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

Hooper L, Summerbell CD, Higgins JPT, Thompson RL, Clements G, Capps N, Davey Smith G, Riemersma R, Ebrahim S

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[Intervention Review]

Reduced or modified dietary fat for preventing cardiovascular disease

Lee Hooper[1], Carolyn D Summerbell[2], Julian PT Higgins[3], Rachel L Thompson[4], Gillian Clements[5], Nigel Capps[6], George Davey Smith[7], Rudolph Riemersma[8], Shah Ebrahim[9]

[1]School of Medicine, Health Policy & Practice, University of East Anglia, Norwich, UK. [2]School of Health and Social Care, University of Teesside, Middlesbrough, UK. [3]MRC Biostatistics Unit, Cambridge, UK. [4]The Wessex Institute for Health R & D, Southampton General Hospital, Southampton, UK. [5]Royal Shrewsbury Hospital NHS Trust, Shrewsbury, UK. [6]Department of Clinical Biochemistry, Royal Princess Hospital NHS Trust, Telford, UK. [7]Department of Social Medicine, University of Bristol, Bristol, UK. [8]Department of Medicine, Cardiovascular Research Unit, University of Edinburgh, Edinburgh, UK. [9]Department of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, UK

Contact address: Lee Hooper, School of Medicine, Health Policy & Practice, University of East Anglia, Norwich, NR4 7TJ, UK. l.hooper@uea.ac.uk.

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ABSTRACT

Background

Reduction or modification of dietary fat can improve total cholesterol levels, but may also have a variety of effects, both positive and negative, on other cardiovascular risk factors.

Objectives

The aim of this systematic review was to assess the effect of reduction or modification of dietary fats on total and cardiovascular mortality and cardiovascular morbidity over at least 6 months, using all available randomized clinical trials.

Search strategy

The Cochrane Library, MEDLINE, EMBASE, CAB Abstracts, CVRCT registry and related Cochrane Groups' trial registers were searched through spring 1998, SIGLE to January 1999. Trials known to experts in the field and biographies were included through May 1999.

Selection criteria

Trials fulfilled the following criteria: 1) randomized 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) healthy adult humans, 5) intervention at least six months, 6) mortality or cardiovascular morbidity data available. Inclusion decisions were duplicated, disagreement resolved by discussion or a third party.

Data collection and analysis

Rate data were extracted by two independent reviewers and meta-analysis performed using random effects methodology. Meta-regression and funnel plots were used.

Main results

Twenty seven studies were included (40 intervention arms, 30,901 person-years). There was no significant effect on total mortality (rate ratio 0.98, 95% CI 0.86 to 1.12), a trend towards protection form cardiovascular mortality (rate ratio 0.91, 95% CI 0.77 to 1.07), and significant protection from cardiovascular events (rate ratio 0.84, 95% CI 0.72 to 0.99). The latter became non-significant on sensitivity analysis.

Trials where participants were involved for more than 2 years showed significant reductions in the rate of cardiovascular events and a suggestion of protection from total mortality. The degree of protection from cardiovascular events appeared similar in high and low risk groups, but was statistically significant only in the former.

Authors' conclusions

The findings are suggestive of a small but potentially important reduction in cardiovascular risk in trials longer than two years. Lifestyle advice to all those at high risk of cardiovascular disease (especially where statins are unavailable or rationed), and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates.

PLAIN LANGUAGE SUMMARY

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

Cutting down how much fat we eat or replacing some saturated (animal) fats by plant oils and unsaturated spreads may reduce risk of heart disease, probably including fatal heart disease. Heart disease includes heart attacks, chest pain, strokes and the need for heart surgery. This change in how we eat seems to protect us better if we stick to it for at least two years. People who already have heart disease, and those who do not have heart disease, benefit in the same way.

BACKGROUND

There has been a great deal of research carried out in the area of diet and cardiovascular disease, the diet-heart hypothesis. Much of this has been invested in long term prospective observational studies looking at dietary patterns and subsequent cardiovascular events. This work is powerful at providing associations between dietary factors and cardiovascular risk. However, intervention studies are needed to clarify cause and effect, and it is essential that intervention trials form the basis of evidence based practice in this area.

