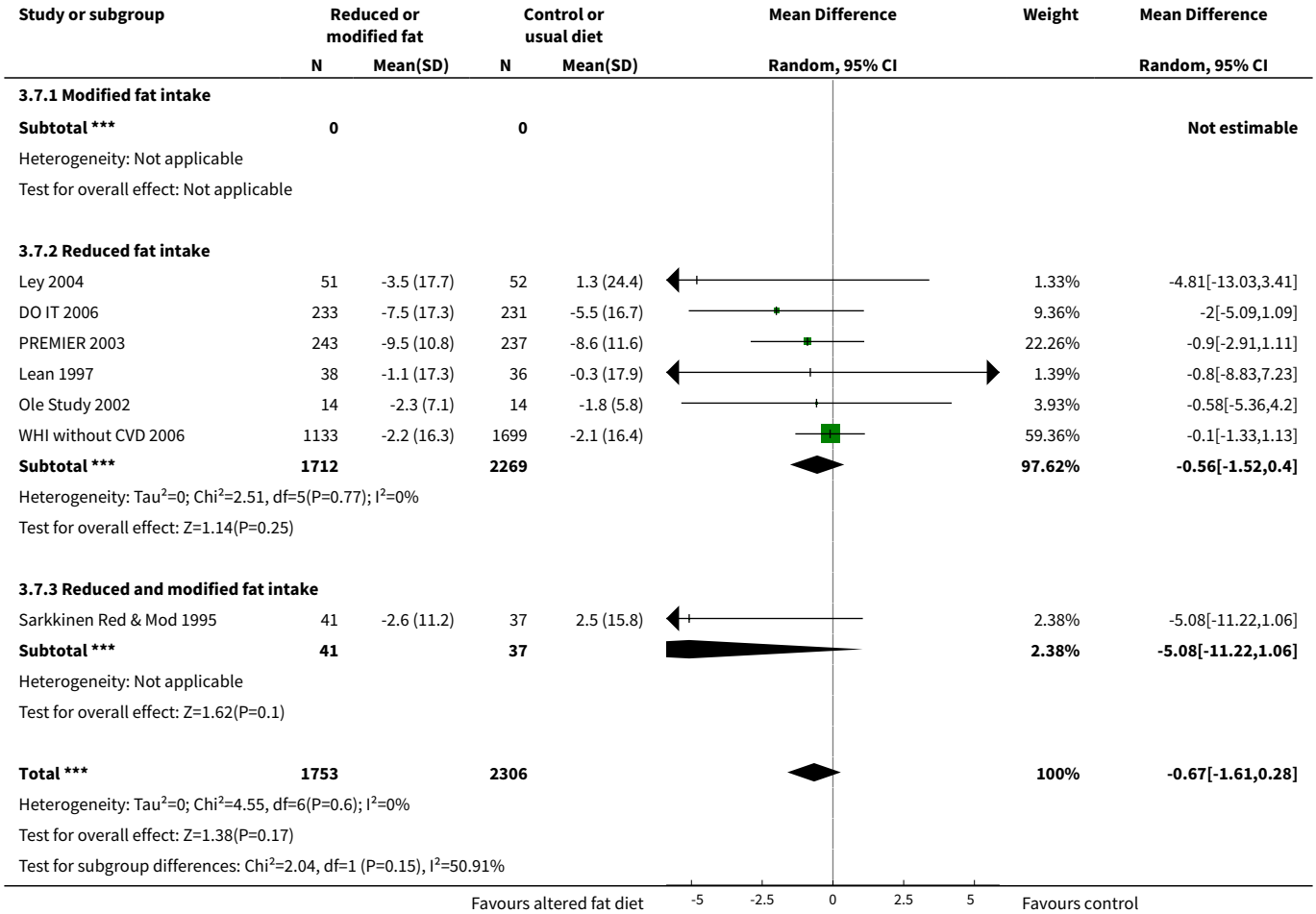
Analysis 3.6. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 6 Triglycerides, mmol/L.



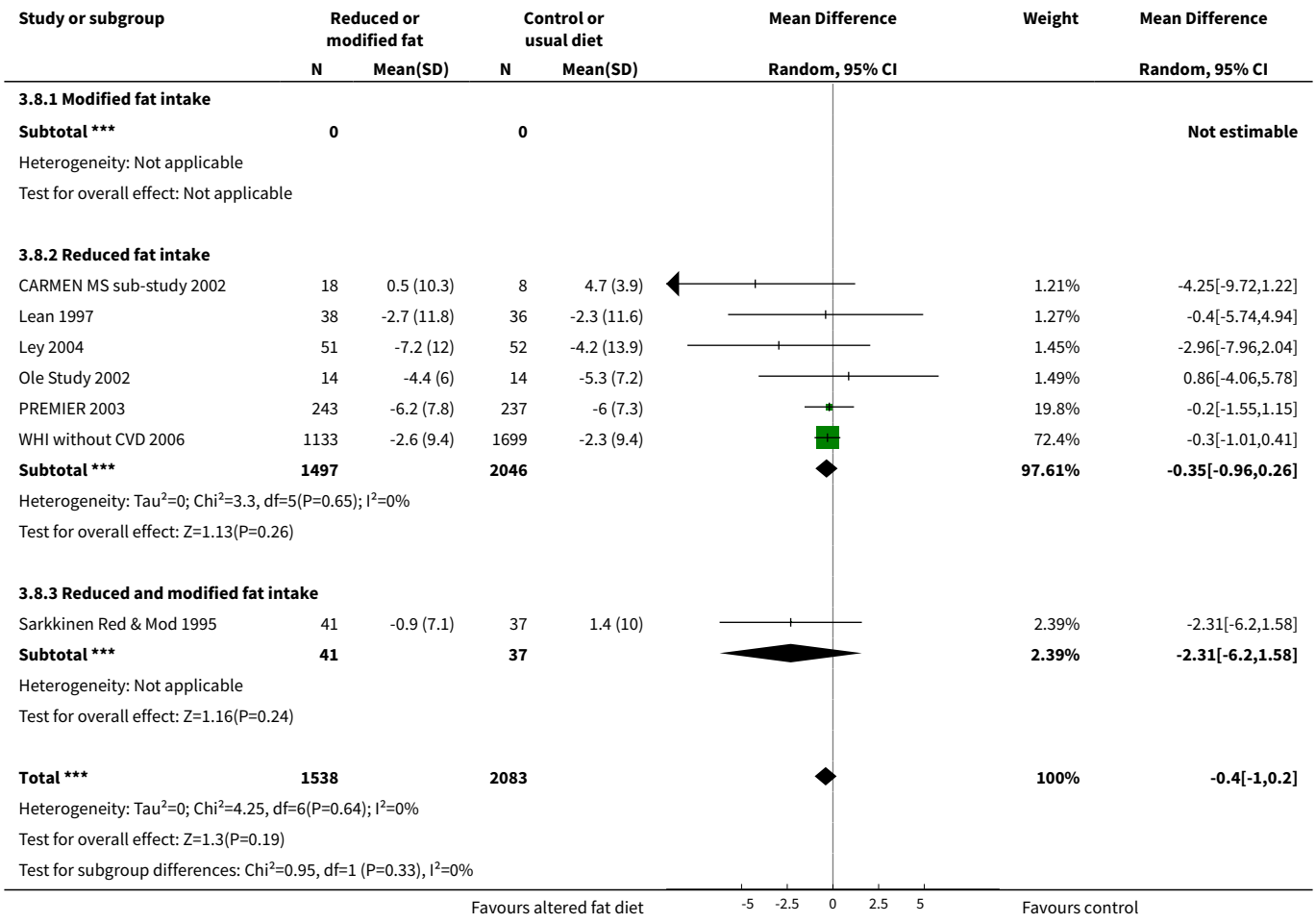
Study or subgroup	Reduced or modified fat N	Mean(SD)	Control or usual diet N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.6.1 Modified fat intake							
Due Mod fat 2008	39	-0.1 (0.5)	24	-0.1 (0.3)		34.41%	-0.04[-0.22,0.14]
Dullaart 1992	16	1.3 (1.2)	20	1.8 (2.2)		0.86%	-0.5[-1.64,0.64]
Houtsmuller 1979	48	0.8 (0.6)	48	1.1 (0.6)		19.53%	-0.26[-0.5,-0.02]
Sarkkinen Fat Mod 1995	41	1.4 (0.8)	12	1.4 (0.8)		3.85%	0.02[-0.52,0.56]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		41.35%	-0.1[-0.26,0.06]
Subtotal ***	**365**		**341**			**100%**	**-0.11[-0.22,-0]**
Heterogeneity: Tau^2=0; Chi^2=2.76, df=4(P=0.6); I^2=0%							
Test for overall effect: Z=2.02(P=0.04)							
3.6.2 Reduced fat intake							
CARMEN 2000	159	-0.1 (0.6)	77	-0.1 (0.6)		0%	0.05[-0.1,0.21]
CARMEN MS sub-study 2002	18	0.1 (0.8)	8	-0.4 (1)		0%	0.5[-0.27,1.26]
DO IT 2006	233	-0.4 (0.7)	231	-0.2 (1)		0%	-0.14[-0.29,0.01]
Due Low fat 2008	43	-0.1 (0.5)	24	-0.1 (0.3)		0%	-0.04[-0.22,0.14]
Lean 1997	39	-0.3 (0.6)	34	-0.2 (0.6)		0%	-0.02[-0.28,0.24]
Ley 2004	51	0.4 (0.7)	52	0.1 (1.6)		0%	0.25[-0.22,0.72]
Moy 2001	117	-0.4 (2)	118	-0.1 (1.9)		0%	-0.34[-0.84,0.16]
Ole Study 2002	14	0.2 (0.4)	14	0.2 (0.9)		0%	0.02[-0.47,0.51]
Sarkkinen Red Fat 1995	40	1.4 (0.8)	12	1.4 (0.8)		0%	0.06[-0.47,0.59]
Seppelt 1996	35	0.1 (0.5)	32	0.1 (0.4)		0%	-0.04[-0.25,0.17]
Simon 1997	34	1.4 (1.1)	37	1.3 (0.6)		0%	0.1[-0.3,0.5]



Analysis 3.7. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 7 Systolic Blood Pressure, mmHg.



