Reduced or modified dietary fat for preventing cardiovascular disease

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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.

**Medical Subject Headings (MeSH)**

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

**MeSH check words**

Adult; Aged; Humans; Middle Aged

**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):

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\Delta \text{serum cholesterol (in mg/dl)} = 2.16 \times \Delta \text{dietary saturated fat intake (as percentage of energy)} - 1.65 \times \Delta \text{dietary polyunsaturated intake (as percentage of energy)} + 6.77 \times \Delta \text{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 multifactorial. 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 Cochrane 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 I² 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, subgrouping 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

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing 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 Mod 1995 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 women 1989); 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 women 1989; 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...
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 women 1989, 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 Mod 1995; 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 women 1989; 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.

**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 women 1989, 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 Mod 1995 Rose 1965, Minnesota Coron men 1989, Minnesota Coron women 1989,
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 Mod
1995, Dullaart 1992, Rose 1965, Ball 1965, Boyd 1988, Minnesota Coron men 1989,
Minnesota Coron women 1989, 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, I² 0%, 71,790 participants, 4292 deaths, peffect 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, I² 34%, 11,441 participants, 1120 deaths, peffect 0.81), reduced fat vs usual diet (RR 0.97, 95% CI 0.90 to 1.04, I² 0%, 58,130 participants, 2936 deaths, peffect 0.42), or reduced and modified fat vs usual diet (RR 0.97, 95% CI 0.76 to 1.23, I² 0%, 2219 participants, 236 deaths, peffect 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.

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 metaregressions 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

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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, I² 0%, 65,978 participants, 1407 cardiovascular deaths, p\textsubscript{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, I² 45%, 10,788 participants, 593 cardiovascular deaths, p\textsubscript{effect} 0.46); reduced fat vs usual diet RR 0.96 (95% CI 0.82 to 1.13, I² 0%, 52,971 participants, 602 cardiovascular deaths, p\textsubscript{effect} 0.65); or reduced and modified fat vs usual diet RR 0.98 (95% CI 0.76 to 1.27, I² 0%, 2219 participants, 212 cardiovascular deaths, p\textsubscript{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, I² 50%, 65,508 participants, 4887 people with cardiovascular events, p\textsubscript{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).

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, I² 61%, 11,660 participants, 855 people with CVD events, p\textsubscript{effect} 0.07); reduced and modified fat vs usual diet RR 0.77 (95% CI 0.57 to 1.03, I² 40%, 3193 participants, 400 people with events, p\textsubscript{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, I² 17%, 50,655 participants, 3632 people with CVD events, p\textsubscript{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 nonfatal myocardial infarcts, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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, $p_{\text{effect}}$ 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 more 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, I² 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/m², 95% CI −0.72 to −0.23, I² 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/m², 95% CI −1.30 to 0.91, I² 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/m², 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, I² 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, I² 0%, p<effect 0.54); reduced fat intake MD −0.01mmol/L (95% CI −0.02 to 0.01, 15 comparisons, 7082 participants, I² 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, I² 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 −0.14 to −0.05, 15 comparisons, 7602 participants, I² 0%, p<effect <0.00001)
- 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, I² 59%, p<effect <0.00001); reduced fat intake MD −0.10mmol/L (95% CI −0.14 to −0.05, 15 comparisons, 7602 participants, I² 0%, p<effect <0.00001); reduced and modified fat intake MD −0.26mmol/L (95% CI −0.47 to −0.04, 5 comparisons, 2131 participants, I² 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 \(-0.08\text{mmol/L}, 95\% \text{CI} -0.13 \text{ to } -0.03\), no heterogeneity)
• Total mortality, reduced and modified fat intake: three studies reported total cholesterol (MD \(-0.33\text{mmol/L}, 95\% \text{CI} -0.61 \text{ to } -0.06\), I\(^2\) 65%)
• Cardiovascular mortality, modified fat intake: two studies reported total cholesterol (MD \(-0.32\text{mmol/L}, 95\% \text{CI} -0.67 \text{ to } 0.04\), no heterogeneity)
• Cardiovascular mortality, reduced fat intake: four studies reported total cholesterol (MD \(-0.08\text{mmol/L}, 95\% \text{CI} -0.14 \text{ to } -0.02\), no heterogeneity)
• Cardiovascular mortality, reduced and modified fat intake: three studies reported total cholesterol (MD \(-0.33\text{mmol/L}, 95\% \text{CI} -0.61 \text{ to } -0.06\), I\(^2\) 65%)
• Cardiovascular events, modified fat intake: four studies reported total cholesterol (MD \(-0.44\text{mmol/L}, 95\% \text{CI} -0.54 \text{ to } -0.35\), no heterogeneity)
• Cardiovascular events, reduced fat intake: three studies reported total cholesterol (MD \(-0.08\text{mmol/L}, 95\% \text{CI} -0.14 \text{ to } -0.02\), no heterogeneity)
• Cardiovascular events, reduced and modified fat intake: three studies reported total cholesterol (MD \(-0.33\text{mmol/L}, 95\% \text{CI} -0.61 \text{ to } -0.06\), I\(^2\) 65%)

**Triglycerides:** Modified fat intake and reduced and modified fat intake studies both reduced fasting triglycerides (modified fat intake MD \(-0.11\text{mmol/L}, 95\% \text{CI} -0.22 \text{ to } -0.00\), 5 comparisons, 706 participants, I\(^2\) 0%, p\(_{\text{effect}}\) 0.04; reduced and modified fat intake MD \(-0.27\text{mmol/L}, 95\% \text{CI} -0.53 \text{ to } -0.00\), 3 comparisons, 218 participants, I\(^2\) 0%, p\(_{\text{effect}}\) 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 \(-0.00\text{mmol/L}, 95\% \text{CI} -0.00 \text{ to } 0.00\), 13 comparisons, 6875 participants, I\(^2\) 0%, p\(_{\text{effect}}\) 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 \(-0.10\text{mol/L}, 95\% \text{CI} -0.26 \text{ to } 0.06\))
• Total mortality, reduced fat intake: four studies reported triglycerides (MD \(-0.02\text{mmol/L}, 95\% \text{CI} -0.13 \text{ to } 0.08\), no heterogeneity)
• Total mortality, reduced and modified fat intake: two studies reported triglycerides (MD \(-0.31\text{mmol/L}, 95\% \text{CI} -0.62 \text{ to } -0.01\), no heterogeneity)
• Cardiovascular mortality, modified fat intake: no studies reported triglycerides
• Cardiovascular mortality, reduced fat intake: four studies reported triglycerides (MD \(-0.02\text{mmol/L}, 95\% \text{CI} -0.13 \text{ to } 0.08\), no heterogeneity)
• Cardiovascular mortality, reduced and modified fat intake: two studies reported triglycerides (MD \(-0.31\text{mmol/L}, 95\% \text{CI} -0.62 \text{ to } -0.01\), no heterogeneity)
• Cardiovascular events, modified fat intake: one study reported triglycerides (MD $-0.26\text{mmol/L}$, 95%CI $-0.50$ to $-0.02$)

• Cardiovascular events, reduced fat intake: four studies reported triglycerides (MD $-0.50\text{mmol/L}$, 95%CI $-1.05$ to $0.05$, $I^2 52\%$)

• Cardiovascular events, reduced and modified fat intake: two studies reported triglycerides (MD $-0.31\text{mmol/L}$, 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 $-0.56\text{mmHg}$, 95% CI $-11.22$ to $1.06$, 6 comparisons, 3981 participants, $I^2 0\%$, $p_{\text{effect}} 0.25$; diastolic BP MD $-0.35\text{mmHg}$, 95% CI $-0.96$ to $0.26$, 6 comparisons, 3543 participants, $I^2 0\%$, $p_{\text{effect}} 0.26$). 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 $-0.55\text{mmHg}$, 95%CI $-1.54$ to $0.43$, no heterogeneity)

• Total mortality, reduced fat intake: three studies reported dBP (MD $-0.32\text{mmHg}$, 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 $-0.67\text{mmHg}$, 95%CI $-2.23$ to $0.89$, no heterogeneity)

• Cardiovascular mortality, reduced fat intake: two studies reported dBP (MD $-0.43\text{mmHg}$, 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 $-0.55\text{mmHg}$, 95%CI $-11.22$ to $1.06$, no heterogeneity)

• Cardiovascular events, reduced fat intake: three studies reported dBP (MD $-0.32\text{mmHg}$, 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).

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, I² 54%) and body mass index (MD −0.47kgm⁻², 95%CI −0.72 to −0.23, 5972 participants, I² 51%). Similar modest improvements were seen in LDL cholesterol (MD −0.10mmol/L, 95%CI −0.14 to −0.05, 5971 participants, I² 0%) and total cholesterol (MD −0.10mmol/L, 95%CI −0.14 to −0.05, 7602 participants, I² 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, I^2 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, I^2 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 −0.44 mmol/L, 95% CI −0.60 to −0.28, 2280 participants, I^2 59%) and modestly reduce fasting serum triglycerides (MD −0.11 mmol/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, I^2 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, I² 51%), serum LDL cholesterol (MD −0.21mmol/L, 95%CI −0.35 to −0.08, 627 participants, I² 0%) and fasting serum triglycerides (MD −0.27mmol/L, 95%CI −0.53 to −0.00, 218 participants, I² 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 subgrouping, 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).

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.
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 complete 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; Shepheard 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 individual’s 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.

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**CHARACTERISTICS OF STUDIES**

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

Anderson 1990
### Azadbakht 2007

**Methods**

RCT

**Participants**

Overweight and obese people (Iran)

**Interventions**

Reduced fat diet vs usual diet

Control aims: no diet intervention

Intervention aims: 25% from fats, 20% from protein, 55% 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) | 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 |
| 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 |

**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) | 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 |
| 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 |
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%, MUFA 7%, PUFA 7%, protein 15%, CHO 65%, 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) |
| 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 |
| 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) All outcomes | Low risk | Not relevant for primary and secondary outcomes as all trialists asked for data |
| Other bias | Low risk | |

Ball 1965
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)%
Saturated fat intake: unclear

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
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    | Low risk           | “allocated at random to one of two groups at each hospital”                            |
| Allocation concealment        | Unclear risk       | Randomisation method not clearly described                                            |
| Blinding                      | High risk          | Participants were not blinded, the researcher who assessed outcomes was blinded to treatment arm |
| Incomplete outcome data       | Unclear risk       | Unclear if any lost to follow up                                                      |
| Selective reporting           | Low risk           | Not relevant for primary and secondary outcomes as all trialists asked for data       |
| Other bias                    | Low risk           |                                                                                       |
| Free of systematic difference | Unclear risk       | See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Free of dietary differences   | 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
  - 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) | High risk          | Participants not blinded, but outcome assessors blinded to intervention                 |
| Incomplete outcome data (attrition bias)  | 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

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*Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.*
Intervention: unclear how many randomised, 217 analysed
Mean years in trial: unclear (max duration 0.5 years)
% 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) | High risk | Participants knew their allocation, unclear for outcome assessor |
| 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 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 |
| Incomplete outcome data (attrition bias) | 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)

| 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) | High risk | Participants were not blinded, those assessing physical outcomes were blinded, those assessing symptoms were not |
| Incomplete outcome data (attrition bias) | 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% post-menopausal)
(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 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
  - **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 Massachusetts, but not those from the other 3 centres, and allocation could not be altered later
  - **Blinding (performance bias and detection bias)**: High risk
    - Participants not blinded, unclear about researchers
  - **Incomplete outcome data (attrition bias)**: 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
    - 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
    - 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 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) | High risk          | Participants were clear about whether they were in the control or an intervention group |
| Incomplete outcome data (attrition bias)       | 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           | Trial shop used by both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Free of systematic difference in care?         | Low risk           | See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies |
| Free of dietary differences other than fat?    | Low risk           | |

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)

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
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 |
|------|--------------------|-----------------------|
| 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)
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) | High risk | Participants not blinded, researchers unclear |
| Incomplete outcome data (attrition bias) | 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%
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    | Low risk           | randomised using sealed envelopes                                                     |
| (selection bias)              |                    |                                                                                        |
| Allocation concealment        | Unclear risk       | Unclear if envelopes were opaque                                                      |
| (selection bias)              |                    |                                                                                        |
| Blinding                      | High risk          | Physician blinding: yes                                                                 |
| (performance bias and detection bias) All outcomes | | Participant blinding: unclear |
| Incomplete outcome data       | Low risk           | GPs contacted for information on mortality and morbidity when patients did not attend |
| (attrition bias)              |                    |                                                                                        |
| Selective reporting           | Low risk           | Not relevant for primary and secondary outcomes as all trialists asked for data       |
| (reporting bias)              |                    |                                                                                        |
| Other bias                    | Low risk           |                                                                                        |
| 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 |
| 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) | High risk | Not for dietary intervention. |
| Incomplete outcome data (attrition bias) | 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%, MUFA 5-15%, PUFA 0-10%, protein 10-20%, CHO 45-55%, added sugars 5-15%, alcohol <5%, glycaemic index high, energy density high, energy intake ad libitum