Most intervention studies which have been carried out have studied 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 reviews of the effect of dietary advice on change on lipid levels (Brunner 1997; Clarke 1997; Denke 1995; Mensink 1992) and reviews on the effect of lipid level alterations on cardiovascular morbidity and mortality (Law 1994; Walsh 1995; Rubins 1995). Other risk factors dealt with in a similar way are blood pressure measurements (Bucher 1996; Law 1991), body weight (SIGN 1996), angiographic measurements (Marchioli 1994), antioxidant intake (Ness 1997) and alcohol (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 will strongly affect lipid profile, and may also affect oxidative state, rate of cholesterol efflux from fibroblasts, blood pressure, weight, insulin resistance, post-prandial triacylglycerol response, blood clotting factors and platelet aggregation. There may also be other effects which we are not yet aware of. 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. 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.

The most commonly advised and studied dietary intervention for protection against cardiovascular disease is the low or modified fat

diet which aims to modify serum lipid levels. This has crystallized as the American Heart Association Step 1 and 2 diets. These still form the basis of more extensive dietary recommendations by the American Heart Association (Stone 1996; Krauss 1996). How effective are these alterations in dietary fat at reducing cardiovascular morbidity and mortality?

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 randomized clinical trials.

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 6 of these groups randomized. Randomization was excluded where it was clear that allocation concealment did not occur (e.g. divisions based on days of the week or first letter of the family name 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 randomized 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. 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. 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 mechanism of action of these fats is probably mainly anti-thrombotic or anti-arrhythmic), high fibre diets and garlic (as pulses, fruits and vegetables may have various effects other than lipid lowering), low calorie diets 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).

Trials were only included where primary outcome data (mortality or cardiovascular morbidity) could be collected (by communication with authors if necessary).

Types of outcome measures

Primary outcomes:

The main outcomes were total and cardiovascular mortality. The other important outcome was combined cardiovascular events, which 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) and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty).

Secondary outcomes:

Secondary outcomes included risk factor changes (weight, blood pressure, total, LDL or HDL cholesterol and triglyceride levels) and quality of life measures (feelings of health, time off work).

Search methods for identification of studies

The following sources have been included in the literature search process. The Cochrane Library, MEDLINE, EMBASE, CAB Abstracts, CVRCT Registry, SIGLE, bibliographies and experts. A comprehensive search strategy was developed to search for nutrition based randomized controlled trials with morbidity or mortality outcomes. This search strategy was used for this review and will be used for subsequent reviews.

MEDLINE on SilverPlatter was searched for randomized controlled trials on diet and cardiovascular disease or mortality from 1966 to May 1998 with the following search strategy:

explode "NUTRITION"/adverse-effects , classification , contraindications , drug-effects , education , mortality , methods , nursing , physiology , utilization

explode "DIET"/ adverse-effects , blood , contraindications , drug-effects , metabolism , mortality , methods , nursing , physiology , utilization

explode "DIET-THERAPY"/ all subheadings

explode "LIPIDS"/ administration-and-dosage , adverse-effects , therapeutic-use

explode "FOOD"/administration-and-dosage , adverse-effects , drug-effects , therapeutic-use