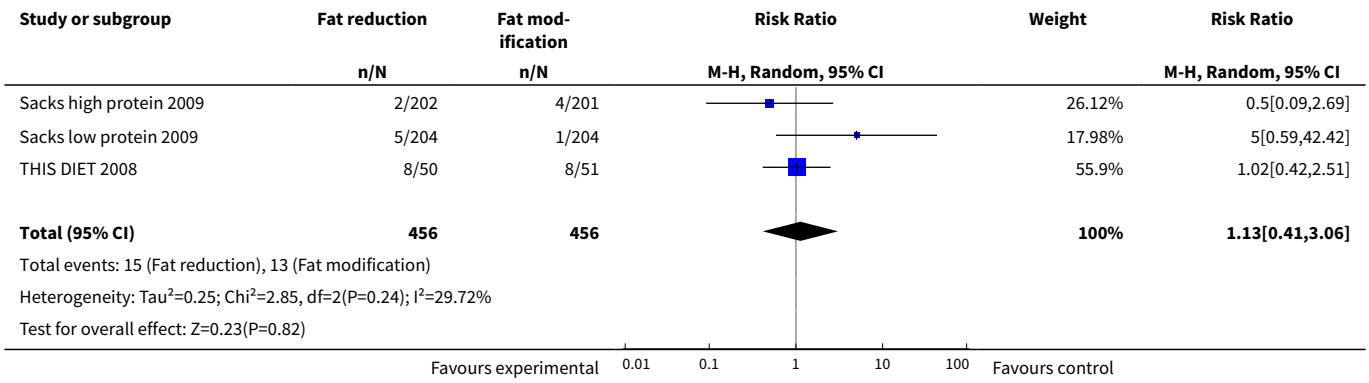
Analysis 3.8. Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 8 Diastolic Blood Pressure, mmHg.



Comparison 4. fat reduction vs fat modification - primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Cardiovascular mortality	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Combined cardiovascular events	3	912	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.41, 3.06]

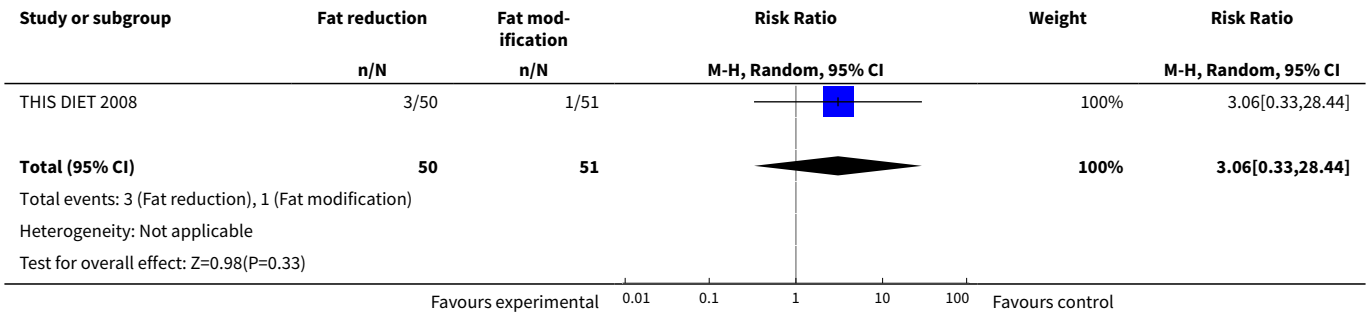
Analysis 4.3. Comparison 4 fat reduction vs fat modification - primary outcomes, Outcome 3 Combined cardiovascular events.



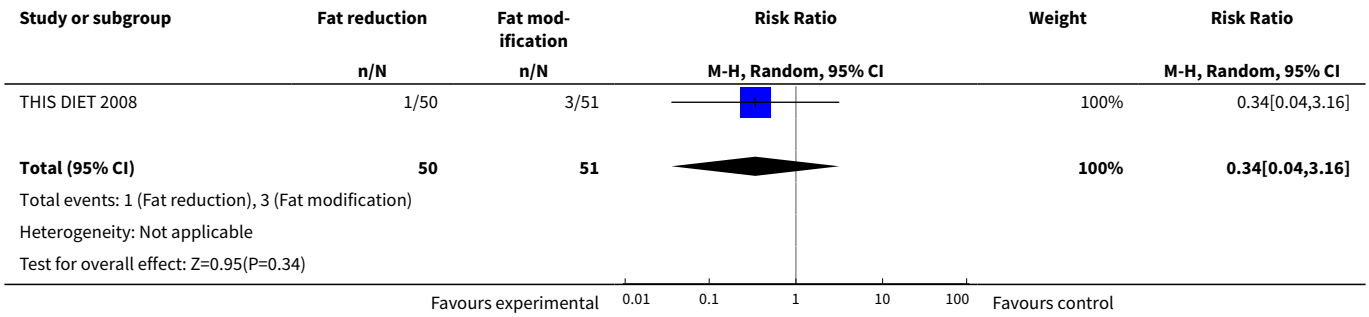
Comparison 5. fat reduction vs fat modification - secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction	1	101	Risk Ratio (M-H, Random, 95% CI)	3.06 [0.33, 28.44]
2 Stroke	1	101	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.16]
3 Cancer deaths	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cancer diagnoses	2	811	Risk Ratio (M-H, Random, 95% CI)	2.07 [0.27, 15.98]
5 Diabetes diagnoses	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-fatal MI	1	101	Risk Ratio (M-H, Random, 95% CI)	3.06 [0.33, 28.44]

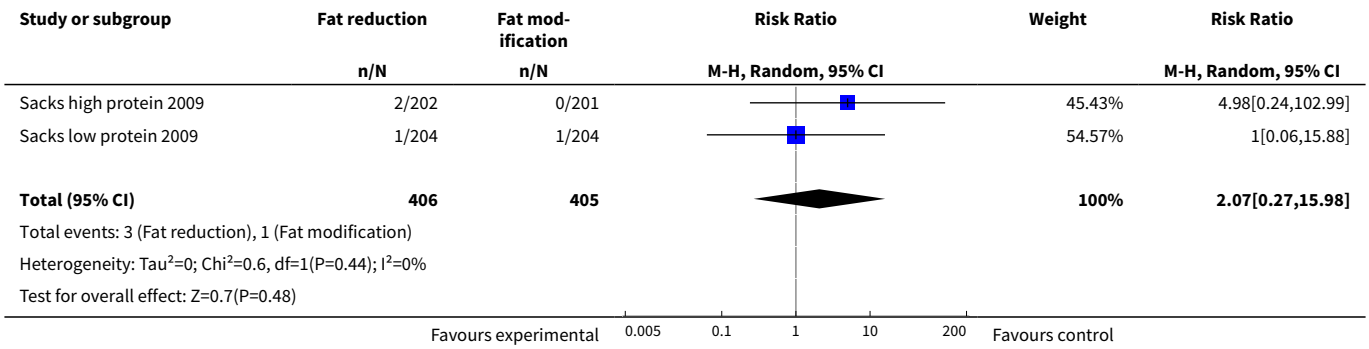
Analysis 5.1. Comparison 5 fat reduction vs fat modification - secondary outcomes, Outcome 1 Myocardial infarction.



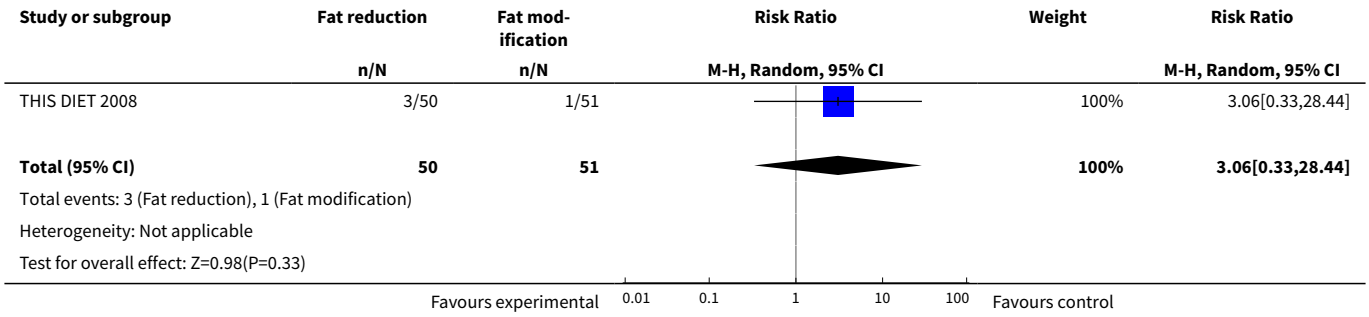
Analysis 5.2. Comparison 5 fat reduction vs fat modification - secondary outcomes, Outcome 2 Stroke.