Low fat aims: 20-30% E from fat, SFA <10%, MUFA 5-15%, PUFA 5-10%, protein 10-20%, CHO 55-65%, added sugars <10%, alcohol <5%, 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

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) | High risk | Participants were aware of their own allocated diet, those assessing outcomes unclear |
| Incomplete outcome data (attrition bias) | 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)
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%, PUFA 5-10%, protein 10-20%, CHO 40-50%, added sugars <10%, alcohol <5%, glycaemic index low, energy density high, energy intake ad libitum
Low fat aims: 20-30%E from fat, SFA <10%, MUFA 5-15%, PUFA 5-10%, protein 10-20%, CHO 55-65%, added sugars <10%, alcohol <5%, 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
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 Mod fat 2008
### Methods

| Participants | RCT |
|--------------|-----|
| 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, CHO45-55%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 |  
| 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) All outcomes | Low risk | Not relevant for primary and secondary outcomes as all trialists asked for data |  
| Other bias | Low risk | Yes, advice and shop system was the same across all groups |  
| Free of systematic difference in care? | Low risk | |
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 |
| Setting: community |
| Outcomes | Stated trial outcomes: albuminuria and serum lipoproteins 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 |
### 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
- Control aims: dietary advice for total fat 38-42%E, dietary cholesterol 500mg/day, protein 18-22% E, CHO 38-42%, 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) | High risk | Neither participants nor physicians appear blinded |
| Incomplete outcome data (attrition bias) | 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 | 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
- 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 |
|------|--------------------|-----------------------|
| 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) | High risk | Participants were not blinded, unclear about researchers |
| Incomplete outcome data (attrition bias) | 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 | Notes |
|--------------|-------|
| 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
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) | High risk | Participants were not blinded, outcome assessors were |
| Incomplete outcome data (attrition bias) | 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 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) | High risk | Participants knew allocation, unclear whether researchers did also |
| Incomplete outcome data (attrition bias) | 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       | Low risk           |                                                                                       |
| Allocation concealment           | Low risk           | “stratification by physician, gender, age, randomisation by research associate, centrally, using random numbers generated by computer” |
| Blinding (performance bias)      | High risk          | Participants not blinded, physicians were                                             |
| Incomplete outcome data          | Unclear risk       | Unclear, deaths, cancer and CV events are drop-outs - unclear if any data missing. ITT analysis performed |
| Selective reporting              | Low risk           | Not relevant for primary and secondary outcomes as all trialists asked for data      |
| Other bias                       | Low risk           |                                                                                        |
| Free of systematic difference    | High risk          | More frequent visits for intervention group. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| Dietary differences other than  | High risk          | Dietary fibre advice also in intervention group                                        |
| fat?                             |                    |                                                                                        |

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

**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**

| 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) | High risk | Participants were aware of assignment, researchers uncertain |
| 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

| 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 women 1989

**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
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                | Low risk           | “stratified randomisation”                                                            |
| Allocation concealment                    | Unclear risk       | Randomisation method not clearly described                                           |
| Blinding                                  | Low risk           | Physician blinding: adequate                                                          |
|                                           |                    | Participant blinding: adequate                                                        |
| Incomplete outcome data                   | High risk          | No, participants appear to have been lost on leaving the institution                 |
| Selective reporting                       | Low risk           | Not relevant for primary and secondary outcomes as all trialists asked for data      |
| Other bias                                | 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 systematic difference in care?    | Low risk           | See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies |
| Free of dietary differences other than fat? | Low risk           |                                                                                      |

### 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), control 38.0 (sd unclear)%
Saturated fat intake (at 2 years): low fat 11.5 (sd unclear), control 14.4 (sd unclear)%
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) 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
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

BiasAuthors’ judgementSupport for judgement
Random sequence generation (selection bias)Unclear risk“using random numbers, by blocks within hospitals”
Allocation concealment (selection bias)Unclear riskRandomisation method not clearly described
Blinding (performance bias and detection bias)All outcomesHigh risk
Physician blinding: adequate
Participant blinding: inadequate
Incomplete outcome data (attrition bias)All outcomesHigh risk
Data collection was thorough, but some participants dropped out and contact was lost
Selective reporting (reporting bias)All outcomesLow riskNot relevant for primary and secondary outcomes as all trialists asked for data
Other biasLow 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 riskSee Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies

MSFAT 1997

MethodsRCT
ParticipantsHealthy 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)

InterventionsReduced 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

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
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

| 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 | 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) | High risk | Participants aware of allocation, those analysing biochemistry were not |
| Incomplete outcome data (attrition bias) | 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 | Sex 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)
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 |                     |
| 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 ch ol 650-750mg/d, P/S 0.4
Intervention B: total fat 30% E, SFA <9% E, dietary ch ol 350-450mg/d, PUFA 15% E, P/S 1.5
Intervention X: total fat 30% E, SFA <9% E, dietary ch ol 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

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
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                                                                 |
|-----------------------------------------|--------------------|---------------------------------------------------------------------------------------|
| Random sequence generation              | Low risk           | Stratified randomisation by the statistical centre                                     |
| Allocation concealment                  | Low risk           |                                                                                       |
| Blinding                                | 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                 | High risk          | Dropouts do not appear to have been followed for death or CV events. Death, cancer and CV events for participants otherwise still included in the study were collated as a reason for study exclusion |
| Selective reporting                     | 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%, SFA 16-18%, dietary chol 650-750mg/d, P/S 0.4
Intervention C: total fat 40%, SFA <9%, dietary chol 350-450mg/d, PUFA 18-20%, 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
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    | Low risk           | Stratified randomisation by the statistical centre                                     |
| Allocation concealment        | Low risk           |                                                                                        |
| Blinding                      | Low risk           | All reduced saturated fat and purchased blinded foods from a trial shop, double blind  |
| Incomplete outcome data       | 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           | Low risk           | Not relevant for primary and secondary outcomes as all trialists asked for data       |
| Other bias                    | Low risk           |                                                                                        |
| Free of systematic difference | 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   | 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)

Interventions
Reduced and modified fat vs usual diet
Control aims: total fat 40%, SFA 16-18%, 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 |
| 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) 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) All outcomes 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)
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 Participants 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

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
Mean years in trial: control 0.68, intervention 0.70
% 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 |

| Setting: | community |

| Outcomes | Stated trial outcomes: body weight, body fat, lipids, glucose, insulin |
| 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 |
| 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

### 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)** | 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)** | 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 | 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 systematic difference in care?** | High risk | Differences in fruit and vegetables, fish etc. as above. |
| **Free of dietary differences other than fat?** | High risk | |

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
- 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) | High risk          | Participants not blinded, physicians unclear                                            |
| Incomplete outcome data (attrition bias) | 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  
% 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 |

**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) | High risk | Outcome assessors blinded, participants not. |
| Incomplete outcome data (attrition bias) | 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 |
| Free of dietary differences other than fat? | High risk | Fibre, fruit and vegetable goals in intervention group |

**PREMIER 2003**
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 6 months, 180 mins/week of moderate physical activity, limited sodium, 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 intake, 9-12 portions fruit and veg |

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    | Low risk           | Randomisation was carried out centrally by computer programme, stratified by clinic and baseline BP, blocked |
| Allocation concealment        | Low risk           |                       |
| Blinding (performance bias and detection bias) | 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       | Low risk           | All those randomised were included in the analysis of both events and blood pressure |
| Selective reporting           | 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)
**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%, protein 15%, 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  
**Notes**  
**Risk of bias**  
| Bias                             | Authors’ judgement | Support for judgement                                      |
|---------------------------------|--------------------|-----------------------------------------------------------|
| Random sequence generation      | Low risk           | Following 3 or 6 weeks compliance with control diet run-in, stratified block randomisation with tables of random numbers |
| Allocation concealment          | 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 |

**Outcomes**  
Stated trial outcomes: metabolic effects  
Data available on total mortality? yes (no events)  
Cardiovascular mortality? yes (no events)  
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  

**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 |
| 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
### Interventions

**Reduced fat vs Modified fat diet**

- **Reduced fat aims:**
  - Total fat: 20% E
  - SFA: ≤8% E
  - MUFA: 6% E
  - PUFA: 6% E
  - Dietary chol: 150mg/1000kcal
  - CHO: 55% E
  - 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
  - Modified fat: 35.1 (sd 7.0)%E

- Saturated fat intake (at 2 years):
  - Low fat: 8.9 (sd 3.8)%E
  - Modified 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 |
| **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 | Identical follow up for all groups |

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_Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15._
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 counseling, 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 counseling, 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 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
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, rape-seed oil, butter and semi-skinned 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 |
| Blinding (performance bias and detection bias) All outcomes | High risk | Participants and researchers knew allocation |
### 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) | High risk          | Participants and researchers knew allocation                                           |
| Incomplete outcome data (attrition bias)       | Unclear risk       | Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing |

### 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, rape-seed 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 34 (sd 4), cont 36 (sd 5)%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**

- **Incomplete outcome data (attrition bias)**
  - Unclear risk
  - Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing

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Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
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, rape-seed 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
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 Mod 1995

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)

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    | Low risk           | “randomisation stratified for men and women, singles and couples, random number tables” |
| Allocation concealment        | Unclear risk       | Randomisation method not clearly described |
| Blinding (performance bias)   | High risk          | Participants and researchers knew allocation |
| Incomplete outcome data       | Unclear risk       | Unclear, deaths, cancer and CV events are drop-outs, trialists asked for data - unclear if any data missing |
| Selective reporting           | 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)  Unclear risk  Blinding unclear for participants and researchers

Incomplete outcome data (attrition bias)  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 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 dietary 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 |
|---|

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| 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) Other bias | Low risk | Not relevant for primary and secondary outcomes as all trialists asked for data |
| Free of systematic difference in care? | High risk | Very different contact time with dietitian, but medical appointments same in both groups. See Control and Intervention Methods in Interventions section of the Table of Characteristics of Included Studies |
| 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  
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
- 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)    | High risk          | Physician blinding: unclear Participant blinding: inadequate              |
| Incomplete outcome data (attrition bias)          | 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

| 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%, MUFA 10%, CHO 54-57%
- Modified fat aims: total fat 37-40%E, SFA ≤10%, 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**
  - **Random sequence generation** (selection bias)
    - Low risk
    - “randomly assigned”
  - **Allocation concealment** (selection bias)
    - Unclear risk
    - No details provided
  - **Blinding** (performance bias and detection bias)
    - 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
  - **Selective reporting** (reporting bias)
    - Unclear risk
    - Unclear
  - **Other bias**
    - Low risk
    - Similar intervention in both groups
  - Free of systematic difference in care?
    - Low risk
  - 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 |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection     | Low risk           | “random numbers”      |
|   bias)                                   |                    |                       |
| Allocation concealment (selection bias)   | Unclear risk       | Randomisation method not clearly described |
| Blinding (performance bias and detection  | High risk          | Physician blinding: adequate participant blinding: inadequate |
|   bias) All outcomes                      |                    |                       |
| Incomplete outcome data (attrition bias)  | Low risk           | Survival analysis used |
|   All 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          | 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    | Low risk           | See Control and Intervention Aims in Interventions section of the Table of Characteristics of Included Studies |
|   fat?                                    |                    |                       |

THIS DIET 2008
### 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
- **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
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) 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, 5 veg/d, 3 fruit/d, 16 oz veg juice and 30 g/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              | Low risk           | Randomisation via computer programme             |
| (selection bias)                        |                    |                                                 |
| Allocation concealment                  | Low risk           |                                                 |
| (selection bias)                        |                    |                                                 |
| Blinding                                | High risk          | Participants aware of allocation                |
| (performance bias and detection         |                    |                                                 |
| bias)                                   |                    |                                                 |
| Incomplete outcome data                 | Low risk           | Monitoring of national death register and medical|
| (attrition bias)                        |                    | records                                         |
| All outcomes                            |                    |                                                 |
| Selective reporting                     | Low risk           | Not relevant for primary and secondary outcomes |
| (reporting bias)                        |                    | as all trialists asked for data                 |
| All outcomes                            |                    |                                                 |
| 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  | High risk          | Fruit and veg intervention in low fat arm, not in|
| fat?                                    |                    | 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