explode "VITAMINS"/administration-and-dosage , adverse-effects , therapeutic-use

"SELENIUM"/administration-and-dosage , adverse-effects , therapeutic-use

"CALCIUM"/administration-and-dosage , adverse-effects , therapeutic-use

explode "CHLORIDES"/administration-and-dosage , adverse-effects , therapeutic-use
"MAGNESIUM"/administration-and-dosage , adverse-effects , therapeutic-use
"PHOSPHORUS,-DIETARY"/ all subheadings
"POTASSIUM,-DIETARY"/ all subheadings
explode "SODIUM-CHLORIDE"/ all subheadings
explode "TRACE-ELEMENTS"/administration-and-dosage , adverse-effects , therapeutic-use
explode "FLUORIDES"/administration-and-dosage , adverse-effects , therapeutic-use
MEDITERRAN* in TI,AB
explode "ANTIOXIDANTS"/administration-and-dosage , adverse-effects , therapeutic-use
#1 or #2 or #3 or #4 or #5 or #6 or #7
#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#18 or #19
LIPID* near (LOW* or REDUC* or MODIFI*)
DIET* in TI,AB
FAT* near (LOW* or MODIFI* or ANIMAL* or VEGETABLE* or ACID* or MONO?UNSAT* or POLY?UNSAT* or SATURAT* or UNSATUR*)
OIL* near (VEGETABLE* or OLIVE* or RAPE* or SUNFLOW* or LINSEED* or MONO?UNSAT* or POLY?UNSAT* or SATURAT* or UNSATUR*)
MEAT* in TI,AB
WEIGHT* near (REDUC* in TI,AB)
SLIMM* in TI,AB
FISH in TI,AB
ANTI?OXIDA* in TI,AB
VITAMIN* in TI,AB
MINERAL* in TI,AB
SALT* in TI,AB
SODIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
VEGETABLE* in TI,AB
FRUIT* in TI,AB
POTASSIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
LEGUM* in TI,AB
SOY* in TI,AB
#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
#39 or #40
OAT* in TI,AB
FOLIC* in TI,AB
FOLATE* in TI,AB
IRON* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
FERROUS* in TI,AB
FERRIC* in TI,AB
MARG?RINE* in TI,AB
BUTTER* in TI,AB
STARCH* in TI,AB
GRAIN* in TI,AB
NUT in TI,AB
NUTS in TI,AB
CAFFEIN* in TI,AB
COFFEE* in TI,AB
MULTI?VITAMIN* in TI,AB
CALCIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
SELENIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
MAGNESIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
MANGANESE* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
RETINOL* in TI,AB
CAROTENE* in TI,AB
BETA?CAROTENE* in TI,AB
THIAMIN* in TI,AB
RIBOFLAV* in TI,AB
PYRIDOXIN* in TI,AB
ASCORB* in TI,AB
TOCOPHEROL* in TI,AB
ALPHA?TOCOPHER* in TI,AB
MOLYBDENUM* in TI,AB
COBALAMIN* in TI,AB
BIOTIN* in TI,AB
FOLACIN* in TI,AB
NIACIN* in TI,AB
NICOTINIC* in TI,AB
PANTOTHEN* in TI,AB
PHOSPHORUS* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
CHROMIUM* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
COBALT* in TI,AB
IODINE* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
GARLIC* in TI, AB
ZINC* near (ORAL* or SUPPLEMEN* or ADD* or CAPSUL* or TABLET* or HIGH* or LOW* or ENRICH*)
#42 or #43 or #44 or #45 or #46 or #47
#48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57
#58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67
#68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77
#78 or #79 or #80 or #81 or #82

#20 or #41 or #83 or #84 or #85 or #86 or #87
explode "CARDIOVASCULAR-DISEASES"/ complications , diet-therapy , epidemiology , etiology , mortality , prevention-and-control , rehabilitation , secondary , therapy
explode "CEREBROVASCULAR-DISORDERS"/ complications , diet-therapy , epidemiology , etiology , mortality , prevention-and-control , rehabilitation , therapy
explode "NEOPLASMS"/ diet-therapy , mortality , prevention-and-control
CORONARY* near (BYPAS* or GRAFT* or DISEASE* or EVENT*)
CEREBRO?VASCULA*
CARDIO?VASC*
MYOCARDIAL* near (INFARCT* or RE?VASCULAR* or ISCH?EMI*)
MORTAL*
MORBID* near (HEART* or CORONARY* or ISCH?EM* or MYOCARD*)
VASCULAR* near (PERIPHERAL* or DISEASE* or COMPLICATION*)
ANGINA*
STROKE*
HEART* near (DISEASE* or ATTACK* or BYPASS*)
#91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #89 or #90
#102 and #88
(TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
RANDOMIZED-CONTROLLED-TRIAL in PT
CONTROLLED-CLINICAL-TRIAL in PT
RANDOMIZED-CONTROLLED-TRIALS
RANDOM-ALLOCATION
DOUBLE-BLIND-METHOD
SINGLE-BLIND-METHOD
#107 or #108 or #109 or #110 or #105 or #106
#103 not #104
explode "CHILD"/ all subheadings
explode "ADULT"/ all subheadings
#113 and #114
#113 not #115
111 and #112
#117 not #116