Analysis 5.4. Comparison 5 fat reduction vs fat modification - secondary outcomes, Outcome 4 Cancer diagnoses.



Analysis 5.6. Comparison 5 fat reduction vs fat modification - secondary outcomes, Outcome 6 Non-fatal MI.



Comparison 6. fat reduction vs fat modification - tertiary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight, kg	6	1057	Mean Difference (IV, Random, 95% CI)	-0.25 [-1.88, 1.39]
2 BMI, kg/m2	5	345	Mean Difference (IV, Random, 95% CI)	0.06 [-0.79, 0.92]

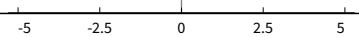
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 LDL cholesterol, mmol/L	9	1275	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.13, 0.12]
4 HDL cholesterol, mmol/Lkg	9	1275	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.06, 0.02]
5 Total cholesterol, mmol/L	7	1130	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.18, 0.09]
6 Triglycerides, mmol/L	9	1275	Mean Difference (IV, Random, 95% CI)	0.05 [-0.02, 0.12]
7 Systolic Blood Pressure, mmHg	6	1068	Mean Difference (IV, Random, 95% CI)	-0.13 [-2.16, 1.90]
8 Diastolic Blood Pressure, mmHg	6	1068	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.90, 1.43]
9 Dropouts	9	1353	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.58, 1.22]

Analysis 6.1. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 1 Weight, kg.

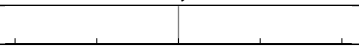
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Azadbakht 2007	44	-1.2 (7.3)	45	-5 (16.8)		7.53%	3.8[-1.55,9.15]
Due Low vs Mod 2008	43	2.2 (4.4)	39	2.5 (4.5)		25.46%	-0.3[-2.21,1.61]
McAuley 2005	24	93.2 (15.1)	28	87.1 (15.6)		3.49%	6.1[-2.26,14.46]
Sacks high protein 2009	201	-3.8 (14.2)	201	-3.5 (14.2)		18.37%	-0.3[-3.08,2.48]
Sacks low protein 2009	201	-3 (14.2)	201	-3.2 (14.2)		18.37%	0.2[-2.58,2.98]
Strychar 2009	15	-0.8 (3)	15	1.6 (1.8)		26.77%	-2.43[-4.2,-0.66]
Total * **	**528**		**529**			**100%**	**-0.25[-1.88,1.39]**
Heterogeneity: Tau²=1.79; Chi²=9.57, df=5(P=0.09); I²=47.78%							
Test for overall effect: Z=0.3(P=0.77)							

Analysis 6.2. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 2 BMI, kg/m2.

Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Due Low vs Mod 2008	43	0.7 (1.3)	39	0.8 (1.4)		31.88%	-0.1[-0.7,0.5]
McAuley 2005	30	34.9 (5.6)	29	31.5 (5.1)		7.81%	3.4[0.67,6.13]
Sarkkinen Red vs Mod1995	40	26.2 (3.2)	41	26.3 (3.6)		17.74%	-0.1[-1.58,1.38]
Strychar 2009	15	-0.2 (1)	15	0.6 (0.6)		32.07%	-0.8[-1.39,-0.21]
THIS DIET 2008	46	29 (6)	47	28 (5)		10.5%	1[-1.25,3.25]
Total * **	**174**		**171**			**100%**	**0.06[-0.79,0.92]**
Heterogeneity: Tau²=0.51; Chi²=11.59, df=4(P=0.02); I²=65.47%							



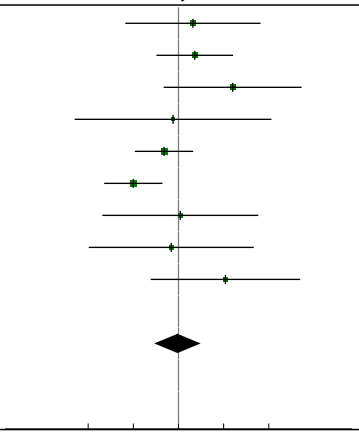
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.15(P=0.88)							



Favours low fat — Favours modified fat

Analysis 6.3. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 3 LDL cholesterol, mmol/L.

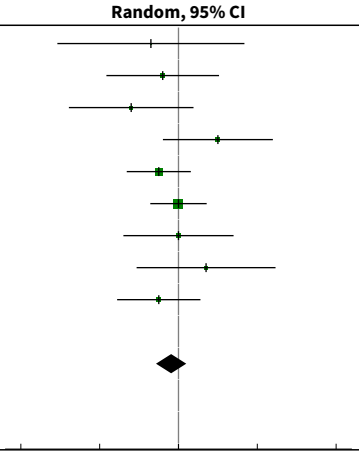
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Azadbakht 2007	44	-0.1 (1)	45	-0.2 (0.8)		8.5%	0.08[-0.29,0.45]
Due Low vs Mod 2008	43	0 (0.5)	39	-0.1 (0.5)		16.7%	0.09[-0.12,0.3]
McAuley 2005	24	3.8 (0.7)	28	3.5 (0.7)		8.27%	0.3[-0.08,0.68]
Rivellese 1994	27	4.8 (0.9)	17	4.9 (0.9)		4.71%	-0.03[-0.57,0.51]
Sacks high protein 2009	201	3.1 (0.9)	201	3.2 (0.8)		20.67%	-0.08[-0.24,0.08]
Sacks low protein 2009	201	3 (0.8)	201	3.3 (0.9)		20.67%	-0.25[-0.41,-0.09]
Sarkkinen Red vs Mod1995	40	4.3 (1)	41	4.3 (1)		6.87%	0.01[-0.42,0.44]
Strychar 2009	15	-0.2 (0.7)	15	-0.2 (0.6)		6.28%	-0.04[-0.5,0.42]
THIS DIET 2008	46	2.8 (1.2)	47	2.5 (0.8)		7.33%	0.26[-0.15,0.67]
Total ***	**641**		**634**			**100%**	**-0.01[-0.13,0.12]**
Heterogeneity: Tau^2=0.01; Chi^2=13.64, df=8(P=0.09); I^2=41.33%							
Test for overall effect: Z=0.09(P=0.93)							



Favours low fat — Favours modified fat

Analysis 6.4. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 4 HDL cholesterol, mmol/Lkg.

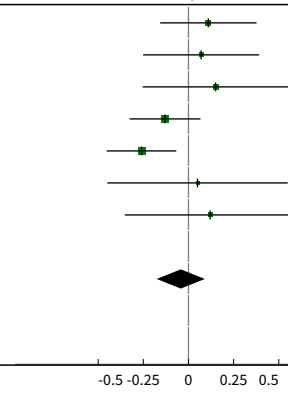
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Azadbakht 2007	44	0.1 (0.6)	45	0.2 (0.5)		2.62%	-0.07[-0.31,0.17]
Due Low vs Mod 2008	43	0.1 (0.3)	39	0.1 (0.3)		7.23%	-0.04[-0.18,0.1]
McAuley 2005	24	1.1 (0.3)	28	1.3 (0.3)		5.9%	-0.12[-0.28,0.04]
Rivellese 1994	27	1.2 (0.3)	17	1.1 (0.2)		7.58%	0.1[-0.04,0.24]
Sacks high protein 2009	201	1.4 (0.4)	201	1.4 (0.4)		22.33%	-0.05[-0.13,0.03]
Sacks low protein 2009	201	1.3 (0.4)	201	1.3 (0.3)		28.83%	0[-0.07,0.07]
Sarkkinen Red vs Mod1995	40	1.4 (0.3)	41	1.4 (0.3)		7.55%	0[-0.14,0.14]
Strychar 2009	15	0.1 (0.3)	15	-0 (0.2)		4.75%	0.07[-0.11,0.25]
THIS DIET 2008	46	1.1 (0.3)	47	1.1 (0.3)		13.21%	-0.05[-0.16,0.06]
Total ***	**641**		**634**			**100%**	**-0.02[-0.06,0.02]**
Heterogeneity: Tau^2=0; Chi^2=6.83, df=8(P=0.55); I^2=0%							
Test for overall effect: Z=0.95(P=0.34)							



Favours modified fat — Favours low fat

Analysis 6.5. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 5 Total cholesterol, mmol/L.

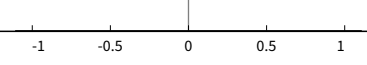
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Azadbakht 2007	44	-0.1 (0.5)	45	-0.3 (0.7)		16.65%	0.11[-0.16,0.38]
Due Low vs Mod 2008	43	0 (0.7)	39	-0.1 (0.8)		12.82%	0.07[-0.25,0.39]
Rivellese 1994	27	6.8 (0.8)	17	6.6 (0.6)		8.98%	0.15[-0.25,0.55]
Sacks high protein 2009	201	5.1 (1)	201	5.2 (1)		23.97%	-0.13[-0.33,0.07]
Sacks low protein 2009	201	5 (1)	201	5.2 (1)		24.47%	-0.26[-0.45,-0.07]
Sarkkinen Red vs Mod1995	40	6.4 (1.2)	41	6.3 (1.1)		6.25%	0.05[-0.45,0.55]
Strychar 2009	15	-0.1 (0.7)	15	-0.2 (0.7)		6.88%	0.12[-0.35,0.59]
Total ***	**571**		**559**			**100%**	**-0.04[-0.18,0.09]**
Heterogeneity: Tau²=0.01; Chi²=8.56, df=6(P=0.2); I²=29.89%							
Test for overall effect: Z=0.63(P=0.53)							



Favours low fat — Favours modified fat

Analysis 6.6. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 6 Triglycerides, mmol/L.