**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**

| 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)                      | High risk          | Participants aware of allocation |
| Incomplete outcome data (attrition bias)                            | 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**

| Bias                                                                 | Low risk           |
|----------------------------------------------------------------------|--------------------|
| Free of systematic difference in care?                              | High risk          |
| Free of dietary differences other than fat?                         | High risk          |

**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
Setting: community

Outcomes
- Stated trial outcomes: breast cancer, mortality, other cancers, cardiovascular events, diabetes
- 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 diagnoses*
- 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
- 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) | High risk         | Participants not blinded, not relevant for assessment of mortality by researchers |
| 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           |                                                            |
| 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 |

Abbreviations:
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)                       |
| Amtzenius 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                              |
| Bergstrom 1967     | Intervention and randomised follow up less than 6 months                              |
| Bierenbaum 1963    | No appropriate control group (and not low fat vs modified fat)                       |
| Bloemhoff 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                              |
| Butowskki 1998     | Not randomised                                                                        |
| Byers 1995         | No appropriate control group (and not low fat vs modified fat)                       |
| Caggia 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                              |

*Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.*
| Study                  | Reason for exclusion                                      |
|-----------------------|----------------------------------------------------------|
| 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 |
| 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 |
| Denmark 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) |
| 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) |
| Study                  | Reason for exclusion                                                                 |
|------------------------|---------------------------------------------------------------------------------------|
| 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                              |
| 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                              |
| Study            | Reason for exclusion |
|------------------|----------------------|
| 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 |
| 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 |
| Study                     | Reason for exclusion                                      |
|--------------------------|-----------------------------------------------------------|
| Laitinen 1993            | Multifactorial intervention                               |
| 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 |
| Luszczyńska 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 |
| Markkmann 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   |
| 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 |
| Study                        | Reason for exclusion                                                                 |
|------------------------------|---------------------------------------------------------------------------------------|
| 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) |
| 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                                                                        |
| Study                  | Reason for exclusion                                                                 |
|-----------------------|---------------------------------------------------------------------------------------|
| 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                                                                         |
| 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                               |
| 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)                         |
Study | Reason for exclusion
--- | ---
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
Wasserman 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
Wentraub 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
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 |
|---------|-----|
| 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%, 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 |

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
### 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) accrued 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

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*Hooper et al.* Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
| 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] |
| Outcome or subgroup title                      | No. of studies | No. of participants | Statistical method                   | Effect size          |
|-----------------------------------------------|----------------|---------------------|--------------------------------------|----------------------|
| 3.3 Reduced and modified fat intake           | 6              | 3193                | Risk Ratio (M-H, Random, 95% CI)     | 0.77 [0.57, 1.03]    |

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

**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] |
| 4 HDL cholesterol, mmol/L.kg | 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] |
| Outcome or subgroup title                         | No. of studies | No. of participants | Statistical method                        | Effect size          |
|-------------------------------------------------|----------------|---------------------|------------------------------------------|----------------------|
| 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)     | −5.09 [−3.25, 3.24]  |
| 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]       |
| 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]  |

### 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]    |

### 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]       |
### Outcome or subgroup title

|                         | No. of studies | No. of participants | Statistical method                    | Effect size          |
|-------------------------|----------------|---------------------|---------------------------------------|----------------------|
| 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]   |

### Comparison 6

**fat reduction vs fat modification - tertiary outcomes**

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 1 fat modification or reduction vs usual diet - primary outcomes
Outcome: 1 Total mortality

| Study or subgroup | reduced or modified | usual diet | Risk Ratio | Weight | Risk Ratio
|------------------|---------------------|------------|-----------|--------|-----------|
|                 | n     | n     | (95% CI)   |        | (95% CI)   |
| Veterans Admin. 1949 | 1744/124 | 1771/112 | 1.27 | 0.01 (0.83, 1.95) |
| Iva 1965        | 854    | 126   | 1.97 | 0.03 (0.51, 7.90) |
| Oslo Diet Heart 1964 | 482/266 | 65/236 | 3.25 | 0.14 (0.54, 1.02) |
| MRC 1968        | 207/199 | 32/194 | 1.55 | 0.08 (0.55, 4.14) |
| NHSD Food trial | 41/43  | 0.92 | 3.35 | 0.16 (0.84, 4.04) |
| Minnesota Coron men 1989 | 1525/2197 | 1532/746 | 1.91 | 1.03 (0.69, 1.48) |
| Minnesota Coron women 1989 | 1112/244 | 1532/742 | 1.57 | 1.14 (0.86, 1.51) |
| Sydney Diet Heart 1970 | 392/211 | 281/237 | 1.45 | 0.66 (0.35, 2.86) |

Subtotal (95% CI) 5788 5653 * 30.8% 1.02 (0.88, 1.18) |

Total events 5788 (reduced or modified diet), 5653 (usual diet)
Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.33, df = 7, P = 0.16; I^2 = 34%
Test for overall effect: Z = 2.44 (P = 0.01)

2 Reduced fat intake

Bul 1965 | 201/33 | 29/29 | I.1 | 0.07 (0.51, 1.50) |
WHO 2006 | 157/973 | 19/146 | 0.72 | 1.18 (0.46, 2.30) |
Brock 1994 | 19/66 | 267/72 | 0.12 | 0.63 (0.20, 1.96) |
Polyt Prevention 1996 | 412/1037 | 41/43 | 1.19 | 0.90 (0.61, 1.40) |
Lay 2004 | 6/4 | 6/88 | 0.17 | 0.88 (0.03, 1.61) |
WHOCCS 2001 | 0/50 | 1/56 | 0.05 | 0.57 (0.02, 1.14) |
PREDIMED 2003 | 32/29 | 1/28 | 0.05 | 0.33 (0.01, 1.12) |
DO-TT 2006 | 170/244 | 21/241 | 0.09 | 0.79 (0.43, 1.47) |

WHO without CVD 2006 | 150/1194 | 149/1292 | 1.01 | 0.08 (0.07, 1.16) |
WHO 2007 | 152/137 | 140/150 | 0.74 | 0.09 (0.07, 1.12) |

Subtotal (95% CI) 23932 34198 * 63.6% 0.97 (0.90, 1.04) |

Total events 23932 (reduced or modified diet), 34198 (usual diet)
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.86, df = 3 (P = 0.60); I^2 = 0%
Test for overall effect: Z = 1.64 (P = 0.49)

3 Reduced and modified fat intake

DASH 1989 | 111/1038 | 113/1015 | 0.98 | 0.01 (0.76, 1.25) |
STARS 1992 | 1/17 | 32/28 | 0.12 | 0.83 (0.04, 1.62) |
Sondergaard 2002 | 4/8 | 4/6 | 0.13 | 0.29 (0.04, 1.15) |

Subtotal (95% CI) 3113 1106 * 5.6% 0.97 (0.76, 1.25) |

Total events 3113 (reduced or modified diet), 1106 (usual diet)
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.01, df = 1 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 0.56 (P = 0.57)

Total (95% CI) 34033 40957 * 100.0% 0.98 (0.83, 1.14) |

Total events 34033 (reduced or modified diet), 40957 (usual diet)
Heterogeneity: Tau^2 = 0.00; Chi^2 = 15.52, df = 20 (P = 0.74); I^2 = 0%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 = 0%
## Analysis 1.2

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 2 Cardiovascular mortality

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|------------------------|-----------|--------------------|--------|--------------------|
|                  | n | nH |                  |        |                   |
| I Modified fat intake  |             |           |                    |        |                   |
| Veterans Affairs 1969 | 52(42)     | 81(62)   | 1.08(0.95-1.23)    | 0.05  | 0.92(0.76-1.11)    |
| Aus 1965          | 8/54       | 10/56    | 0.31(0.15-0.66)    | 0.03  | 0.36(0.15-0.88)    |
| Oslo Diet Heart 1966 | 38/306   | 32/206   | 0.76(0.56-1.06)    | 0.07  | 0.71(0.56-0.90)    |
| MRC 1948           | 21/199     | 20/194   | 1.13(0.68-1.90)    | 0.06  | 1.05(0.63-1.76)    |
| Minnesota Coron men 1989 | 922/197   | 942/194  | 1.32(0.74-2.30)    | 0.08  | 0.88(0.44-1.78)    |
| Minnesota Coron women 1989 | 652/244  | 532/230  | 0.81(0.57-1.16)    | 0.09  | 0.77(0.50-1.20)    |
| **Subtotal (95% CI)** | **5424** | **5364** |                   |        |                   |
|                  |        |        | 44.0%              | 0.92  | 0.73(1.15)         |

Total events: 287 (reduced or modified fat), 396 (usual diet)

Heterogeneity: $\chi^2 = 50.6$, $df = 5$, $P = 0.03$, $I^2 = 51$

Test for overall effect: $Z = 0.14$, $P = 0.15$

2 Reduced fat intake

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|------------------------|-----------|--------------------|--------|--------------------|
|                  | n | nH |                  |        |                   |
| I Modified fat intake  |             |           |                    |        |                   |
| SUB 1994          | 29/219    | 23/196   | 1.09(0.69-1.72)    | 0.07  | 0.82(0.53-1.25)    |
| Sub 1994          | 0/66      | 1/67     | 0.02(0.00-1.64)    | 0.04  | 0.03(0.00-1.49)    |
| Lyr 2004          | 1/88      | 4/88     | 0.25(0.03-2.19)    | 0.02  | 0.25(0.03-2.19)    |
| DID 2006          | 3/346     | 1/344    | 1.33(0.31-5.70)    | 0.06  | 0.76(0.13-4.30)    |
| VVW without CYD 2006 | 179/633  | 158/673  | 2.10(0.81-5.26)    | 0.08  | 1.25(0.77-2.02)    |
| VVW and CYD 2006  | 43/390    | 62/369   | 0.54(0.34-0.85)    | 0.08  | 0.50(0.32-0.80)    |
| VVW 2007          | 2/1537    | 5/1551   | 0.23(0.04-1.28)    | 0.09  | 0.23(0.04-1.28)    |
| **Subtotal (95% CI)** | **21601** | **31570** |                   |        |                   |
|                  |        |        | 40.2%              | 0.96  | 0.82(1.13)         |

Total events: 341 (reduced or modified fat), 481 (usual diet)

Heterogeneity: $\chi^2 = 12.9$, $df = 4$, $P = 0.03$, $I^2 = 24$

Test for overall effect: $Z = 0.48$, $P = 0.63$

3 Reduced and modified fat intake

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|------------------------|-----------|--------------------|--------|--------------------|
|                  | n | nH |                  |        |                   |
| I Modified fat intake  |             |           |                    |        |                   |
| DARTA 1999        | 250/1470  | 150/1310 | 1.51(0.80-2.84)    | 0.07  | 1.05(0.77-1.44)    |
| STARS 1995        | 5/217     | 3/218    | 0.23(0.06-0.92)    | 0.05  | 0.12(0.02-0.76)    |
| Sondergard 2003   | 5/84      | 1/83     | 0.24(0.03-1.88)    | 0.08  | 0.13(0.02-0.84)    |
| **Subtotal (95% CI)** | **1113**  | **1106** |                   |        |                   |
|                  |        |        | 15.8%              | 0.28  | 0.76(1.27)         |

Total events: 105 (reduced or modified fat), 107 (usual diet)

Heterogeneity: $\chi^2 = 4.0$, $df = 1$, $P = 0.05$, $I^2 = 0$

Test for overall effect: $Z = 0.5$, $P = 0.60$

4 Total (95% CI)

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|------------------------|-----------|--------------------|--------|--------------------|
|                  | n | nH |                  |        |                   |
| I Modified fat intake  |             |           |                    |        |                   |
| Total events: 423 (reduced or modified fat), 474 (usual diet)
| Heterogeneity: $\chi^2 = 4.7$, $df = 1$, $P = 0.05$, $I^2 = 0$
| Test for overall effect: $Z = 1.1$, $P = 0.23$
| Test for subgroup differences: $\chi^2 = 0.17$, $df = 1$, $P = 0.01$, $I^2 = 0$

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 1 fat modification or reduction vs usual diet - primary outcomes
Outcome: 3 Combined cardiovascular events