An additional MEDLINE (SilverPlatter 1966 to June 1998) search strategy was run to collect papers where only lipid outcomes were mentioned.

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

These search strategies were adapted for use on the Cochrane Library (to 1998 issue 2), EMBASE (Ovid on line to May 1998), the CVRCT Registry (May 1998), CAB Abstracts (Ovid on-line, 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 Cochrane (to 1998 issue 1).

Cochrane Review Groups in areas related to this review include the Diabetes Group (now the proposed 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.
Bibliographies of all identified systematic reviews, major non-systematic reviews and included trials were searched for further trials.
Experts in the field were contacted (May 1999) for references to studies not yet identified by the search process. The 60 experts were defined as persons who served as author (not necessarily the primary author) on a trial meeting inclusion criteria for the review, or the contact author for any relevant systematic review or extensive non-systematic review. All contacted authors of trials were also asked whether they knew of trials which may have been missed.
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

DATA COLLECTION
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; or the trial did not address a low or modified fat diet; or the trial was exclusively in children less than 18 years old, pregnant women or the critically ill; or the trial was of less than 6 months duration; or the intervention was multi-factorial. When a title/abstract could not be rejected with certainty, the full text of the article was obtained for further evaluation.
The inclusion of studies was assessed independently by two assessors (LH and RLT) and differences between reviewers' results resolved by discussion and, when necessary, in consultation with a third reviewer (RAR). 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.
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 extracted by two reviewers (LH and RLT). Differences were resolved by discussion.
DATA SYNTHESIS
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.
Pre-specified analyses included:
Meta-analysis of data on the following outcomes:
· total mortality
· cardiovascular mortality
· combined cardiovascular events
Each of these was ranked according to the percentage energy from fat in the control group, starting high.
Meta-analysis, sub grouping by
· trials with mean follow-up time over 2 years
· initial level of risk (low, medium, high)
· mode of intervention (advice, supplementation or provision of diet)
for total mortality and total cardiovascular events as outcomes.
Meta-regression on total mortality outcome and total cardiovascular events by change in
· difference in total fat as a percentage of energy between the intervention and control groups
· difference in total serum cholesterol between the intervention and control groups
The data 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. Trials where it was known that there were no events in either intervention group were included in the review for completeness, but could not be included in the meta-analysis. Where trials ran one control group and more than one included intervention group, data from each intervention group were used and the events and patient-years in the control group were divided into equal shares. This resulted in fractional numbers of events in some cases. 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.
Meta-analysis was performed (by JPTH) using random effects methodology (DerSimonian 1986) within S-PLUS (Higgins 1999). Random effects meta-regression (Berkley 1995) was per-

formed using the STATA command metareg (Sharp 1998). Funnel plots were drawn to examine the possibility of publication bias (Egger 1997).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of ongoing studies.

Twenty seven studies are included in the review and are described in the table 'characteristics of included studies'. Four more trials are ongoing, described in the table 'characteristics of ongoing studies'. 219 trials have been excluded, and the reasons for these exclusions are described in the list of references. After the trial author and year the number in brackets refers to the reason for exclusion. These are as follows:

1: the trial was not randomized, or was not adequately randomized, or there were less than six groups for cluster randomization,

2: there was no control group, or no usual or control diet or placebo group for the dietary intervention arm of the trial,

3: the stated aim of the intervention was not reduction or modification of dietary fat or cholesterol intake (increasing omega-3 fats was excluded),

4: the intervention was multi factorial and the effects of the dietary intervention could not be separated from those of other types of intervention,

5: the intervention group were not adult humans, or were acutely ill or were pregnant,

6: the intervention (diet provided or supplementation) did not continue for at least 6 months (or 26 weeks or 180 days) or (dietary advice) the participants were not followed up for at least 6 months,

7: neither mortality nor cardiovascular morbidity data were available (this was only decided definitely after contact with at least one author), trials where it was known that no events occurred were included.