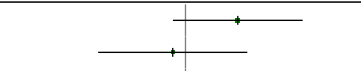
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Azadbakht 2007	44	-0 (0.1)	45	-0.1 (0.4)		29.71%	0.08[-0.04,0.2]
Due Low vs Mod 2008	43	-0.1 (0.5)	39	-0.1 (0.5)		11.25%	0[-0.21,0.21]
McAuley 2005	24	1.6 (0.8)	28	1.2 (0.6)		3.75%	0.41[0.03,0.79]
Rivellese 1994	27	1.5 (0.7)	17	1.6 (0.7)		3.01%	-0.07[-0.49,0.35]
Sacks high protein 2009	201	1.4 (0.8)	201	1.3 (0.8)		20.54%	0.02[-0.13,0.17]
Sacks low protein 2009	201	1.4 (0.9)	201	1.5 (1)		13.85%	-0.11[-0.3,0.08]
Sarkkinen Red vs Mod1995	40	1.4 (0.8)	41	1.4 (0.8)		4.19%	0.04[-0.32,0.4]
Strychar 2009	15	0.1 (0.5)	15	-0 (0.2)		7.77%	0.17[-0.09,0.43]
THIS DIET 2008	46	1.5 (0.8)	47	1.4 (0.7)		5.92%	0.16[-0.14,0.46]
Total ***	**641**		**634**			**100%**	**0.05[-0.02,0.12]**
Heterogeneity: Tau²=0; Chi²=8.52, df=8(P=0.38); I²=6.07%							
Test for overall effect: Z=1.34(P=0.18)							



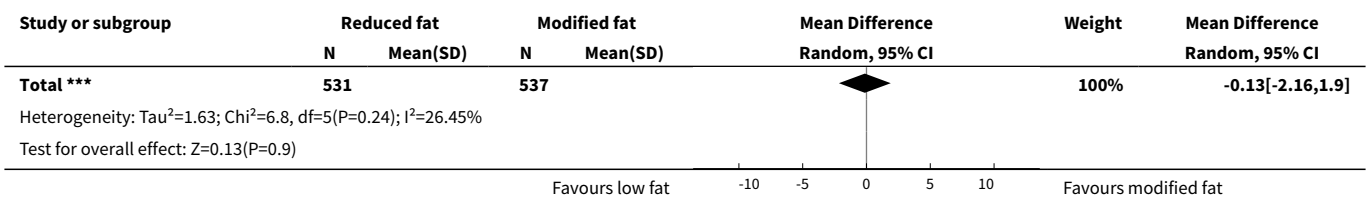
Favours low fat — Favours modified fat

Analysis 6.7. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 7 Systolic Blood Pressure, mmHg.

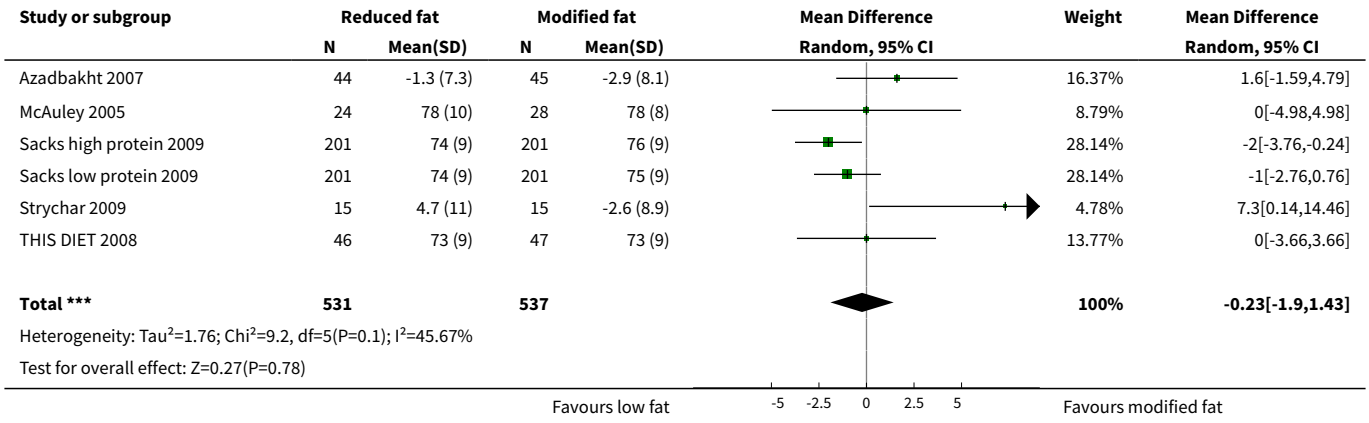
Study or subgroup	Reduced fat N	Reduced fat Mean(SD)	Modified fat N	Modified fat Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Azadbakht 2007	44	-3.3 (8)	45	-7.4 (15.4)		12.88%	4.1[-0.98,9.18]
McAuley 2005	24	120 (12)	28	121 (9)		10.24%	-1[-6.84,4.84]
Sacks high protein 2009	201	118 (13)	201	120 (14)		31.26%	-2[-4.64,0.64]
Sacks low protein 2009	201	117 (12)	201	118 (12)		35.17%	-1[-3.35,1.35]
Strychar 2009	15	3.9 (14.4)	15	-0.2 (21.1)		2.39%	4.1[-8.83,17.03]
THIS DIET 2008	46	124 (16)	47	120 (17)		8.07%	4[-2.71,10.71]



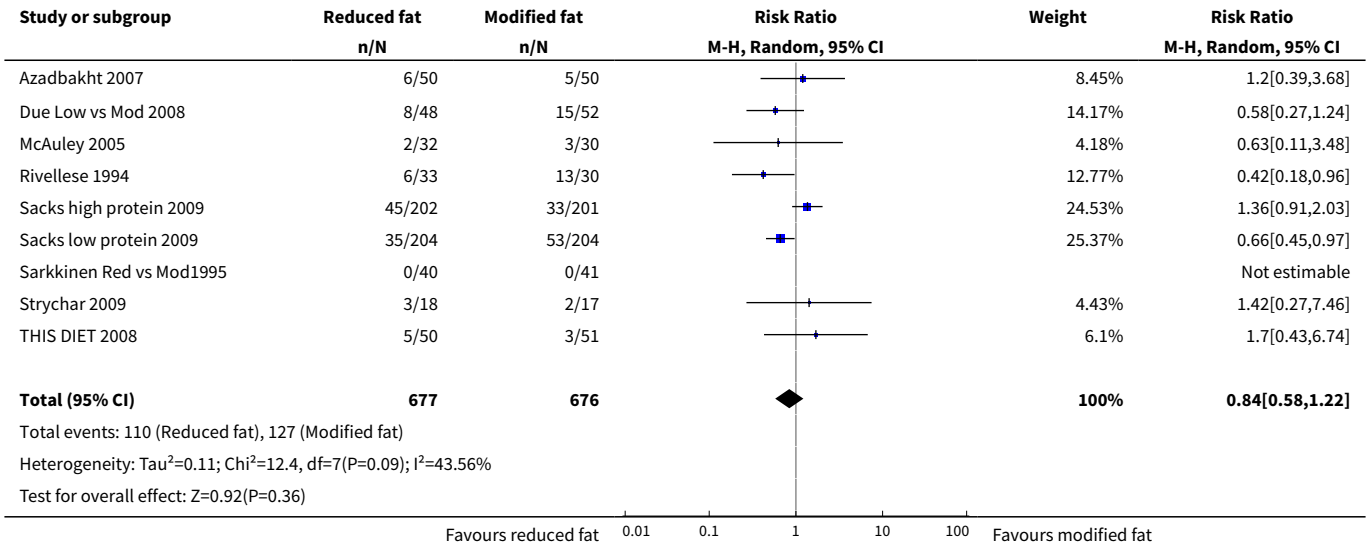
Favours low fat — Favours modified fat



Analysis 6.8. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 8 Diastolic Blood Pressure, mmHg.



Analysis 6.9. Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 9 Dropouts.