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|-------------------------|-----------|---------------------|--------|---------------------|
| 1 Modified fat intake | Nune 1945 | 26/54 | 11/26 | 3.4 | 1.14 (0.67, 1.93) |
| Harvard 1948 | 97/294 | 123/62 | 8.8 | 0.79 (0.64, 1.00) |
| Oslo Diet Heart 1966 | 64/206 | 90/206 | 8.1 | 0.81 (0.55, 1.20) |
| NHNS Open 2nd Mod 1968 | 11/12 | 31/14 | 3.2 | 0.70 (0.36, 1.34) |
| NHNS Open 1st mod 1968 | 4/118 | 1/172 | 0.3 | 1.95 (0.22, 17.35) |
| PMRC 1968 | 62/199 | 178/194 | 7.6 | 0.80 (0.54, 1.17) |
| Minnesota Coronon women 1989 | 672/936 | 510/233 | 3.7 | 1.30 (0.97, 1.76) |
| Minnesota Coronon men 1989 | 672/936 | 782/194 | 6.5 | 0.95 (0.62, 1.48) |
| Houtteman 1979 | 861 | 2009 | 2.3 | 0.27 (0.14, 0.53) |

Subtotal (99% CI) 5035 5725 42.7% 0.82 (0.66, 1.02)

Total events: 471 (reduced or modified fat), 497 (usual diet)
Heterogeneity: Tau² = 0.00; CH² = 20.43, df = 4 (P = 0.00); I² = 41%
Test for overall effect: Z = 1.79 (P = 0.077)

2 Reduced fat intake

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|-------------------------|-----------|---------------------|--------|---------------------|
| NHR 1994 | 39/123 | 43/129 | 5.4 | 0.95 (0.66, 1.36) |
| Leeds 1994 | 60/66 | 26/77 | 0.1 | 0.20 (0.00, 4.15) |
| Ley 2004 | 1188 | 1688 | 2.1 | 0.68 (0.36, 1.14) |
| May 2001 | 511/17 | 31/18 | 0.6 | 1.68 (0.41, 6.57) |
| PREMIER 2003 | 92/249 | 2/288 | 0.1 | 0.20 (0.00, 4.13) |
| ODN 1996 | 282/292 | 495/294 | 4.3 | 0.68 (0.42, 1.07) |
| VMH without CHO 2006 | 1132/1833 | 1777/2792 | 3.7 | 0.95 (0.89, 1.03) |
| VMH with CHO 2006 | 225/908 | 311/397 | 1.3 | 1.09 (0.94, 1.27) |

Subtotal (99% CI) 20450 3620 | 37.8% 0.97 (0.87, 1.08)

Total events: 2127 (reduced or modified fat), 2193 (usual diet)
Heterogeneity: Tau² = 0.23; CH² = 8.64, df = 7 (P = 0.30); I² = 17%

Test for overall effect: Z = 0.64 (P = 0.52)

3 Reduced and modified fat intake

| Study or subgroup | reduced or modified fat intake | usual diet | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|-------------------|-----------|---------------------|--------|---------------------|
| NHNS Open 2nd DHP 1968 | 20/140 | 20/140 | 0.1 | 0.14 (0.00, 3.34) |
| NHNS Open 1st DHP 1968 | 197/127 | 117/171 | 5.2 | 0.65 (0.32, 1.35) |
| DHART 1996 | 136/1016 | 147/1013 | 0.9 | 0.92 (0.74, 1.15) |
| STAR 1993 | 808 | 2908 | 2.5 | 0.41 (0.22, 0.78) |
| Zargar 1993 | 45/269 | 45/262 | 0.1 | 0.08 (0.00, 1.13) |
| McNich 2002 | 45/15 | 80/15 | 0.1 | 0.13 (0.00, 3.79) |

Subtotal (99% CI) 1721 1472 20.9% 0.77 (0.57, 1.03)

Total events: 185 (reduced or modified fat), 213 (usual diet)
Heterogeneity: Tau² = 0.04; CH² = 8.64, df = 5 (P = 0.44); I² = 42%
Test for overall effect: Z = 1.77 (P = 0.077)

Total (99% CI) 28106 37602 100.0% 0.86 (0.77, 0.96)

Test for subgroup differences: CH² = 3.11, df = 2 (P = 0.17), I² = 43%

Test for overall effect: Z = 2.71 (P = 0.0062)

Test for subgroup differences: CH² = 4.20, df = 2 (P = 0.040), I² = 90%

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 2 fat modification or reduction vs usual diet - secondary outcomes
Outcome: 1 Myocardial infarctions

| Study or subgroup | Reduced or modified fat | Usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------|-------------------------|------------|------------|--------|------------------|
| Modified diet     |                         |            |            |        |                  |
| Hoehn-Rieken 1979 | 95/121                  | 65/65      | 0.72       | 0.313  | 0.59 - 0.88      |
| Minnesota Cohort 1989 | 69/234                 | 74/134    | 1.47       | 0.786  | 1.05 - 2.05      |
| Minnesota Cohort 1998 | 62/339                 | 47/330    | 1.32       | 0.87   | 0.93 - 2.00      |
| HRC 1988          | 39/199                  | 40/194     | 0.99       | 0.85   | 0.85 - 1.13      |
| NDHS Open 1st mod 1988 | 4/98                   | 4/249     | 0.90       | 0.82   | 0.55 - 1.46      |
| NDHS Open 2nd mod 1988 | 1/12                   | 1/23      | 1.00       | 0.89   | 0.40 - 2.68      |
| Oslo-Diet Heart 1996 | 39/206                 | 54/206    | 0.73       | 0.83   | 0.52 - 1.23      |
| Rose 1965         | 165/424                 | 5/26      | 0.76       | 0.91   | 0.57 - 1.23      |
| Veterans Admin 1969 | 5/424                  | 7/122     | 0.79       | 0.84   | 0.51 - 1.51      |
| **Subtotal (95% CI)** | **935**                | **5896**  | **37.4%**  | **0.91 [0.72, 1.16]** |

Total events: 2791 (reduced or modified fat), 3980 (usual diet)
Heterogeneity: $I^2 = 45.5%, Q = 11.42, df = 8 (P = 0.02) I^2 = 50$
Test for overall effect: $Z = 2.73 (P = 0.006)$

2 Reduced for intake

| Study or subgroup | Reduced or modified fat | Usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------|-------------------------|------------|------------|--------|------------------|
| Bul RNS           | 31/122                  | 39/129     | 0.72       | 0.313  | 0.59 - 0.88      |
| OX II 2006        | 8/246                   | 13/244     | 0.62       | 0.836  | 0.37 - 1.07      |
| Levy 2004         | 48/8                     | 3/28      | 1.33       | 0.32   | 0.88 - 2.02      |
| May 2001          | 2/17                    | 1/11      | 0.22       | 0.20   | 0.07 - 0.65      |
| PREHIBR 2003      | 9/269                   | 2/28      | 0.02       | 0.01   | 0.22 - 0.83      |
| WHS without OX 2006 | 435/1551               | 671/2554   | 0.38       | 0.97   | 0.86 - 1.08      |
| **Subtotal (95% CI)** | **20384**              | **30138**  | **45.4%**  | **0.97 [0.86, 1.08]** |

Total events: 4891 (reduced or modified intake), 7232 (usual intake)
Heterogeneity: $I^2 = 50.5%, Q = 11.31, df = 8 (P = 0.056) I^2 = 50$
Test for overall effect: $Z = 2.41 (P = 0.016)$

3 Reduced and modified intake

| Study or subgroup | Reduced or modified fat | Usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------|-------------------------|------------|------------|--------|------------------|
| SMART 1988        | 132/1018                | 144/1053   | 0.60       | 0.91   | 0.77 - 1.15      |
| NDHS Open 2nd mod 1988 | 9/79                  | 21/45     | 0.44       | 0.61   | 0.27 - 0.82      |
| Sondergaard 2003  | 2/8                      | 3/63      | 0.33       | 0.42   | 0.11 - 1.58      |
| SMITS 1992        | 1/72                    | 2/28      | 0.50       | 0.32   | 0.08 - 3.39      |
| **Subtotal (95% CI)** | **1292**               | **1246**   | **17.2%**  | **0.99 [0.72, 1.31]** |

Total events: 153 (reduced or modified intake), 151 (usual intake)
Heterogeneity: $I^2 = 50.5%, Q = 12.6, df = 8 (P = 0.026) I^2 = 50$
Test for overall effect: $Z = 2.01 (P = 0.043)$

**Total (95% CI)**

| Reduced or modified fat | Usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------------|------------|------------|--------|------------------|
| 27661                   | 37280      | 0.99       | 0.99   | 0.86 - 1.02      |

Total events: 153 (reduced or modified intake), 151 (usual intake)
Heterogeneity: $I^2 = 50.5%, Q = 12.6, df = 8 (P = 0.026) I^2 = 50$
Test for overall effect: $Z = 2.01 (P = 0.043)$

Test for subgroup differences: $I^2 = 50.5%, Q = 12.6, df = 8 (P = 0.026) I^2 = 50$

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 2 Stroke

| Study or subgroup | Reduced or modified diet | Usual diet | Risk Ratio H Random 25% CI | Weight | Risk Ratio H Random 25% CI |
|-------------------|--------------------------|------------|---------------------------|--------|---------------------------|
| 1                 |                          |            |                           | 0.1%   | 0.1 (0.0, 1.0)            |
|                   | Minnesota Coronary MPRW | 50/147     |                           |        |                           |
|                   | Minnesota Coronary MPRW | 5/234      |                           |        |                           |
|                   | Ohio Diet Heart Study   | 5/206      |                           |        |                           |
|                   | Minnesota Adult MPRW    | 10/401     |                           |        |                           |
| **Subtotal (95% CI)** |                         |            |                           | 3.8%   | 0.70 (0.36, 1.36)         |
|                   | Total events: 39 (reduced or modified diet), 31 (usual diet) | | | | |
|                   | Heterogeneity: Tau^2 = 0.05, Chi^2 = 3.24, df = 3 (P = 0.33), I^2 = 8% | | | | |
|                   | Test for overall effect: Z = 0.88 (P = 0.38) | | | | |
| 2 Reduced fat intake | May 2001 | 1/18 | 0.3% | 0.20 (0.01, 1.98) | | |
|                   | May 2001 | 1/17 | 0.2% | 1.00 (0.06, 15.50) | | |
|                   | WHI with CHD 2006 | 206/1048 | 51.2% | 1.01 (0.46, 1.98) | | |
|                   | WHI without CHD 2006 | 3292/2703 | 44.1% | 1.02 (0.67, 1.52) | | |
| **Subtotal (95% CI)** |                          |            |                           | 95.7% | 1.01 (0.90, 1.13)         |
|                   | Total events: 43 (reduced or modified diet), 44 (usual diet) | | | | |
|                   | Heterogeneity: Tau^2 = 0.10, Chi^2 = 5.10, df = 3 (P = 0.22), I^2 = 28% | | | | |
|                   | Test for overall effect: Z = 0.75 (P = 0.45) | | | | |
| 3 Reduced and modified fat intake | 19746 | 29500 | 0.5% | 0.60 (0.08, 4.04) | | |
|                   | Sondergaard 2003 | 148/363 | 0.3% | 0.66 (0.39, 1.19) | | |
|                   | SAMS 1992 | 25/127 | 0.1% | 0.75 (0.31, 1.83) | | |
| **Subtotal (95% CI)** |                          |            |                           | 0.5%   | 0.40 (0.08, 2.04)         |
|                   | Total events: 67 (reduced or modified diet), 63 (usual diet) | | | | |
|                   | Heterogeneity: Tau^2 = 0.40, Chi^2 = 10.9, df = 8 (P = 0.09), I^2 = 28% | | | | |
|                   | Test for overall effect: Z = 1.12 (P = 0.27) | | | | |
| **Total (95% CI)** |                          | 34780      | 100.0% | 0.99 (0.89, 1.11) | | |
|                   | Total events: 437 (reduced or modified diet), 433 (usual diet) | | | | |
|                   | Heterogeneity: Tau^2 = 0.40, Chi^2 = 8.4, df = 8 (P = 0.08), I^2 = 20% | | | | |
|                   | Test for overall effect: Z = 0.68 (P = 0.49) | | | | |
|                   | Test for subgroup differences: Chi^2 = 2.41, df = 2 (P = 0.22), I^2 = 10% | | | | |
### Analysis 2.3
Comparison 2 fat modification or reduction vs usual diet - secondary outcomes, Outcome 3 Cancer deaths