A few studies remain where contact with the authors has not yet been established, or contact with the authors has not yet ascertained whether it is known that events occurred. These studies have been included on all criteria above except for number 7. They are at the end of the list of Studies awaiting assessment, labelled 'Z pending', other studies in this list have not yet been assessed for inclusion in duplicate.

The 27 included trials comprise 40 distinct intervention arms. Papers describing these trials range in publication date from 1964 to 1998, and were conducted in North America (11), Europe (15) and Australia (1). Seven of the trials include only people at high risk of cardiovascular disease, six at moderate risk, 14 at low risk. All of the high risk trials were men only, women were included in five low risk trials and eleven low or medium risk trials. Thus most of the included events occurred in men.

Of the 40 intervention arms only 17 provide useable event data, and only 8 provide data on more than 10 events in total.

Dietary interventions varied from trials which provided the majority of food for their participants over several years of study (2), trials which advised diets with dietary fat restriction or modification (17), and those which provided a combination of dietary advice and supplementation (8). The goals of the dietary alteration varied enormously, aiming for fat levels between 15 and 45 per cent of dietary energy, either reducing total fat or replacing saturated by unsaturated fats, sometimes aiming to reduce dietary cholesterol. Specific advice was sometimes given as to type of carbohydrates to be used, calorie restrictions, amounts of fibre, amounts of fruit and vegetables, poultry and fish. Supplements included oil (to be drunk daily or used in cooking), low or modified fat foods supplied by a trial shop, margarines, milk, oily fish, vitamin supplements and fibrous biscuits.

Of the 40 intervention arms included 15 aimed only to lower total fat intake (of which two had cardiovascular events), 14 aimed to modify the type of fat eaten (of which ten had cardiovascular events), nine arms aimed to both lower total fat and modify the type of fat eaten (of which five had cardiovascular events), one aimed only to lower dietary cholesterol intake and the final arm did not state what its dietary aims were (neither of these two had events).

Of these trials only nine stated that an intended outcome was to assess mortality or cardiovascular morbidity of some sort. A further 13 intended to monitor lipid or cardiovascular risk factor outcomes, and the remainder aimed to assess the following outcomes: bile acid kinetics, feasibility of dietary intervention, occurrence of retinopathy or skin cancer and recurrence of neoplastic polyps.

Risk of bias in included studies

All trials included were randomized controlled trials. Those with detected pseudo random allocation (for example where participants are randomized according to birth date or alphabetically from their name) were excluded. It is often difficult to assess whether the allocation group was concealed from the person deciding on eligibility for the trial, but the actual phrase describing the process of randomization (from published or unpublished material) is included in the table on characteristics of included studies. Allocation concealment was not duplicate data extracted, but for most studies it would probably be 'unclear'.

Physician blinding (for the purpose of diagnosing outcomes) makes little difference where total mortality is the outcome, but is important for all other outcomes. Blinding was adequate for 11 trials, inadequate for three and unclear for 13.

Participant blinding is difficult in dietary trials, but possible where all or some food is provided by the trial. Participant blinding was adequate for three trials, inadequate for 22 and unclear for two.

A systematic difference in care between the control and intervention groups (such that any differences in the results of the trial might result from these differences and not the dietary intervention) was not present in 17 trials, "minor" in eight, present in one and unclear in one. There was never any indication that there was a difference in the use of medications between the control and intervention groups (which could potentially have swamped out any differential effects of diet).