ADDITIONAL TABLES

Table 1. Sensitivity analyses of primary outcomes

Outcome	Sensitivity Analysis	Subgroup	Risk ratio (95% CI)	Number of studies / participants/ events	I^2
Total mortality	Mantel-Haenszel, Fixed effects	Overall analysis	0.98 (0.93 to 1.04)	21/ 71795 / 4292	0%
Total mortality	Mantel-Haenszel, Fixed effects	Modified fat intake	1.03 (0.92 to 1.14)	8/ 11441/ 1120	34%
Total mortality	Mantel-Haenszel, Fixed effects	Reduced fat intake	0.97 (0.90 to 1.04)	10/ 58130/ 2936	0%
Total mortality	Mantel-Haenszel, Fixed effects	Reduced & modified fat intake	0.96 (0.76 to 1.22)	2/ 2224/ 236	0%
Total mortality	Peto Odds Ratio (fixed effects)	Overall analysis	OR 0.98 (0.92 to 1.05)	21/ 71795 / 4292	0%
Total mortality	Peto Odds Ratio (fixed effects)	Modified fat intake	OR 1.03 (0.91 to 1.18)	8/ 11441/ 1120	39%
Total mortality	Peto Odds Ratio (fixed effects)	Reduced fat intake	OR 0.97 (0.90 to 1.04)	10/ 58130/ 2936	0%
Total mortality	Peto Odds Ratio (fixed effects)	Reduced and modified fat intake	OR 0.96 (0.73 to 1.25)	2/ 2224/ 236	0%
Total mortality	Excluding WHI	Overall analysis	0.98 (0.91 to 1.07)	20/ 22960/ 1888	0%
Total mortality	Excluding WHI	Reduced fat intake	0.94 (0.80 to 1.10)	9/ 9295/ 532	0%
Total mortality	Excluding studies with systematic difference in care	Overall analysis	1.03 (0.92 to 1.16)	6/ 10715/ 882	0%
Total mortality	Excluding studies with systematic difference in care	Modified fat intake	1.03 (0.92 to 1.16)	5/ 10178/ 881	0%
Total mortality	Excluding studies with systematic difference in care	Reduced fat intake	0.33 (0.01 to 8.12)	1/ 537/ 1	NR
Total mortality	Excluding studies with systematic difference in care	Reduced & modified fat intake	NR	0/ 0/ 0	NR
Total mortality	Excluding studies with systematic differences in diet other than fat	Overall analysis	1.03 (0.93 to 1.13)	12/ 16060/ 1320	0%
Total mortality	Excluding studies with systematic differences in diet other than fat	Modified fat intake	1.05 (0.93 to 1.18)	7/ 11029/ 1005	7%
Total mortality	Excluding studies with systematic differences in diet other than fat	Reduced fat intake	0.90 (0.60 to 1.34)	4/ 2998/ 89	0%

Table 1. Sensitivity analyses of primary outcomes *(Continued)*

Total mortality	Excluding studies with systematic differences in diet other than fat	Reduced & modified fat intake	0.98 (0.76 to 1.25)	1/ 2033/ 224	NR
Cardiovascular mortality	Mantel-Haenszel, Fixed effects	Overall analysis	0.95 (0.85 to 1.05)	16/ 65983/ 1407	0%
Cardiovascular mortality	Mantel-Haenszel, Fixed effects	Modified fat intake	0.92 (0.79 to 1.08)	6/ 10788/ 593	45%
Cardiovascular mortality	Mantel-Haenszel, Fixed effects	Reduced fat intake	0.96 (0.82 to 1.12)	7/ 52971/ 602	0%
Cardiovascular mortality	Mantel-Haenszel, Fixed effects	Reduced & modified fat intake	0.98 (0.76 to 1.26)	3/ 2224/ 212	0%
Cardiovascular mortality	Peto Odds Ratio (fixed effects)	Overall analysis	OR 0.94 (0.84 to 1.05)	16/ 65983/ 1407	11%
Cardiovascular mortality	Peto Odds Ratio (fixed effects)	Modified fat intake	OR 0.91 (0.77 to 1.08)	6/ 10788/ 593	51%
Cardiovascular mortality	Peto Odds Ratio (fixed effects)	Reduced fat intake	OR 0.96 (0.81 to 1.13)	7/ 52971/ 602	0%
Cardiovascular mortality	Peto Odds Ratio (fixed effects)	Reduced & Modified fat intake	OR 0.97 (0.73 to 1.29)	3/ 2224/ 212	0%
Cardiovascular mortality	Excluding WHI	5Overall analysis	0.91 (0.79 to 1.04)	14/ 17148/ 874	7%
Cardiovascular mortality	Excluding WHI	Reduced fat intake	0.74 (0.47 to 1.17)	5/ 4136/ 69	0%
Cardiovascular mortality	Excluding studies with systematic difference in care	Overall analysis	0.97 (0.70 to 1.33)	4/ 9983/ 451	59%
Cardiovascular mortality	Excluding studies with systematic difference in care	Modified fat intake	0.97 (0.70 to 1.33)	4/ 9983/ 451	59%
Cardiovascular mortality	Excluding studies with systematic difference in care	Reduced fat intake	NR	0/ 0/ 0	NR
Cardiovascular mortality	Excluding studies with systematic difference in care	Reduced & modified fat intake	NR	0/ 0/ 0	NR
Cardiovascular mortality	Excluding studies with systematic differences in diet other than fat	Overall analysis	0.95 (0.80 to 1.13)	9/ 12970/ 748	22%
Cardiovascular mortality	Excluding studies with systematic differences in diet other than fat	Modified fat intake	0.97 (0.75 to 1.26)	5/ 10376/ 503	47%
Cardiovascular mortality	Excluding studies with systematic differences in diet other than fat	Reduced fat intake	0.75 (0.40 to 1.42)	3/ 561/ 44	3%
Cardiovascular mortality	Excluding studies with systematic differences in diet other than fat	Reduced & modified fat intake	1.01 (0.77 to 1.31)	1/ 2033/ 201	NR

Table 1. Sensitivity analyses of primary outcomes *(Continued)*

Combined cardiovascular events	Mantel-Haenszel, Fixed effects	Overall analysis	0.93 (0.88 to 0.98)	23/ 65508/ 4887	50%
Combined cardiovascular events	Mantel-Haenszel, Fixed effects	Modified fat intake	0.83 (0.73 to 0.93)	9/ 11660/ 855	61%
Combined cardiovascular events	Mantel-Haenszel, Fixed effects	Reduced fat intake	0.96 (0.91 to 1.03)	8/ 50655/ 3632	17%
Combined cardiovascular events	Mantel-Haenszel, Fixed effects	Reduced & modified fat intake	0.84 (0.71 to 1.00)	6/ 3193/ 400	40%
Combined cardiovascular events	Peto Odds Ratio (fixed effects)	Overall analysis	OR 0.92 (0.86 to 0.97)	23/ 65508/ 4887	61%
Combined cardiovascular events	Peto Odds Ratio (fixed effects)	Modified fat intake	OR 0.78 (0.67 to 0.91)	9/ 11660/ 855	70%
Combined cardiovascular events	Peto Odds Ratio (fixed effects)	Reduced fat intake	OR 0.96 (0.90 to 1.03)	8/ 50655/ 3632	30%
Combined cardiovascular events	Peto Odds Ratio (fixed effects)	Reduced & modified fat intake	OR 0.79 (0.63 to 1.00)	6/ 3193/ 400	60%
Combined cardiovascular events	Excluding WHI	Overall analysis	0.81 (0.70 to 0.93)	21/ 16673/ 1442	39%
Combined cardiovascular events	Excluding WHI	Reduced fat intake	0.82 (0.63 to 1.05)	6/ 1820/ 187	0%
Combined cardiovascular events	Excluding studies with systematic difference in care	Overall analysis	0.93 (0.77 to 1.12)	9/ 12158/ 533	12%
Combined cardiovascular events	Excluding studies with systematic difference in care	Modified fat intake	0.95 (0.77 to 1.17)	6/ 10753/ 527	24%
Combined cardiovascular events	Excluding studies with systematic difference in care	Reduced fat intake	0.20 (0.01 to 4.13)	1/ 537/ 2	NR
Combined cardiovascular events	Excluding studies with systematic difference in care	Reduced & modified fat intake	0.28 (0.04 to 2.15)	2/ 868/ 4	0%
Combined cardiovascular events	Excluding studies with systematic differences in diet other than fat	Overall analysis	0.85 (0.72 to 1.01)	14/ 14710/ 1097	42%
Combined cardiovascular events	Excluding studies with systematic differences in diet other than fat	Modified fat intake	0.84 (0.65 to 1.09)	8/ 11248/ 701	63%
Combined cardiovascular events	Excluding studies with systematic differences in diet other than fat	Reduced fat intake	0.87 (0.63 to 1.20)	3/ 561/ 109	0%
Combined cardiovascular events	Excluding studies with systematic differences in diet other than fat	Reduced & modified fat intake	0.91 (0.73 to 1.13)	3/ 2901/ 287	0%