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 3 Cancer deaths

| Study or subgroup | reduced or modified | usual diet | Risk Ratio | Weight | Risk Ratio |
|------------------|--------------------|-----------|------------|--------|------------|
|                  | n (%)              | n (%)     | (H) Random | (95% CI) | (H) Random |
| Subtotal (95% CI) | 4905               | 4938      | 3.1%       | 1.46   | 0.96, 2.21 |
| Reduced fat intake |                   |           |            |        |            |
| IFPACS 2001      | 1050              | 1056     | 1.0%       | 0.37   | 0.22, 0.89 |
| DOH 2004         | 9046              | 10214    | 0.7%       | 0.88   | 0.36, 2.13 |
| Loy 2004         | 116               | 2185     | 1.1%       | 0.44   | 0.17, 1.34 |
| VITAL 2007       | 139 (137)         | 152 (151)|            |        |            |
| VITAL without CVD 2006 | 95/1954            | 145/2924  | 84.5%     | 0.19   | 0.09, 0.43 |
| Subtotal (95% CI) | 21,662             | 31,230    | 96.5%      | 0.97   | 0.90, 1.05 |
| Reduced and modified fat intake |                    |           |            |        |            |
| DARIAT 1998      | 4/10 (1)         | 6/10 (1)  | 0.3%       | 0.44   | 0.19, 2.25 |
| Svedergard 2005  | 116               | 543      | 0.1%       | 3.77   | 0.12, 42.08 |
| Subtotal (95% CI) | 1086               | 1078      | 0.4%       | 0.81   | 0.25, 2.61 |

Total (95% CI) 27513 37246 100.0% 0.99 0.91, 1.06

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

Test for subgroup differences: X² = 3.12, df = 2 (P = 0.08)
Analysis 2.4

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 4 Cancer diagnoses

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio | Weight | Risk Ratio |
|------------------|------------------------|-----------|------------|--------|------------|
|                  | n/n                  | n/n       |            |        |            |
| Modified for intake |                       |           |            |        |            |
| NDHIS Open 1st mod 1968 | 0/348 | 1/555 | 0.60 | 0.03 [0.01, 0.79] |
| Veterans Admin 1969 | 70454 | 59492 | 0.27 | 1.18 [0.88, 1.62] |
| Subtotal (95% CI) | 772                   | 763       | 2.08 | 1.17 [0.85, 1.60] |
| Total events: 16 (reduced or modified fat), 60 (usual diet) | | | | |
| Heterogeneity: Q = 656.0, df = 15, p < 0.001, I² = 77.6% | | | | |
| Test for overall effect Z = 1.07 (P = 0.14) | | | | |
| Reduced for intake |                       |           |            |        |            |
| CO 5T 2006 | 8246 | 16241 | 0.04 | 0.47 [0.21, 1.12] |
| Ley 2004 | 349 | 388 | 0.16 | 0.00 [0.01, 1.00] |
| McKeown-Eyase 1994 | 1778 | 1687 | 0.19 | 1.15 [0.82, 1.64] |
| Total events: 2389 (reduced or modified fat), 2511 (usual diet) | | | | |
| Heterogeneity: Q = 971.6, df = 14, p < 0.001, I² = 81.6% | | | | |
| Test for overall effect Z = 1.22 (P = 0.22) | | | | |
| Modified and usual intake | | | | |
| Total events: 2389 (reduced or modified fat), 2511 (usual diet) | | | | |
| Heterogeneity: Q = 971.6, df = 14, p < 0.001, I² = 81.6% | | | | |
| Test for overall effect Z = 1.22 (P = 0.22) | | | | |
| Total (95% CI) | 24334 | 34533 | 100.0 | 0.96 [0.91, 1.01] |
### Analysis 2.5

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease  
Comparison: 2 fat modification or reduction vs usual diet - secondary outcomes  
Outcome: 5 Diabetes diagnoses

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio | Weight | Risk Ratio |
|------------------|------------------------|------------|------------|--------|------------|
|                  | n | nH | n | nH | |
| 1: Modified fat intake | 0 | 0 | Not estimable |
| Subgroup (99% CI) | 0.06 (0.01, 0.66) |
| Test for overall effect: Z = 1.77 (P = 0.04) |
| 2: Reduced fat intake | 0 | 0 | Not estimable |
| Subgroup (99% CI) | 0.06 (0.01, 0.66) |
| Test for overall effect: Z = 1.77 (P = 0.04) |

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
**Analysis 2.6**

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 6 Non-fatal MI

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------|-------------------------|-----------|------------|--------|-----------------|
|                   | n/N                     | n/N       |            |        |                 |
| **1. Modified for male** |                         |           |            |        |                 |
| PMC 1958          | 25/199                  | 25/194    | 8.3%       | 0.97   | 0.08, 1.64      |
| NHDS Open 1st mod 1968 | 41/41                | 1/41      | 6.6%       | 3.12   | 0.49, 24.88     |
| NHDS Open 2nd mod 1968 | 11/12                | 2/140     | 0.9%       | 0.17   | 0.02, 3.60      |
| Oslo Diet Heart 1966 | 28/206                 | 1/206     | 88%        | 0.79   | 0.04, 14.72     |
| Rye 1965          | 13/54                   | 6/26      | 20.8%      | 1.25   | 0.50, 3.25      |
| Veterans Affairs 1968 | 15/194                | 2/194     | 5.3%       | 0.42   | 0.03, 1.12      |
| **Subtotal (95% CI)** | 1343                   | 1329      | 26.5%      | 0.66   | 0.66, 1.16      |
|                   |                         |           |            |        |                 |
|                   | Total events: 96 (reduced or modified fat), 46 (usual diet) |         |            |        |                 |
|                   | Heterogeneity: $T^2 = 50$, $Q^2 = 3.38$, df = 5, $p = 0.67$, $I^2 = 0\%$ |
|                   | Test for overall effect: $Z = 0.99$ (P = 0.32) |

**2. Reduced for male**

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------|-------------------------|-----------|------------|--------|-----------------|
|                   | n/N                     | n/N       |            |        |                 |
| Tail 1958         | 2/1123                  | 2/1129    | 7.6%       | 1.00   | 0.38, 2.73      |
| Mayo 2001         | 3/1117                  | 1/1118    | 0.5%       | 2.02   | 0.19, 21.94     |
| PREPARE 2003      | 0/68                    | 2/68      | 0.3%       | 0.02   | 0.01, 6.17      |
| VAF with CHD 2004 | 16/508                  | 1/516     | 19.0%      | 1.27   | 0.13, 18.13     |
| VAF without CHD 2004 | 35/3063                | 358/37055 | 15.0%      | 0.89   | 0.48, 1.66      |
| **Subtotal (95% CI)** | 20950                  | 29809     | 62.5%      | 1.06   | 0.80, 1.00      |
|                   |                         |           |            |        |                 |
|                   | Total events: 35 (reduced or modified fat), 49 (usual diet) |         |            |        |                 |
|                   | Heterogeneity: $T^2 = 50$, $Q^2 = 7.95$, df = 4, $p = 0.09$, $I^2 = 52\%$ |
|                   | Test for overall effect: $Z = 0.48$ (P = 0.64) |

**3. Reduced and modified intake**

| Study or subgroup | reduced or modified fat | usual diet | Risk Ratio | Weight | Risk Ratio 95% CI |
|-------------------|-------------------------|-----------|------------|--------|-----------------|
|                   | n/N                     | n/N       |            |        |                 |
| SMART 1989        | 25/1018                 | 47/1015   | 11.1%      | 0.97   | 0.48, 1.14      |
| NHDS Open 2nd mod 1968 | 4/119                | 2/140     | 0.3%       | 0.16   | 0.02, 8.25      |
| **Subtotal (95% CI)** | 1197                   | 1155      | 11.4%      | 0.72   | 0.47, 1.10      |
|                   |                         |           |            |        |                 |
|                   | Total events: 71 (reduced or modified fat), 80 (usual diet) |         |            |        |                 |
|                   | Heterogeneity: $T^2 = 50$, $Q^2 = 10.2$, df = 2, $p = 0.24$, $I^2 = 23\%$ |
|                   | Test for overall effect: $Z = 0.94$ (P = 0.35) |
|                   | Test for subgroup differences: $CH^2 = 2.46$, df = 2 (P = 0.29), $I^2 = 6\%$ |

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Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
Analysis 3.1
Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 1 Weight, kg

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 3 fat modification or reduction vs usual diet - tertiary outcomes
Outcome: 1 Weight, kg
Analysis 3.2
Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 2 BMI, kg/m²

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 3 fat modification or reduction vs usual diet - tertiary outcomes
Outcome: 2 BMI, kg/m²

| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean difference | 95% CI | P-value |
|-------------------|-------------------------|-----------------------|-----------------|-------|---------|
| 1 Modified fat intake |                         |                       |                 |       |         |
| Diet Review 2008  | 29                      | 34                    | 1.2 (1.25)      |       | <0.01   |
| Salsinola Fat Trial 1995 | 41                  | 41                   | 1.2 (1.25)      |       | <0.01   |
| **Subtotal (95% CI)** | **58**                 | **92**                | **0.34 [-0.99, 0.31]** |       |         |
| 2 Reduced fat intake |                         |                       |                 |       |         |
| UDO Fat Review 2008 | 3                      | 1                     | 1.2 (1.15)      |       | <0.01   |
| Lean Trial 1997   | 42                      | 42                   | 1.2 (1.25)      |       | <0.01   |
| May 2001          | 42                      | 42                   | 1.2 (1.25)      |       | <0.01   |
| Salsinola Fat Trial 1995 | 41                  | 41                   | 1.2 (1.25)      |       | <0.01   |
| **Subtotal (95% CI)** | **166**                | **166**               | **0.00 [-0.16, 0.14]** |       |         |

Total 2001: 214 | 214 | 0.00 [-0.16, 0.14]

**Subtotal (95% CI)** | **2491** | **5181** | **0.00 [-0.72, 0.23]** |       |         |

3 Reduced and modified fat intake

**Subtotal (95% CI)** | **70** | **41** | **0.00 [-0.36, 0.91]** |       |         |

Test for overall effect Z = 0.38 (P = 0.70)

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
### Analysis 3.3
Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 3 LDL cholesterol, mmol/L

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 3 LDL cholesterol, mmol/L

| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean Difference | Weight | Mean Difference |
|-------------------|-------------------------|-----------------------|----------------|--------|----------------|
|                  | N | Mean (SE) | N | Mean (SE) |                  |            |
| Modified fat intake | | | | | | |
| Due Marte 2008 | 39 | -0.06 (0.48) | 24 | 0.14 (0.46) | 0.21 | 0.7 | 1.3 | -0.32 | 0.02 |
| Salonen et al. 1995 | 40 | 4.20 (0.70) | 12 | 6.26 (0.37) | 0.23 | 0.3 | -0.09 | 0.12 |
| Subtotal (95% CI) | 79 | 36 | 100.0 % | -0.20 | -0.67, 0.27 |
| Heterogeneity: Tau² = 0.00, Chi² = 1.00, df = 1 (P = 0.31), I² = 0 |
| Test for overall effect: Z = 1.40 (P = 0.16) |

Reduced fat intake

| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean Difference | Weight | Mean Difference |
|-------------------|-------------------------|-----------------------|----------------|--------|----------------|
|                  | N | Mean (SE) | N | Mean (SE) |                  |            |
| Anderson 1993 | 47 | -0.66 (0.35) | 51 | -0.4 (0.43) | 0.25 | 0.1 | 0.4 | -0.34 | 0.04 |
| CAPRIN 2000 | 34 | 0.00 (0.45) | 37 | -0.03 (0.45) | 0.26 | 0.1 | 0.3 | -0.02 | 0.14 |
| CAPRIN 15 sub-study 2002 | 45 | -0.03 (0.49) | 40 | 0.14 (0.38) | 0.27 | 0.1 | 0.3 | -0.01 | 0.17 |
| DO IT 2006 | 233 | 0.05 (0.10) | 250 | 0.00 (0.09) | 0.28 | 0.1 | 0.3 | 0.05 | 0.16 |
| Duc Los fist 2008 | 43 | 0.01 (0.07) | 38 | 0.13 (0.13) | 0.29 | 0.1 | 0.3 | -0.01 | 0.17 |
| Larn 1997 | 27 | -0.17 (0.20) | 28 | 0.02 (0.17) | 0.30 | 0.1 | 0.3 | -0.14 | 0.19 |
| Lop 2001 | 33 | -0.02 (0.04) | 31 | -0.16 (0.12) | 0.31 | 0.1 | 0.3 | -0.14 | 0.28 |
| May 2001 | 117 | -0.09 (0.01) | 118 | -0.04 (0.01) | 0.32 | 0.1 | 0.3 | -0.04 | 0.04 |
| Ole Study 2002 | 14 | -0.03 (0.04) | 14 | 0.09 (0.03) | 0.33 | 0.1 | 0.3 | -0.07 | 0.24 |
| Salonen Ret Fat 1993 | 40 | -1.26 (0.15) | 43 | -1.36 (0.07) | 0.34 | 0.1 | 0.3 | -1.26 | 0.22 |
| Stroke 1994 | 35 | -0.68 (0.14) | 32 | -0.61 (0.06) | 0.35 | 0.1 | 0.3 | -0.63 | 0.28 |
| Sort 1997 | 34 | 2.79 (0.30) | 37 | 3.08 (0.46) | 0.36 | 0.1 | 0.3 | 0.45 | 0.20 |
| VHWW 2007 | 1388 | 0.23 (0.00) | 1313 | 1.23 (0.27) | 0.37 | 0.1 | 0.3 | 1.00 | 0.05 |
| VHWW with CHO 2009 | 1313 | -0.25 (0.05) | 1699 | -0.15 (0.03) | 0.38 | 0.1 | 0.3 | -0.10 | 0.03 |
| Subtotal (95% CI) | 3269 | 3702 | 100.0 % | -0.10 | -0.14, 0.05 |
| Heterogeneity: Tau² = 0.00, Chi² = 0.00, df = 1 (P = 0.99), I² = 0 |
| Test for overall effect: Z = 0.52 (P = 0.60) |