Effects of interventions

Overall 18,196 people were included in the 27 included trials (8647 in the control groups, 9549 in the intervention groups), over 30,901 person-years of observation (15096 control, 15806 intervention). Details of the extracted rate data are seen in Table 1, 'Outcome data from included trials'. 1430 total deaths were documented (520 in high risk groups), 812 cardiovascular deaths (393 in high risk groups) and 1216 combined cardiovascular events (721 in high risk groups).

Of the 27 trials, 13 were documented as having had no mortality and/or no cardiovascular events. Three trials had known events, but it has not been possible to ascertain the randomization group for these people (Oxford Retinopathy 34 deaths, BDIT Pilot Studies three deaths, Low Fat in Breast CA at least two deaths). All of the seven trials which included high risk participants (DART, London Corn/Olive, London Low Fat, MRC Soya, Oslo Diet-Heart, STARS, Sydney Diet-Heart) did have documented events, as did four trials in low risk groups (Minnesota Coronary, National Diet-Heart, Veterans Admin and Veterans Skin CA).

Data on quality of life outcomes were only found for one trial, and so were not extracted.

Funnel Plot

A funnel plot was drawn to indicate whether publication bias was likely (using total mortality data). Only trials with events can be plotted by this method. The funnel plot appears fairly symmetrical suggesting an absence of serious bias. The funnel plot can be viewed on the web site of the Cochrane Heart Group (http://www.epi.bris.ac.uk/cochrane/heart.htm).

Inter-rater agreement

The kappa statistic for inter-rater agreement on including or excluding potential trials was 0.61.

Meta-analyses

The numerical results of all meta-analyses performed are shown in Table 2, 'Results of random effects meta-analyses and sub grouping'. (As meta-analysis was performed using rate data it is not possible to display the pictorial results of these calculations within the Cochrane Library. They can be viewed on the web site of the Cochrane Heart Group (http://www.epi.bris.ac.uk/cochrane/heart.htm).

Meta-analysis suggests that, over 30,901 person-years of observation, for people of varying risk of cardiovascular disease, there is no significant effect of alteration in quantity and/or quality of dietary fat on total mortality. Our best estimate of the rate ratio is 0.98 (95% CI 0.86 to 1.12). A rate ratio of 1.0 would indicate no effect, less than 1.0 suggests benefit from the intervention (in this case dietary fat modification), and greater than 1.0 suggests harm from the intervention.

The effect on cardiovascular mortality suggests a trend towards protection by modification of dietary fat, but this is not statistically significant, rate ratio 0.91 (95% CI 0.77 to 1.07). The trend towards protection is strengthened when the effect on combined cardiovascular events is considered, this is significant, with a rate ratio of 0.84 (95% CI 0.719 to 0.986).

Meta-analysis was repeated excluding the results of the Oslo Diet-Heart trial which provided oily fish to participants in the low dietary fat arm. As oily fish appears to reduce mortality and cardiovascular events in high risk people (Hooper 1999), it may be the oily fish rather than the low fat diet providing the observed effect. Removing the Oslo Diet-Heart trial attenuated the rate ratios for all three main outcomes (total mortality 1.02, 95% CI 0.91, 1.14; cardiovascular mortality 0.94, 95% CI 0.79, 1.11; combined cardiovascular events 0.86, 95% CI 0.72, 1.03). The rate ratio for combined cardiovascular events was no longer significant.

Each of the intervention arms in each of the trials was ranked according to the percentage energy from fat in the control group, starting high, for each of the three preceding meta-analyses. There was no obvious trend (to the eye) as a result of this ordering.

Sub grouping

Within the above meta-analyses there was no significant statistical heterogeneity, however the trials performed varying interventions on groups at very different cardiovascular risk so that some clinical heterogeneity was certainly present. For this reason random effects meta-analysis was performed (Mosteller 1992), and the effects of this clinical heterogeneity was explored by sub-group analysis and meta-regression (Thompson 1991).

Sub grouping was by mean follow-up time in trial, by initial level of cardiovascular risk and by the style of dietary intervention. These were each explored for two outcomes, total mortality and combined cardiovascular events.