Table 2. Subgrouping data for primary outcomes

Analysis described	Total mortality: Number of studies, participants, events	Total mortality: Relative Risk (95% CI), Heterogeneity - I^2, %	CVD mortality: Number of studies, participants, events	CVD mortality: Relative Risk (95% CI), Heterogeneity - I^2, %	CVD events: Number of studies, participants, events	CVD events: Relative Risk (95% CI), Heterogeneity - I^2, %
Main meta-analysis	21, 71790, 4292	0.98 (0.93 to 1.04), 0	16, 65978, 1407	0.94 (0.85 to 1.04), 0	23, 65508, 4887	**0.86 (0.77 to 0.96), 50**
Sub-group 'mean follow-up ≤2 years'	9, 12272, 767	1.05 (0.91 to 1.20), 0	6, 11434, 523	1.04 (0.88 to 1.23), 0	12, 13844, 689	0.95 (0.84 to 1.09), 0
Sub-group 'mean follow-up >2 years'	12, 59518, 3525	0.97 (0.91 to 1.03), 0	10, 54544, 884	0.89 (0.78 to 1.01), 0	11, 51664, 4198	**0.78 (0.67 to 0.92), 72**
Sub-group 'low CVD risk'	10, 66776, 3717	0.99 (0.93 to 1.05), 0	6, 59682, 879	0.93 (0.77 to 1.13), 35	10, 58338, 3408	0.93 (0.82 to 1.05), 13
Sub-group 'moderate CVD risk'	3, 1200, 47	0.69 (0.39 to 1.21), 0	2, 663, 23	0.66 (0.28 to 1.53), 0	5, 1537, 143	0.57 (0.33 to 0.99), 53
Sub-group 'high CVD risk'	8, 3814, 528	0.95 (0.78 to 1.17), 24	8, 5633, 505	0.95 (0.80 to 1.12), 0	8, 5633, 1336	0.88 (0.75 to 1.02), 58
Sub-group 'Dietary advice'	13, 60320, 3201	0.98 (0.92 to 1.05), 0	9, 54703, 796	0.97 (0.85 to 1.12), 0	12, 52595, 3998	0.85 (0.72 to 1.00), 62
Sub-group 'dietary advice plus supplementation'	4, 1372, 219	0.80 (0.63 to 1.02), 0	4, 1372, 169	0.87 (0.62 to 1.21), 15	4, 1372, 395	**0.78 (0.66 to 0.92), 0**
Sub-group 'diet provided'	4, 10098, 872	1.03 (0.92 to 1.15), 0	3, 9903, 442	0.93 (0.69 to 1.26), 63	7, 11541, 494	0.91 (0.73 to 1.14), 19
Sub-group 'total fat in control <30%E'	4, 3592, 81	0.93 (0.61 to 1.43), 0	2, 618, 25	0.76 (0.35 to 1.64), 0	3, 1155, 152	0.82 (0.65 to 1.03), 1
Sub-group 'total fat in control 30-34.9%E'	4, 3450, 333	0.91 (0.46 to 1.81), 23	3, 3344, 21	0.72 (0.15 to 3.53), 51	5, 1429, 74	0.93 (0.62 to 1.39), 0
Sub-group 'total fat in control 35-39.9%E'	8, 62820, 3311	1.00 (0.94 to 1.07), 0	6, 60088, 1054	1.00 (0.88 to 1.12), 0	10, 60919, 4034	0.96 (0.84 to 1.10), 44
Sub-group 'total fat in control 40+%E'	3, 1491, 454	0.96 (0.83 to 1.11), 0	3, 1491, 227	0.80 (0.63 to 1.02), 0	3, 1491, 435	0.83 (0.71 to 0.97), 0
Sub-group 'saturated fat in control <10%E'	2, 3625, 316	0.97 (0.79 to 1.20), 0	1, 3088, 7	0.40 (0.08 to 2.08), -	1, 537, 2	0.20 (0.01 to 4.13), -
Sub-group 'saturated fat in control 10-14.9%E'	5, 50089, 2520	1.01 (0.77 to 1.32), 32	5, 49631, 558	0.98 (0.83 to 1.16), 0	11, 51610, 3565	0.97 (0.87 to 1.07), 10
Sub-group 'saturated fat in control 15-19.9%E'	6, 14598, 1134	1.02 (0.92 to 1.13), 0	4, 11966, 657	0.90 (0.74 to 1.11), 37	5, 11991, 793	0.86 (0.68 to 1.09), 64

Table 2. Subgrouping data for primary outcomes *(Continued)*

Sub-group 'saturated fat in control 20+%E'	0, 0, 0	-	0, 0, 0	-	0, 0, 0	-
Sub-group 'studies of men'	11, 9604, 1224	0.97 (0.87 to 1.08), 7	9, 8951, 735	0.89 (0.77 to 1.02), 0	13, 10589, 1162	**0.82 (0.74 to 0.90), 0**
Sub-group 'studies of women'	5, 59130, 2960	0.99 (0.92 to 1.07), 0	4, 56587, 658	1.03 (0.88 to 1.20), 0	4, 53605, 3566	1.04 (0.89 to 1.21), 53
Sub-group 'studies of men and women'	5, 3056, 108	0.84 (0.58 to 1.22), 0	3, 440, 14	0.45 (0.15 to 1.37), 0	6, 1314, 159	0.60 (0.32 to 1.13), 66
Sub-group 'community setting'	17, 61692, 3420	0.97 (0.91 to 1.03), 0	13, 56077, 965	0.95 (0.84 to 1.07), 0	20, 55605, 4405	**0.84 (0.73 to 0.95), 51**
Sub-group 'residential setting'	4, 10098, 872	1.03 (0.92 to 1.15), 0	3, 9903, 442	0.93 (0.69 to 1.26), 63	3, 9903, 482	0.94 (0.71 to 1.24), 63
Sub-group 'published in 1960s'	6, 2178, 580	0.92 (0.80 to 1.06), 2	5, 1983, 326	0.80, 0.64 to 1.00), 11	9, 3621, 638	**0.81 (0.71 to 0.92), 0**
Sub-group 'published in 1970s'	3, 9515, 584	1.13 (0.95 to 1.33), 9	2, 9057, 304	1.06 (0.85 to 1.33), 0	3, 9159, 301	0.71 (0.35 to 1.43), 88
Sub-group 'published in 1980s'	1, 2033, 224	0.98 (0.76 to 1.25), -	1, 2033, 201	1.01 (0.77 to 1.31), -	1, 2033, 283	0.92 (0.74 to 1.15), -
Sub-group 'published in 1990s'	5, 4880, 137	0.90 (0.65 to 1.26), 0	3, 364, 11	0.27 (0.07 to 1.08), 0	3, 364, 57	**0.51 (0.32 to 0.81), 0**
Sub-group 'published since 2000'	6, 53184, 2767	0.98 (0.91 to 1.05), 0	5, 52541, 565	0.98 (0.83 to 1.15), 0	7, 50331, 3608	0.96 (0.85 to 1.08), 29

Table 3. Meta-regression, exploring effects of dietary changes on the primary outcomes

Outcome / Variable	Total mortality, coefficient (95% CI), number of studies, I^2	Cardiovascular mortality, coefficient (95% CI), number of studies, I^2	Cardiovascular events, coefficient (95% CI), number of studies, I^2	CVD events (co-regression with duration) coefficient (95% CI), number of studies, I^2,
Difference in total fat intake, %E	-0.010 (-0.030 to 0.010), 20, 0%*	-0.023 (-0.074 to 0.029), 14, 4%	-0.012 (-0.037 to 0.012), 21, 25%	-0.016 (-0.045 to 0.013), 21, 23%
Difference in SFA intake, %E	0.005 (-0.016 to 0.026), 18, 0%	-0.006 (-0.050 to 0.037), 14, 3%	-.013 (-0.043 to 0.017), 21, 19%	-0.008 (-0.048 to 0.032), 21, 22%
Difference in MUFA intake, %E	-0.036 (-0.112 to 0.040), 15, 0%	-0.073 (-0.203 to 0.056), 13, 3%	-0.023 (-0.067 to 0.021), 14, 41%	-0.024 (-0.071 to 0.022), 14, 36%
Difference in PUFA intake, %E	-0.004 (-0.016 to 0.008), 17, 0%	-0.000 (-0.027 to 0.026), 14, 4%	-0.002 (-0.022 to 0.019), 19, 24%	-0.006 (-0.032 to 0.021), 19, 27%
Difference in trans fat intake, %E	Insufficient data, 2 studies	Insufficient data, 2 studies	Insufficient data, 2 studies	Insufficient data, 2 studies

Table 3. Meta-regression, exploring effects of dietary changes on the primary outcomes *(Continued)*

Difference in weight, kg	-0.035 (-0.138 to 0.068), 14, 0%	-0.067 (-0.240 to 0.106), 9, 17%	-0.038 (-0.154 to 0.078), 14, 47%	-0.033 (-0.118 to 0.052), 14, 15%**
Difference in LDL cholesterol, mmol/L	-0.948 (-5.752 to 3.856), 6, 0%	-2.909 (-10.529 to 4.710), 6, 0%	-1.600 (-3.815 to 0.616), 7, 28%	-1.465 (-4.094 to 1.164), 7, 25%
Difference in serum total cholesterol, mmol/L	0.024 (-0.168 to 0.217), 18, 0%	-0.187 (-0.505 to 0.131), 15, 0%	-0.155 (-0.554 to 0.244), 17, 49%	-0.155 (-0.635 to 0.325), 17, 53%
Study duration, years	-0.004 (-0.024 to 0.016), 22, 0%	-0.014 (-0.072 to 0.044), 16, 4%	-0.037 (-0.106 to 0.032), 24, 45%	