3 Reduced and modified fat intake

| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean Difference | Weight | Mean Difference |
|-------------------|-------------------------|-----------------------|----------------|--------|----------------|
|                  | N | Mean (SE) | N | Mean (SE) |                  |            |
| Salonen Ret Fat 1993 | 41 | 4.21 (0.54) | 12 | 4.36 (0.37) | 0.40 | 0.2 | 0.6 | -0.05 | 0.25 |
| Subtotal (95% CI) | 347 | 280 | 100.0 % | -0.23 | -0.35, 0.08 |
| Heterogeneity: Tau² = 0.00, Chi² = 0.00, df = 3 (P = 0.99), I² = 0 |
| Test for overall effect: Z = 3.34 (P = 0.001) |
Analysis 3.4
Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 4 HDL cholesterol, mmol/Lkg

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 3 fat modification or reduction vs usual diet - tertiary outcomes
Outcome: 4 HDL cholesterol, mmol/Lkg
**Analysis 3.5**

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

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

Outcome: 5 Total cholesterol, mmol/L

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| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean Difference | Weight | Phen Difference |
|------------------|-------------------------|-----------------------|----------------|--------|----------------|
|                  | N | Mean(SD) | N | Mean(SD) | %Randomized 5% CI | %Randomized 5% CI |
| 1 Reduced fat intake |           |               |           |               |                   |                   |
| Due Roc 2008     | 79 | 0.06 (0.05) | 24 | 0.11 (0.04) | 1.14 | -0.23 | 0.39 | 0.13 |
| Hoye 1985        | 48 | 0.53 (0.03) | 48 | 0.63 (0.04) | 1.38 | -0.07 | 0.12 |
| NCHS 1992        | 50 | -0.19 (0.07) | 50 | -0.18 (0.07) | 0.54 | -0.01 | 0.07 | 0.62 |
| NCHS 1968        | 311 | -0.02 (0.04) | 309 | -0.03 (0.04) | 0.77 | 0.01 | 0.06 | 0.55 |
| Rose 1975        | 38 | 0.39 (0.4) | 38 | 0.32 (0.3) | 0.77 | -0.01 | 0.10 | 0.06 |
| Salt Repl Food 1996 | 41 | 0.63 (0.12) | 41 | 0.65 (0.14) | 0.84 | -0.02 | 0.018 | 0.28 |
| Sydney Diet Heart Study | 221 | 0.6 (0.2) | 227 | 0.6 (0.1) | 0.91 | -0.01 | 0.09 | 0.81 |
| Veterans Admin 1966 | 433 | 0.43 (0.37) | 430 | 0.5 (0.37) | 0.99 | 0.01 | 0.09 | 0.06 |
| **Total**         | 1161 |               | 1119 |               | 100.0% | -0.46 | -0.66 | -0.28 |

Subtotal (95% CI) 1161 1119 100.0% -0.46 [-0.66, -0.28]

Heterogeneity: Tau^2 = 0.02; Q(df = 10) = 20 (P = 0.02); I^2 = 18%

Test for overall effect: Z = 5.42 (P < 0.0001)

2 Reduced fat intake

Anderson 1991 | 47 | 0.09 (0.06) | 51 | 0.04 (0.07) | 0.16 | -0.17 | 0.19 | 0.07 |
| BIDT Diet Study 1994 | 54 | 0.18 (0.06) | 54 | 0.28 (0.07) | 1.52 | -0.34 | 0.54 | 0.04 |
| CAPRIN 2000 | 159 | -0.23 (0.06) | 177 | -0.14 (0.03) | 0.67 | -0.08 | 0.26 | 0.08 |
| CAPRIN H5 sub-study 2002 | 32 | -0.21 (0.09) | 38 | -0.11 (0.04) | 0.65 | -0.15 | 0.76 | 0.54 |
| DC IIT 2006 | 333 | 0.12 (0.06) | 321 | 0.12 (0.07) | 0.66 | -0.46 | 0.23 | 0.11 |
| Due Roc 1975 | 43 | 0.01 (0.07) | 24 | 0.17 (0.04) | 0.22 | -0.14 | 0.46 | 0.16 |
| Lao 1997 | 40 | 0.29 (0.09) | 47 | -0.12 (0.09) | 0.32 | 0.02 | 0.04 | 0.49 |
| Ley 2004 | 51 | 0.2 (0.07) | 52 | 0.13 (0.06) | 0.12 | -0.22 | 0.24 | 0.06 |
| Ole Study 2002 | 14 | 0.1 (0.06) | 14 | 0.19 (0.06) | 0.12 | -0.08 | 0.49 | 0.33 |
| Poly Preven 1996 | 270 | 0.13 (0.07) | 379 | 0.07 (0.07) | 1.63 | -0.02 | 0.07 | 0.05 |
| Salt Repl Food 1993 | 40 | 0.65 (0.19) | 12 | 0.6 (0.13) | 0.69 | -0.16 | 0.87 | 0.33 |
| Taplin 1997 | 25 | -0.01 (0.04) | 22 | 0.16 (0.06) | 0.23 | -0.11 | 0.47 | 0.13 |
| Simon 1997 | 34 | 0.48 (0.07) | 38 | 0.37 (0.12) | 0.11 | -0.84 | 0.44 |

**Total** 1363 1169 100.0% -0.08 [0.82, 0.99]

Heterogeneity: Tau^2 = 0.2; Q(df = 14) = 16 (P = 0.05); I^2 = 17%

Test for overall effect: Z = 2.15 (P = 0.03)

Subtotal (95% CI) 1048 1048 100.0% -0.08 [-0.74, 0.64]

Heterogeneity: Tau^2 = 0.02; Q(df = 4) = 38 (P = 0.08); I^2 = 23%

Test for overall effect: Z = 1.36 (P = 0.18)
Analysis 3.6
Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 6 Triglycerides, mmol/L

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 3 fat modification or reduction vs usual diet - tertiary outcomes
Outcome: 6 Triglycerides, mmol/L

| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean (SD) | N | Mean (SD) | N | Mean Difference | Weight | Fixed effect 95% CI | Random effect 95% CI |
|------------------|------------------------|-----------------------|----------|---|----------|---|----------------|-------|----------------------|---------------------|
| 1 Modified fat intake |                       |                       |          |   |           |   |                |       |                      |                     |
| Due Mollicote 2006 | 39.0 (5.6)             | 24.1 (2.5)            | 14.9     | 34 | 24.1 (2.5) | 24 | 14.9           | 0.04   | -0.22 (-0.32, 0.14) |                     |
| Dubbert 1993     | 18.1 (1.2)             | 20.8 (2.2)            |           |   | 18.1 (1.2) | 16 | 18.1           | 0.04   | -0.30 (-0.50, 0.04) |                     |
| Houwerzil 1979   | 3.7 (0.4)              | 1.0 (0.4)             |           |   | 3.7 (0.4)  | 40 | 3.7            | 0.04   | -0.24 (-0.50, 0.02) |                     |
| Sankaran Fat Mod 1995 | 8.1 (0.8)             | 17.8 (3.8)            |           |   | 8.1 (0.8)  | 12 | 8.1            | 0.04   | -0.22 (-0.52, 0.08) |                     |
| Sydney Diet Heart 1978 | 1.6 (0.7)             | 1.7 (0.7)             |           |   | 1.6 (0.7)  | 237| 1.6           | 0.04   | -0.10 (-0.26, 0.06) |                     |
| **Subtotal (95% CI)** | 365                   | 341                   |           |   | 365       | 341| 100.0%         | -0.11  | -0.23 (-0.00, 0.00) |                     |

Heterogeneity: $\tau^2 = 0.03, \chi^2 = 2.79, df = 4, p = 0.63$; $I^2 = 0.00$
Test for overall effect: $Z = 1.02, p = 0.31$

2 Reduced fat intake
CAPPEN 2000 | 159.0 (3.7) | 77.0 (3.7) | 0.0 | 0.05 | -0.10 (0.31) |
CAPPEN/NS sub-study 2002 | 18.0 (0.5) | 8.0 (0.5) | 0.0 | 0.02 | -0.27 (0.14) |
DOY 2004 | 233.0 (5.0) | 233.0 (5.0) | 0.0 | 0.04 | -0.29 (0.01) |
Due Low fat 2006 | 43.0 (0.5) | 43.0 (0.5) | 0.0 | 0.04 | -0.22 (0.01) |
Lene 1997 | 39.0 (7.5) | 39.0 (7.5) | 0.0 | 0.04 | -0.43 (0.01) |
Ley 1997 | 51.0 (0.1) | 51.0 (0.1) | 0.0 | 0.02 | -0.25 (0.01) |
Moo 2001 | 117.0 (1.2) | 110.0 (1.2) | 0.0 | 0.04 | -0.44 (0.01) |
Ola et al. 2002 | 14.0 (0.7) | 14.0 (0.7) | 0.0 | 0.02 | -0.47 (0.01) |
Sankaran Fat Mod 1995 | 40.0 (3.7) | 40.0 (3.7) | 0.0 | 0.04 | -0.47 (0.01) |
Sengfris 1994 | 35.0 (0.5) | 35.0 (0.5) | 0.0 | 0.04 | -0.25 (0.01) |
Sreel 1997 | 34.0 (3.5) | 34.0 (3.5) | 0.0 | 0.04 | -0.10 (0.01) |
VHIL 2005 | 130.0 (4.6) | 130.0 (4.6) | 0.0 | 0.04 | -0.15 (0.01) |
VNR without CHD 2006 | 143.0 (1.0) | 143.0 (1.0) | 0.0 | 0.04 | -0.22 (0.01) |

**Subtotal (95% CI)** | 3224 | 3631 | 100.0% | 0.00 | (0.00, 0.00)

Heterogeneity: $\tau^2 = 0.01, \chi^2 = 2.37, df = 12, p = 0.69$; $I^2 = 0.00$
Test for overall effect: $Z = 0.60, p = 1.0$

3 Reduced and modified fat intake
Sankaran Fat Mod 1995 | 41.0 (0.6) | 41.0 (0.6) | 0.0 | 0.04 | -0.22 (0.01) |
Sundergaard 2003 | 63.0 (3.9) | 63.0 (3.9) | 0.0 | 0.04 | -0.22 (0.01) |
DOCS 1992 | 26.0 (1.0) | 26.0 (1.0) | 0.0 | 0.04 | -0.22 (0.01) |

**Subtotal (95% CI)** | 88 | 100.0% | -0.27 | (0.00, 0.00)

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 0.20, df = 2, p = 0.65$; $I^2 = 0.00$
Test for overall effect: $Z = 1.47, p = 0.14$

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
## Analysis 3.7

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

Comparison: Fat modification or reduction vs usual diet - tertiary outcomes

Outcome: 7 Systolic Blood Pressure, mmHg

| Study or subgroup     | Reduced or modified diet | Control or usual diet | Mean Difference | Weight |
|----------------------|-------------------------|-----------------------|----------------|--------|
| **Subgroup (95% CI)** | **N** Mean (SD)         | **N** Mean (SD)       |                |        |
| 1 Reduced fat intake |                         |                       |                |        |
| I Reduced fat intake |                         |                       |                |        |
| Lee 2004             | 51 (-5.5 (17.7))        | 52 (1.3 (24.3))       | 1.3% -0.01 (3.46) |
| DO IT 2006           | 233 (-2.5 (17.3))       | 231 (-5.5 (16.7))     | 9.4% 0.9 (5.09) |
| PREMIER 2003         | 243 (-0.5 (16.8))       | 237 (-8.6 (11.6))     | 22.3% -0.9 (3.11) |
| Lee 1997             | 38 (-1.0 (17.3))        | 36 (-0.3 (17.9))      | 1.4% 0.0 (8.83) |
| CDR Study 2002       | 14 (-0.3 (17.7))        | 14 (-1.76 (17.4))     | 39% 0 (5.36) |
| WHR without CVD 2006 | 1133 (-0.2 (14.3))      | 1049 (-2.1 (16.4))    | 594% 0 (0.02) |