APPENDICES

Appendix 1. MEDLINE search strategies 1998

MEDLINE on SilverPlatter - diet and cardiovascular disease or mortality - from 1966 to May 1998

explode "NUTRITION"/adverse-effects , classification , contraindications , drug-effects , education , mortality , methods , nursing , physiology , utilization
explode "DIET"/ adverse-effects , blood , contraindications , drug-effects , metabolism , mortality , methods , nursing , physiology , utilization
explode "DIET-THERAPY"/ all subheadings
explode "LIPIDS"/ administration-and-dosage , adverse-effects , therapeutic-use
explode "FOOD"/administration-and-dosage , adverse-effects , drug-effects , therapeutic-use
explode "VITAMINS"/administration-and-dosage , adverse-effects , therapeutic-use
"SELENIUM"/administration-and-dosage , adverse-effects , therapeutic-use
"CALCIUM"/administration-and-dosage , adverse-effects , therapeutic-use
explode "CHLORIDES"/administration-and-dosage , adverse-effects , therapeutic-use
"MAGNESIUM"/administration-and-dosage , adverse-effects , therapeutic-use
"PHOSPHORUS,-DIETARY"/ all subheadings
"POTASSIUM,-DIETARY"/ all subheadings
explode "SODIUM-CHLORIDE"/ all subheadings
explode "TRACE-ELEMENTS"/administration-and-dosage , adverse-effects , therapeutic-use
explode "FLUORIDES"/administration-and-dosage , adverse-effects , therapeutic-use
MEDITERRAN* in TI,AB
explode "ANTIOXIDANTS"/administration-and-dosage , adverse-effects , therapeutic-use
#1 or #2 or #3 or #4 or #5 or #6 or #7
#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#18 or #19
LIPID* near (LOW* or REDUC* or MODIFI*)
DIET* in TI,AB
FAT* near (LOW* or MODIFI* or ANIMAL* or VEGETABLE* or ACID* or MONO?UNSAT* or POLY?UNSAT* or SATURAT* or UNSATUR*)
OIL* near (VEGETABLE* or OLIVE* or RAPE* or SUNFLOW* or LINSEED* or MONO?UNSAT* or POLY?UNSAT* or SATURAT* or UNSATUR*)
MEAT* in TI,AB
WEIGHT* near (REDUC* in TI,AB)
SLIMM* in TI,AB
FISH in TI,AB
ANTI?OXIDA* in TI,AB
VITAMIN* in TI,AB
MINERAL* in TI,AB
SALT* in TI,AB
SODIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
VEGETABLE* in TI,AB
FRUIT* in TI,AB
POTASSIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)

LEGUM* in TI,AB
SOY* in TI,AB
#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
#39 or #40
OAT* in TI,AB
FOLIC* in TI,AB
FOLATE* in TI,AB
IRON* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
FERROUS* in TI,AB
FERRIC* in TI,AB
MARG?RINE* in TI,AB
BUTTER* in TI,AB
STARCH* in TI,AB
GRAIN* in TI,AB
NUT in TI,AB
NUTS in TI,AB
CAFFEIN* in TI,AB
COFFEE* in TI,AB
MULTI?VITAMIN* in TI,AB
CALCIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
SELENIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
MAGNESIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
MANGANESE* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
RETINOL* in TI,AB
CAROTENE* in TI,AB
BETA?CAROTENE* in TI,AB
THIAMIN* in TI,AB
RIBOFLAV* in TI,AB
PYRIDOXIN* in TI,AB
ASCORB* in TI,AB
TOCOPHEROL* in TI,AB
ALPHA?TOCOPHER* in TI,AB
MOLYBDENUM* in TI,AB
COBALAMIN* in TI,AB
BIOTIN* in TI,AB
FOLACIN* in TI,AB
NIACIN* in TI,AB
NICOTINIC* in TI,AB
PANTOTHEN* in TI,AB
PHOSPHORUS* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
CHROMIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
COBALT* in TI,AB
IODINE* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
GARLIC* in TI, AB
ZINC* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
#42 or #43 or #44 or #45 or #46 or #47
#48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57
#58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67
#68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77
#78 or #79 or #80 or #81 or #82
#20 or #41 or #83 or #84 or #85 or #86 or #87
explode "CARDIOVASCULAR-DISEASES"/ complications , diet-therapy , epidemiology , etiology , mortality , prevention-and-control , rehabilitation , secondary , therapy
explode "CEREBROVASCULAR-DISORDERS"/ complications , diet-therapy , epidemiology , etiology , mortality , prevention-and-control , rehabilitation , therapy
explode "NEOPLASMS"/ diet-therapy , mortality , prevention-and-control
CORONARY* near (BYPAS* or GRAFT* or DISEASE* or EVENT*)
CEREBRO?VASCULA*
CARDIO?VASC*
MYOCARDIAL* near (INFARCT* or RE?VASCULAR* or ISCH?EMI*)
MORTAL*

MORBID* near (HEART* or CORONARY* or ISCH?EM* or MYOCARD*)
VASCULAR* near (PERIPHERAL* or DISEASE* or COMPLICATION*)
ANGINA*
STROKE*
HEART* near (DISEASE* or ATTACK* or BYPASS*)
#91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #89 or #90
#102 and #88
(TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
RANDOMIZED-CONTROLLED-TRIAL in PT
CONTROLLED-CLINICAL-TRIAL in PT
RANDOMIZED-CONTROLLED-TRIALS
RANDOM-ALLOCATION
DOUBLE-BLIND-METHOD
SINGLE-BLIND-METHOD
#107 or #108 or #109 or #110 or #105 or #106
#103 not #104
explode "CHILD"/ all subheadings
explode "ADULT"/ all subheadings
#113 and #114
#113 not #115
111 and #112
#117 not #116

MEDLINE on SilverPlatter - lipid outcomes - 1966 to June 1998

diet* in TI,AB
fib?r* in TI,AB
"Diet,-Atherogenic"
"Diet,-Fat-Restricted"/ all subheadings
explode "Fats"/ all subheadings
explode "Fatty-Acids"/ all subheadings
explode "Oils"/ all subheadings
explode "Dairy-Products"/ all subheadings
explode "Dietary-Fats"/ all subheadings
"Dietary-Fiber"/ all subheadings
"Food,-Fortified"/ all subheadings
explode "Nuts"/ all subheadings
lipid* near (low* or reduc* or modif*)
fat* near (diet* or low* or modifi* or animal* or vegetable* or acid* or mono?unsat* or poly?unsat* or saturat* or unsatur*)
oil* near (vegetable* or olive* or rape* or sunflow* or linseed* or mono?unsat* or poly?unsat* or saturat* or unsatur*)
lard* in TI,AB
meat* in TI,AB
garlic* in TI,AB
legum* in TI,AB
marg?rine* in TI,AB
butter* in TI,AB
bean* in TI,AB
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
explode "Lipoproteins"/ all subheadings
explode "Triglycerides"/ all subheadings
lipid*
cholesterol*
lipoprotein*
triglyceride*
HDL*
LDL*
#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#23 and #32
(TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
RANDOMIZED-CONTROLLED-TRIAL in PT
CONTROLLED-CLINICAL-TRIAL in PT
RANDOMIZED-CONTROLLED-TRIALS

RANDOM-ALLOCATION
DOUBLE-BLIND-METHOD
SINGLE-BLIND-METHOD
#35 or #36 or #37 or #38 or #39 or #40
#33 not #34
explode "Child"/ all subheadings
explode "Adult"/ all subheadings
#43 and #44
#43 not #45
#41 and #42
#47 not #46

Appendix 2. Search strategies June 2010

CENTRAL

#1lipid near (low* or reduc* or modifi*)
#2cholesterol* near (low* or modifi* or reduc*)
#3(#1 OR #2)
#4MeSH descriptor Nutrition Therapy explode all trees
#5diet* or food* or nutrition*
#6(#4 OR #5)
#7(#3 AND #6)
#8fat* near (low* or reduc* or modifi* or animal* or saturat* or unsaturat*)
#9MeSH descriptor Diet, Atherogenic explode all trees
#10MeSH descriptor Diet Therapy explode all trees
#11(#7 OR #8 OR #9 OR #10)
#12MeSH descriptor Cardiovascular Diseases, this term only
#13MeSH descriptor Heart Diseases explode all trees
#14MeSH descriptor Vascular Diseases explode all trees
#15MeSH descriptor Cerebrovascular Disorders, this term only
#16MeSH descriptor Brain Ischemia explode all trees
#17MeSH descriptor Carotid Artery Diseases explode all trees
#18MeSH descriptor Dementia, Vascular explode all trees
#19MeSH descriptor Intracranial Arterial Diseases explode all trees
#20MeSH descriptor Intracranial Embolism and Thrombosis explode all trees
#21MeSH descriptor Intracranial Hemorrhages explode all trees
#22MeSH descriptor Stroke explode all trees
#23coronar* near (bypas* or graft* or disease* or event*)
#24cerebrovasc* or cardiovasc* or mortal* or angina* or stroke or strokes or tia or ischaem* or ischem*
#25myocardi* near (infarct* or revascular* or ischaem* or ischem*)
#26morbid* near (heart* or coronar* or ischaem* or ischem* or myocard*)
#27vascular* near (peripheral* or disease* or complication*)
#28heart* 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)

Ovid MEDLINE

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 Randomized Controlled Trials/
4 Random Allocation/
5 Double-Blind Method/
6 Single-Blind Method/
7 or/1-6
8 Animal/ not Human/
9 7 not 8 (419534)
10 (lipid$ adj5 (low$ or reduc$ or modifi$)).mp.
11 (cholesterol$ adj5 (low$ or modific$ or reduc$)).mp.
12 11 or 10
13 exp Nutrition Therapy/
14 (diet$ or food$ or nutrition$).mp.