**Subgroup (95% CI):** 1712 2669 97.6% -0.56 [-1.52, 0.40]

**Test for overall effect (P = 0.02):**

**Reduced and modified fat intake**

| Study or subgroup     | Reduced or modified diet | Control or usual diet | Mean Difference | Weight |
|----------------------|-------------------------|-----------------------|----------------|--------|
| I Reduced fat intake |                         |                       |                |        |
| Sathiesh Nut & Food | 41 (-2.39 (11.19))     | 37 (4.49 (18.6))      | 2.4% 0.08 [-1.22, 1.06] |

**Subgroup (95% CI):** 41 37 2.4% 0.08 [-1.22, 1.06]

**Test for overall effect (P = 0.02):**

**Total (95% CI):** 1753 2306 100.0% -0.67 [-1.61, 0.28]

**Test for subgroup differences (P = 0.15):**

**Test for overall effect (P = 0.07):**

**Test for subgroup differences (P = 0.15):**

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*Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.*
Analysis 3.8
Comparison 3 fat modification or reduction vs usual diet - tertiary outcomes, Outcome 8 Diastolic Blood Pressure, mmHg

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 3 fat modification or reduction vs usual diet - tertiary outcomes
Outcome: 8 Diastolic Blood Pressure, mmHg

| Study or subgroup | Reduced or modified fat | Control or usual diet | Mean Difference | Weight | Mean Difference |
|------------------|-------------------------|-----------------------|----------------|--------|----------------|
|                  | N Mean(SD)              | N Mean(SD)            |                |        |                |
| Modified diet    |                         |                       |                |        |                |
| Subtotal (95% CI)| 0 0                    |                       |                |        |                |
|                  |                         |                       |                |        |                |
| 2 Reduced fat intake |                         |                       |                |        |                |
| Heterogeneity not applicable |               |                       |                |        |                |
| Test for overall effect not applicable |               |                       |                |        |                |
| CARPEN HS sub-study 2002 | 18 0.45 (0.280) | 8 0.67 (0.29) | 1.23 | 0.12 | 0.12 |
| Lean 1997        | 38 -2.7 (-1.179)       | 36 -2.3 (1.165)       | 1.32 | 0.03 | 0.03 |
| Lay 2004         | 51 -1.16 (1.72)        | 51 -2.4 (1.385)       | 1.32 | 0.03 | 0.03 |
| Ole Study 2002   | 11 -4.0 (0.602)        | 11 -3.6 (1.722)       | 1.32 | 0.03 | 0.03 |
| PREM 2003        | 20 -3.2 (0.7)         | 20 -3.3 (0.7)        | 1.32 | 0.03 | 0.03 |
| WW without CVD 2004 | 113 -2.4 (0.94) | -99 -2.3 (0.94) | 1.32 | 0.03 | 0.03 |
| Subtotal (95% CI)| 1407                    | 2046                  | 97.6 % -0.39 [-0.96, 0.26] |        |                |
|                  |                         |                       |                |        |                |
| 3 Reduced and modified fat intake |               |                       |                |        |                |
| 3 Randomised RCT | 41 -0.39 (0.713)       | 37 1.28 (0.13)        | 2.44 | 0.21 | 0.21 |
| Subtotal (95% CI)| 41 37                  |                       | 2.44 % -2.33 [-6.20, 1.58] |        |                |
|                  |                         |                       |                |        |                |
| Total (95% CI)   | 1538                    | 2083                  | 100.0 % -0.40 [-1.06, 0.20] |        |                |
|                  |                         |                       |                |        |                |

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 4 fat reduction vs fat modification - primary outcomes
Outcome: 3 Combined cardiovascular events

| Study or subgroup | Fat reduction | Fat modification | Risk Ratio | Weight |
|------------------|---------------|------------------|------------|--------|
|                  | a(n)          | b(n)             | Risk Ratio | H(Weight %) | H(Weight %) |
| Total high pres 2009 | 2020          | 2314            | 24.11 | 0.02 | 0.02 |
| Total low pres 2009 | 5204          | 5214            | 14.09 | 0.03 | 0.03 |
| THY DIET 2008     | 993           | 993             | 5.73 | 1.02 | 1.02 |
| Total (95% CI)    | 456           | 456             | 100.0 % 1.13 [0.41, 3.06] |        |    |
|                  |               |                  |            |        |                |

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
Analysis 5.1
Comparison 5 fat reduction vs fat modification - secondary outcomes, Outcome 1 Myocardial infarction

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 5 fat reduction vs fat modification - secondary outcomes
Outcome: 1 Myocardial infarction

| Study or subgroup | Fat reduction | Fat modification | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------|------------------|------------|--------|------------|
|                   | n | n | I² | (95% CI) | n | n | I² | (95% CI) |
| Thyg DET 2008     | 50 | 51 | 100.0 % | 3.06 | 0.53, 20.44 |
| Total (95% CI)    | 50 | 51 | 100.0 % | 3.06 | 0.53, 20.44 |

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 5 fat reduction vs fat modification - secondary outcomes
Outcome: 2 Stroke

| Study or subgroup | Fat reduction | Fat modification | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------|------------------|------------|--------|------------|
|                   | n | n | I² | (95% CI) | n | n | I² | (95% CI) |
| Thyg DET 2008     | 50 | 51 | 100.0 % | 0.34 | 0.06, 3.16 |
| Total (95% CI)    | 50 | 51 | 100.0 % | 0.34 | 0.06, 3.16 |
Analysis 5.4
Comparison 5 fat reduction vs fat modification - secondary outcomes, Outcome 4 Cancer diagnoses

Review: Reduced or modified dietary fat for preventing cardiovascular disease
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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 5 fat reduction vs fat modification - secondary outcomes
Outcome: 6 Non-fatal MI
Analysis 6.1
Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 1 Weight, kg

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 1 Weight, kg

| Study or subgroup | Reduced Fat | Modified Fat | Mean Difference | N | Mean(SD) | N | Mean(SD) | Weight | Mean Difference N(Random 95%) CI |
|------------------|-------------|--------------|----------------|---|----------|---|----------|--------|---------------------------------|
| Acquaye 2007     | 44          | 43           | 0.1(0.77)      | 7.3%| 3.80     | -138.9(-151) |
| Due Low vs Med 2008 | 39         | 38           | 0.2(0.48)      | 15.3%| 0.20     | -231.1(-146.1)|
| Mckeny 2005      | 34          | 31           | 0.3(1.56)      | 3.3%| 6.0      | -22.6(-64.6) |
| Seikos high protein 2009 | 201     | 201          | 0.1(1.42)      | 16.4%| 0.0      | -338(-2.9) |
| Seikos low protein 2009 | 201     | 201          | 0.3(1.42)      | 16.4%| 0.0      | -258(-2.9) |
| Snyders 2009     | 15          | 16           | 1.6(1.48)      | 24.8%| 2.4      | -42.0(-66.6) |
| Total (95% CI)   | 528         | 529          |                | 100%| 0.25     | -1.18(-1.39) |

Heterogeneity: Tau^2 = 1.79, Chi^2 = 5.37 df = 5 (P = 0.39) I^2 = 48%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 2 BMI, kg/m2

| Study or subgroup | Reduced Fat | Modified Fat | Mean Difference | N | Mean(SD) | N | Mean(SD) | Weight | Mean Difference N(Random 95%) CI |
|------------------|-------------|--------------|----------------|---|----------|---|----------|--------|---------------------------------|
| Due Low vs Med 2008 | 43         | 39           | 0.1(1.43)      | 31.9%| 0.10     | -0.75(-0.52) |
| Mckeny 2005      | 30          | 29           | 0.3(1.51)      | 7.8%| 3.40     | -6.6(4.13) |
| Seikos lean vs Med 2005 | 40     | 41           | 0.2(2.84)      | 17.7%| 0.10     | -1.58(1.38) |
| Snyders 2009     | 15          | 15           | 0.1(1.21)      | 32.1%| 0.0      | -1.39(-2.03) |
| Thames DET 2008 | 46          | 47           | 0.1(0.18)      | 13.5%| 0.10     | -1.25(1.32) |
| Total (95% CI)   | 174         | 171          |                | 100%| 0.06     | -0.79(-0.92) |

Heterogeneity: Tau^2 = 0.05, Chi^2 = 11.94 df = 4 (P = 0.02) I^2 = 60%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable
Analysis 6.3
Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 3 LDL cholesterol, mmol/L

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 3 LDL cholesterol, mmol/L

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 4 HDL cholesterol, mmol/Lkg
**Analysis 6.5**

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease

Comparison: 6 fat reduction vs fat modification - tertiary outcomes

Outcome: 5 Total cholesterol, mmol/L

| Study or subgroup | Reduced Fat | Modified Fat | Placebo Difference | Weight | Place Difference |
|------------------|-------------|--------------|--------------------|--------|-----------------|
| Asplund 2007     | 44          | 45           | -0.26 (0.74)       |        |                 |
| Out-Low vs Med 2008 | 43          | 43           | -0.06 (0.39)       |        |                 |
| Treadb 1994      | 27          | 17           | 6.03 (0.56)        |        |                 |
| Taksic high protein 2009 | 201         | 201          | 5.22 (0.94)        |        |                 |
| Taksic low protein 2009 | 201         | 201          | 5.12 (1.01)        |        |                 |
| Sartorius Test vs Med1995 | 40          | 41           | 6.3 (1.11)         |        |                 |
| Stryker 2009     | 15          | 15           | -0.24 (0.44)       |        |                 |
| **Total (95% CI)** | **571**     | **559**      | **100.0 % -0.04 [-0.18, 0.09]** |        |                 |

Heterogeneity: $Q = 35.8$, $I^2 = 85.5$, $df = 6$ ($P < 0.05$), $P = 0.00$.

Text for overall effect: $Z = 12.1$ ($P < 0.05$).

Text for subgroup differences: Not applicable.

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**Analysis 6.6**

**Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 6 Triglycerides, mmol/L**

Review: Reduced or modified dietary fat for preventing cardiovascular disease

Comparison: 6 fat reduction vs fat modification - tertiary outcomes

Outcome: 6 Triglycerides, mmol/L

| Study or subgroup | Reduced Fat | Modified Fat | Placebo Difference | Weight | Place Difference |
|------------------|-------------|--------------|--------------------|--------|-----------------|
| Asplund 2007     | 44          | 45           | -0.11 (0.14)       |        |                 |
| Out-Low vs Med 2008 | 43          | 39           | -0.15 (0.18)       |        |                 |
| Treadb 1994      | 27          | 17           | 1.53 (0.04)        |        |                 |
| Taksic high protein 2009 | 201         | 201          | 1.33 (0.08)        |        |                 |
| Taksic low protein 2009 | 201         | 201          | 1.44 (1)           |        |                 |
| Sartorius Test vs Med1995 | 40          | 41           | 1.4 (0.04)         |        |                 |
| Stryker 2009     | 15          | 15           | -0.03 (0.12)       |        |                 |
| THYS DIT 2008    | 46          | 47           | 0.36 (0.07)        |        |                 |
| **Total (95% CI)** | **641**     | **634**      | **100.0 % 0.05 [0.02, 0.12]** |        |                 |

Heterogeneity: $Q = 93.2$, $I^2 = 90.5$, $df = 6$ ($P = 0.05$), $P = 0.00$.

Text for overall effect: $Z = 1.34$ ($P = 0.18$).

Text for subgroup differences: Not applicable.
Analysis 6.7
Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 7 Systolic Blood Pressure, mmHg

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 7 Systolic Blood Pressure, mmHg

| Study or subgroup | Reduced fat | Modified fat | Placebo or sham | Placebo or sham | Weight | Placebo or sham | Placebo or sham |
|------------------|-------------|--------------|----------------|----------------|--------|----------------|----------------|
|                  | N | Mean(SD) | N | Mean(SD) | Weight | N | Mean(SD) | Weight |
| Axellahlin 2007  | 44 | -5.3 (1.76) | 45 | -7.4 (1.43) | 12.9 % | 6.10 [4.98, 8.18] |
| McWhady 2005    | 24 | 1.0 (2.12) | 24 | 0.0 (2.12) | 10.2 % | -0.01 [-2.96, 2.94] |
| Sacks high protein 2009 | 201 | 10.0 (1.3) | 201 | 10.0 (1.4) | 31.3 % | 2.00 [-0.44, 0.64] |
| Sacks low protein 2009 | 201 | 10.7 (1.2) | 201 | 10.7 (1.2) | 35.2 % | -0.01 [-3.15, 3.05] |
| Strachy 2009     | 15 | 0.9 (1.1) | 15 | 0.2 (1.1) | 2.4 % | 4.01 [1.85, 6.07] |
| Thy & DET 2008   | 46 | 1.0 (1.4) | 47 | 1.0 (1.7) | 8.3 % | 0.01 [-0.27, 0.27] |
| Total (95% CI)   | 537 |            | 100.0 % | -0.13 [-2.16, 1.90] |

Test for overall effect: Z = 2.59 (P = 0.01)

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

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 8 Diastolic Blood Pressure, mmHg

| Study or subgroup | Reduced fat | Modified fat | Placebo or sham | Placebo or sham | Weight | Placebo or sham | Placebo or sham |
|------------------|-------------|--------------|----------------|----------------|--------|----------------|----------------|
|                  | N | Mean(SD) | N | Mean(SD) | Weight | N | Mean(SD) | Weight |
| Axellahlin 2007  | 44 | -1.3 (2.3) | 45 | -2.9 (2.0) | 16.4 % | 1.60 [-2.48, 5.69] |
| McWhady 2005    | 24 | 2.8 (1.1) | 24 | 2.8 (1.1) | 8.8 % | 0.00 [-1.48, 1.48] |
| Sacks high protein 2009 | 201 | 7.4 (1.9) | 201 | 7.6 (1.7) | 28.1 % | -2.00 [-5.16, 1.16] |
| Sacks low protein 2009 | 201 | 7.4 (1.9) | 201 | 7.5 (1.9) | 28.1 % | 1.00 [3.24, 3.24] |
| Strachy 2009     | 15 | 4.7 (1.1) | 15 | 2.4 (1.8) | 4.8 % | 7.30 [4.04, 14.44] |
| Thy & DET 2008   | 46 | 7.3 (1.9) | 47 | 7.3 (1.9) | 13.8 % | 0.00 [-3.16, 3.16] |
| Total (95% CI)   | 537 |            | 100.0 % | -0.23 [-1.90, 1.43] |

Test for overall effect: Z = 2.59 (P = 0.01)

Test for subgroup differences: Not applicable

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 15.
Analysis 6.9
Comparison 6 fat reduction vs fat modification - tertiary outcomes, Outcome 9 Dropouts

Review: Reduced or modified dietary fat for preventing cardiovascular disease
Comparison: 6 fat reduction vs fat modification - tertiary outcomes
Outcome: 9 Dropouts

| Study or subgroup | Reduced fat | Modified fat | Risk Ratio 95% CI | Weight | Risk Ratio 95% CI |
|------------------|-------------|--------------|------------------|--------|------------------|
| Azadbakht 2007   | 670         | 550          | 0.94 [0.79, 1.10]|        | 0.89 [0.70, 1.14]|
| Macleay 2005     | 2722        | 3300         | 0.42 [0.25, 0.69]|        | 0.63 [0.33, 1.21]|
| Redfern 1996     | 633         | 1300         | 3.20 [1.59, 6.44]|        | 0.42 [0.18, 0.99]|
| Total (95% CI)   |             |              | 677 [670, 684]   |        | 0.84 [0.68, 1.02]|

Total events: 112 [Reduced fat], 117 [Modified fat]
Heterogeneity: X² = 12.60, df = 7, P = 0.05, I² = 54%
Test for overall effect: Z = 0.23, P = 0.49

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

MEDITERRANEAN* 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 SUPPLEMENT* 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 SUPPLEMENT* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
FERROUS* in TI,AB
FERRIC* in TI,AB
MARGARINE* 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
MULTIVITAMIN* in TI,AB
CALCIUM* near (ORAL* or SUPPLEMENT* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
SELENIUM* near (ORAL* or SUPPLEMENT* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)

MAGNESIUM* near (ORAL* or SUPPLEMENT* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)

MANGANESE* near (ORAL* or SUPPLEMENT* 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 SUPPLEMENT* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)

CHROMIUM* near (ORAL* or SUPPLEMENT* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)

COBALT* in TI,AB

IODINE* near (ORAL* or SUPPLEMENT* 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*)

CEREBROVASCULA*

CARDIOVASC*

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 #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. (myocard$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).mp. (190649)
26. (morbid$ adj5 (heart$ or coronar$ or ischaem$ or isch$ 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.

WHAT’S NEW

Last assessed as up-to-date: 1 December 2010.

| Date       | Event                                      | Description                                                                                                                                 |
|------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 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 1,290 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

HISTORY

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

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* Indicates the major publication for the study
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.
Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study
Figure 2. Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.
Figure 3. Funnel plot of comparison: fat modification or reduction vs usual diet - total mortality
Figure 4. Funnel plot of comparison: fat modification or reduction vs usual diet - combined cardiovascular events
Figure 5. Summary of findings, for reduced or modified fat diets vs usual diet (primary outcomes)
### Figure 6. Summary of findings, reduced fat vs modified fat diets, cardiovascular events

| Study population | RR 1.62 | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|------------------|---------|-------------------------------|---------------------------------|----------|
| Medium risk population | 157 per 1000 160 per 1000 (65 to 294) | 101 (1 study) | low | |
| Combined cardiovascular events | Follow-up mean 2.3 years | | | |

- 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).

**Cochrane Database Syst Rev.** Author manuscript; available in PMC 2014 September 15.
Figure 7. Summary of findings, reduced or modified dietary fat vs usual diet, important secondary outcomes (myocardial infarction, stroke, cancer diagnosis)
### Table 1
Sensitivity analyses of primary outcomes

| Outcome                        | Sensitivity Analysis                      | Subgroup                                | Risk ratio (95% CI) | Number of studies / participants/ events | I² |
|--------------------------------|-------------------------------------------|-----------------------------------------|---------------------|------------------------------------------|----|
| **Total mortality**            | Mantel-Haenszel, Fixed effects            | Overall analysis                        | 0.98 (0.93 to 1.04) | 21/ 71795 / 4292                          | 0% |
|                                |                                           | Modified fat intake                     | 1.03 (0.92 to 1.14) | 8/11441/ 1120                            | 34%|
|                                |                                           | 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 1.23) | 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% |
|                                |                                           | 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% |
|                                |                                           | 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% |
|                                |                                           | 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% |
|                                | 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 (0.03 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% |
| Outcome                      | Sensitivity Analysis | Subgroup                                      | Risk ratio (95% CI) | Number of studies / participants / events | I² |
|------------------------------|----------------------|-----------------------------------------------|---------------------|------------------------------------------|----|
| Total mortality              |                      | 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         | Overall 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 difference in diet other than fat | Overall analysis                             | 0.95 (0.80 to 1.13) | 9/ 12970/ 748 22%                       |    |
| Cardiovascular mortality     | Excluding studies with systematic difference 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 difference in diet other than fat | Reduced fat intake                            | 0.75 (0.40 to 1.42) | 3/ 561/ 44 3%                           |    |
| Outcome                  | Sensitivity Analysis                                                                 | Subgroup                           | Risk ratio (95% CI) | Number of studies / participants / events | $I^2$ |
|-------------------------|--------------------------------------------------------------------------------------|------------------------------------|---------------------|------------------------------------------|-------|
| 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    |
| 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 (0.03 to 0.41) | 1 / 53 / 2                               | NR    |
| Combined cardiovascular events | Excluding studies with systematic difference in care                                    | Reduced & modified fat intake       | 0.28 (0.04 to 0.8)  | 2 / 368 / 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%    |
| Outcome                                      | Sensitivity Analysis                                      | Subgroup                      | Risk ratio (95% CI) | Number of studies / participants / events | $I^2$ |
|----------------------------------------------|-----------------------------------------------------------|-------------------------------|---------------------|-------------------------------------------|-------|
| 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 | CVD mortality: Number of studies, participants, events | CVD events: Number of studies, participants, events | Relative Risk (95% CI), Heterogeneity - I², % |
|----------------------------------|--------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------|
| Main meta-analysis               | 21, 71790, 4292                                        | 16, 65978, 1407                                        | 23, 65508, 4887                                       | 0.86 (0.77 to 0.96), 50                        |
| Subgroup ‘mean follow-up ≤2 years’ | 9, 12272, 767                                          | 6, 1143, 523                                           | 12, 13844, 689                                        | 0.95 (0.84 to 1.09), 0                           |
| Subgroup ‘mean follow-up >2 years’ | 12, 59518, 3525                                        | 10, 5454, 884                                          | 11, 51664, 4198                                        | 0.78 (0.67 to 0.92), 72                         |
| Sub-group ‘low CVD risk’         | 10, 66776, 3717                                        | 6, 59682, 879                                          | 10, 58338, 3408                                        | 0.93 (0.87 to 1.00), 13                          |
| Subgroup ‘high CVD risk’         | 8, 3814, 528                                           | 8, 5633, 505                                           | 8, 5633, 1336                                         | 0.88 (0.75 to 1.02), 58                          |
| Sub-group ‘Dietary advice’       | 13, 60320, 3201                                        | 9, 54703, 796                                          | 12, 52595, 3998                                        | 0.85 (0.72 to 1.00), 62                          |
| Sub-group ‘dietary advice plus supplementation’ | 4, 1372, 219                                           | 4, 1372, 169                                           | 4, 1372, 395                                          | 0.78 (0.66 to 0.92), 0                           |
| Sub-group ‘total fat in control <30%E’ | 4, 3592, 81                                             | 3, 9903, 442                                           | 7, 11541, 494                                         | 0.91 (0.73 to 1.14), 19                          |
| Sub-group ‘total fat in control 30-34.9%E’ | 4, 3450, 333                                           | 2, 618, 25                                             | 3, 1155, 152                                          | 0.82 (0.65 to 1.03), 1                           |
| Sub-group ‘total fat in control 35-39.9%E’ | 8, 62820, 3311                                         | 3, 3344, 21                                            | 5, 1429, 74                                          | 0.93 (0.62 to 1.39), 0                           |
| Sub-group ‘total fat in control 40+5%E’ | 3, 1491, 454                                           | 3, 1491, 227                                           | 10, 60919, 4034                                        | 0.96 (0.84 to 1.10), 44                          |
| Sub-group ‘saturated fat in control <10%E’ | 2, 3625, 316                                           | 1, 3088, 7                                             | 1, 537, 2                                             | 0.20 (0.01 to 4.13), -                           |
| Sub-group ‘saturated fat in control 10-14.9%E’ | 5, 50089, 2520                                         | 5, 49631, 558                                          | 11, 51610, 3565                                        | 0.97 (0.87 to 1.07), 10                          |
| Sub-group ‘saturated fat in control 15-19.9%E’ | 6, 14598, 1134                                          | 4, 11966, 657                                          | 5, 11991, 793                                         | 0.86 (0.68 to 1.09), 64                          |
| Sub-group ‘saturated fat in control 20+5%E’ | 0, 0, 0                                                 | 0, 0, 0                                                 | 0, 0, 0                                               | 0, 0, 0                                        |
| Sub-group ‘studies of men’       | 11, 9604, 1224                                         | 9, 8951, 735                                           | 13, 10589, 1162                                        | 0.82 (0.74 to 0.90), 0                           |
| Sub-group ‘studies of women’     | 5, 59130, 2960                                         | 4, 56587, 658                                          | 4, 53605, 3566                                        | 1.04 (0.89 to 1.21), 53                          |
| Sub-group ‘studies of men and women’ | 5, 3056, 108                                           | 3, 440, 14                                             | 6, 1314, 159                                         | 0.60 (0.32 to 1.13), 62                          |
| Sub-group ‘community setting’    | 17, 61692, 3420                                        | 13, 56077, 965                                         | 20, 55605, 4405                                        | 0.84 (0.73 to 0.95), 51                          |
| Sub-group ‘residential setting’  | 4, 10098, 872                                          | 3, 9903, 442                                           | 3, 9903, 482                                          | 0.94 (0.71 to 1.24), 63                          |
### Analysis described

| Analysis described | Total mortality: Number of studies, participants, events | Total mortality: Relative Risk (95% CI), Heterogeneity - I², % | CVD mortality: Number of studies, participants, events | CVD mortality: Relative Risk (95% CI), Heterogeneity - I², % | CVD events: Number of studies, participants, events | CVD events: Relative Risk (95% CI), Heterogeneity - I², % |
|-------------------|----------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 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 |

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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%                                      | −0.013 (−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                                                 |
| 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 (−0.106e0.032), 24, 45%                                        |                                                                                |