15 14 or 13
16 12 and 15
17 (fat adj5 (low$ or reduc$ or modifi$ or animal$ or saturat$ or unsatur$)).mp.
18 exp Diet, Atherogenic/
19 exp Diet Therapy/
20 17 or 18 or 19 or 16
21 cardiovascular diseases/ or exp heart diseases/ or exp vascular diseases/
22 cerebrovascular disorders/ or exp brain ischemia/ or exp carotid artery diseases/ or exp dementia, vascular/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp stroke/
23 (coronar$ adj5 (bypas$ or graft$ or disease$ or event$)).mp.
24 (cerebrovasc$ or cardiovasc$ or mortal$ or angina$ or stroke or strokes).mp.
25 (myocardi$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).mp. (190649)
26 (morbid$ adj5 (heart$ or coronar$ or ischaem$ or ischem$ or myocard$)).mp.
27 (vascular$ adj5 (peripheral$ or disease$ or complication$)).mp.
28 (heart$ adj5 (disease$ or attack$ or bypass$)).mp.
29 27 or 26 or 21 or 25 or 28 or 24 or 22 or 23
30 9 and 29 and 20
31 limit 30 to yr="1998 - current"

EMBASE <1980 to 2010 Week 23>

1 cardiovascular diseases/ or exp heart diseases/ or exp vascular diseases/ (1304100)
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/ (320121)
3 (coronar$ adj5 (bypas$ or graft$ or disease$ or event$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (149449)
4 (cerebrovasc$ or cardiovasc$ or mortal$ or angina$ or stroke or strokes).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (838125)
5 (myocardi$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (119244)
6 (morbid$ adj5 (heart$ or coronar$ or ischaem$ or ischem$ or myocard$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (20403)
7 (vascular$ adj5 (peripheral$ or disease$ or complication$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (160186)
8 (heart$ adj5 (disease$ or attack$ or bypass$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (217597)
9 random$.ti,ab. (442747)
10 factorial$.ti,ab. (9473)
11 placebo$.ti,ab. (119397)
12 (doubl$ adj blind$).ti,ab. (90667)
13 (singl$ adj blind$).ti,ab. (8183)
14 double-blind procedure.sh. (78190)
15 randomized controlled trial.sh. (189654)
16 single blind procedure.sh. (9526)
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (553493)
18 animal/ or nonhuman/ or animal experiment/ (3698016)
19 human/ (7063453)
20 19 and 18 (617530)
21 18 not 20 (3080486)
22 17 not 21 (485728)
23 (lipid$ adj5 (low$ or reduc$ or modifi$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (46393)
24 (cholesterol$ adj5 (low$ or modific$ or reduc$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (64458)
25 24 or 23 (89868)
26 (diet$ or food$ or eat$ or nutrition$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (596443)
27 exp nutrition/ (977243)
28 26 or 27 (1182970)
29 28 and 25 (34840)
30 (fat adj5 (low$ or reduc$ or modifi$ or animal$ or saturat$ or unsatur$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (24569)

31 exp lipid diet/ or exp fat intake/ or exp low fat diet/ (31724)
32 31 or 29 or 30 (71041)
33 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5 (1779345)
34 22 and 33 and 32 (3615)
35 limit 34 to yr="2008 -Current" (626)*

*Previous updates were from 1998, so the updated EMBASE searches covered the period January 1998 to June 2010.

F E E D B A C K

Question

Summary

Name: Jos Verbeek
Email Address: jos.verbeek@ttl.fi
Personal Description: Occupation Occupational Physician, Cochrane Review Author

Feedback: Dear Authors,

Many compliments for the enormous amount of work in putting together the evidence on reducing or modifying fat intake as a dietary change to prevent CVD. However, I am of the opinion that you overstated your conclusions and that the recommendation to change to a non-saturated fat diet is not based on sufficient evidence. My arguments are as follows. First of all you have picked one positive outcome out of a dozen of negative outcomes, in fact all other outcomes, to underpin your recommendation. You do not even discuss how come that only this one is supportive and the rest not. I believe that this does not make a strong case for a preventive effect. You do not explain why a much better defined and also plausible outcome as mortality does not show any effect whereas a quite ill-defined effect such as all cardiovascular events does show an effect. In addition, it is difficult to understand why none of the other cardiovascular events, such as myocardial infarctions, shows an effect. I believe that this points much more strongly to no effect than to the overall positive effect that you have formulated.For a person who should decide to change diet, the figures are not very convincing either. Even though you say that this reduces the risk with 14%, in practice, this means that my CVD risk would change from 7% to 6%. Being totally healthy otherwise, it is probably even much lower than that. That is not a big incentive to start changing something important as your diet.
I believe that taking these items into account would further improve the review.

Best wishes

Jos Verbe

Reply

Thank you so much for your thoughts, it is great to get feedback!

We don't agree that we have over-stated our conclusions – we have stated clearly in the abstract that we found no effect on mortality or cardiovascular mortality, but that we did find a small but statistically significant effect on cardiovascular events.

In the abstract we quote the overall effect of reducing or modifying dietary fat on cardiovascular events, but within the review we show that the effect is only seen in longer studies, and in studies that modified fat rather than reducing it. This means that the effect of modifying fat for at least 2 years is considerably greater than the quoted 14%, as the 14% is diluted by reduced fat studies and short studies. The actual effect (of the subgroup of studies that were at least 2 years long and modified fat intake) was around 27% (RR 0.73, 95% CI 0.56 to 0.95, p 0.02, I2 67%, 584 events). However, this was a subgroup analysis and so did not feature in the abstract, and if we had quoted it we would correctly have been challenged for overstating our case.

You worry that there is no supportive evidence of effects on individual cardiovascular events – but there were very few people who experienced myocardial infarction in the studies of modified fat (only 579, with a RR of 0.91, 95% CI 0.72 to 1.16) and even fewer people with stroke (51 people, with a RR of 0.70, 95% CI 0.36 to 1.34). It is quite feasible that reductions in both stroke and MI lead to the reduction in cardiovascular events, but that short term studies diluted the effect seen, and low numbers led to low power, obscuring any effect.

It is not surprising at all that while we saw reductions in cardiovascular events we did not see similar reductions in mortality – fortunately most cardiovascular events are not fatal, and many deaths are not cardiovascular in origin, so if modifying fat intake reduces cardiovascular events the effect on cardiovascular mortality and all-cause mortality will be much less clear.

It is great to hear that your cardiovascular risk is so low – well done! Given your risk is only 7% (or less) even a 50% risk reduction would make only a small difference to you. However, to a person with a larger baseline risk, or for a whole population, a reduction of 14% (or 27% from a long term modified fat diet) is a great help.

With best wishes, Lee and the review team

WHAT'S NEW

Date	Event	Description
21 November 2017	Review declared as stable	This review was split into seven smaller reviews.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 2, 2000

Date	Event	Description
27 March 2012	Amended	New feedback.
27 May 2011	New citation required and conclusions have changed	• The objectives have been clarified and extended • Studies divided by major intervention type: reduced fat, modified fat, reduced and modified fat intervention. Studies comparing reduced with modified fat diets also included. • Analyses run in RevMan as relative risks (rather than as rate ratios) • All meta-analyses, sub-grouping, sensitivity analyses and meta-regressions re-run • Validity assessment updated in all included studies • The first version of the review included 27 studies, 40 intervention arms, 30901 person years. • This update includes 48 studies, including 60 comparisons and 80760 individual participants, published between 1965 and 2009 • Of these 25 comparisons, including 61,958 participants compared a reduced fat diet with usual or control diet, while 15 comparisons, including 13,004 participants compared a modified fat diet with control or usual diet • In this update 10 interventions, including 4,931 participants compared a reduced and modified fat diet with usual or control diet, while nine interventions, including 1290 participants compared a low fat diet with a modified fat diet. The final comparison could not be classified.
27 May 2011	New search has been performed	The searches were updated by the authors to June 2010. New authors have been added.
9 September 2008	Amended	Converted to new review format.
1 February 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All authors were active in the design of the review and in providing critical revisions of the manuscript. Julian Higgins also performed the statistical analyses for the first version of this review, Lee Hooper carried out the statistical analyses for the update; Rachel Thompson, Helen Moore, Diredre Sills and Felicia Roberts (with Indra Tumur and Dorothee Fagard) duplicated the inclusion / exclusion and data extraction of all studies; and Rudolph Riemersma arbitrated on study inclusion where necessary. Shah Ebrahim and Carolyn Summerbell

were primary advisors to the initial review. Lee Hooper originated and was primarily responsible for planning and carrying out the review and was the principal author of the first and update versions.

DECLARATIONS OF INTEREST

LH was employed as a dietitian working in the area of cardiac rehabilitation for much of the duration of the first version of this review. RLT and CDS are also dietitians.

SOURCES OF SUPPORT

Internal sources

- University of East Anglia, UK.

  Help with acquiring papers for the review, time for Lee Hooper to work on the review
- University of Manchester, UK.

  Support with collection of papers for the review.

External sources

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

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

NOTES

This review was split into seven reviews with more specific questions:

Reduction in saturated fat intake for cardiovascular disease

Effects of a long term reduced fat diet on prevention of cardiovascular disease

Effects of a long term modified fat diet on prevention of cardiovascular disease

Effects of a long term reduced and modified fat diet on prevention of cardiovascular disease

Effects of a reduced fat versus a modified fat diet on prevention of cardiovascular disease

Effects of total fat intake on body weight in adults

Effects of total fat intake on body weight in children

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiovascular Diseases [epidemiology] [*prevention & control]; Cholesterol [blood]; Diet, Fat-Restricted [*methods]; Dietary Fats [*administration & dosage]; Fats, Unsaturated [administration & dosage]; Randomized Controlled Trials as Topic; Risk Factors; Triglycerides [blood]

MeSH check words

Adult; Aged; Humans; Middle Aged