Exploring heterogeneity through sub grouping for length of time in trial, for level of cardiovascular risk and for style of intervention still offered no significant effects on mortality, although there was a suggestion of increased protection during trials of more than 2 years.

Trials where participants were involved for more than 2 years on average did show significant reductions in the rate of combined cardiovascular events (the pooled estimate of the rate ratio was 0.76, 95% CI 0.65 to 0.90, compared to a rate ratio of 0.84 for all trials combined). The reduction in events remained statistically significant when the results of the Oslo Diet-Heart trial were omitted from the analysis.

Trials of those at high initial cardiovascular risk (pooled estimate of the rate ratio was 0.84, 95% CI 0.70 to 0.99) suggested very similar levels of protection from combined cardiovascular events

as trials of those at low cardiovascular risk (the pooled estimate of the rate ratio was 0.82, 95% CI 0.56 to 1.20, compared to a rate ratio of 0.84 for all trials combined) despite the estimate for those at low cardiovascular risk not being statistically significant. The style of dietary modification (dietary advice, supplementation or diet provided) did not influence rate ratios.

Meta-regression

Meta-regression was used to explore the effects of changing the percentage of energy from fat and of altering serum cholesterol levels on two outcomes, total mortality and combined cardiovascular events.

For the two calculations involving percentage of energy from total fat, the information extracted from each trial was the percentage of energy from fat achieved in the intervention group, minus the percentage of energy from fat achieved in the control group (so that where the fat intake is lower in the intervention group, the number used is negative). Similarly, for the two calculations involving serum total cholesterol, the information extracted was the serum total cholesterol (in mmol/litre) achieved in the intervention group, minus the serum total cholesterol achieved in the control group (so that where the serum cholesterol is lower in the intervention group, the number used is negative).

The numerical results of all the meta-regressions performed are shown in Table 3, 'Results of random effects meta-regression', the visual representations can be viewed on the web site of the Cochrane Heart Group (http://www.epi.bris.ac.uk/cochrane/heart.htm). Rate ratios for total mortality and total cardiovascular events dropped as the percentage energy from fat fell, and as total serum cholesterol levels fell. However, none of the trends were statistically significant. This may be in part due to the large differences in interventions between the trials. It is also the case that the larger trials did not reduce dietary fat extensively, so that these trials are clustered together leaving only smaller trials to suggest the actual slope of the relationship, making a statistically significant correlation less likely.

DISCUSSION

This review suggests that dietary fat reduction or modification may be protective of cardiovascular events, but this is still not clear.

The National Diet-Heart study (published in 1968) was carried out as a pilot study for a large scale test of the efficacy of dietary fat modification in the general (male) population on cardiovascular morbidity and mortality. The definitive trial was never begun due to cost considerations. It is unlikely now that this failure to conduct the definitive trial will ever be rectified.

Length of follow-up

If dietary fat modification has some immediate effect on mortality or cardiovascular morbidity (for example, by altering clotting) then number of years observation on each individual may not be very important, and effect could be seen in a trial with many participants followed over a short time, as well as in a trial with fewer participants followed over a long time. If their main effect takes some time to manifest itself (for example by slowly altering degree or type of an atherosclerotic plaque) then the effect may be seen after a "lag" period. In this case the trial with many participants followed over a short time may show no effect at all, but the trial with fewer participants followed over a longer time period will be more likely to show an effect, even if the total number of person-years of observation is the same.

In the 4S trial (4S 1994) 4444 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 shows a clear separation between the two randomisation groups at roughly 2 years. For this reason trials within the systematic review were grouped into those with a mean follow-up of two years or less, and those with mean follow-up of more than two years.

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 28 per cent reduction in events, with a best estimate of 16 per cent reduction in events. This effect is seen almost exclusively in those who continue to modify their diet over at least two years. 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, but data on time to event were not available (the rate ratio for combined cardiovascular events is 0.84 overall, 0.96 in trials with mean follow-up of two years or less, 0.76 in trials with a mean follow-up of more than two years).

Total mortality was examined as there is no 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 is 0.98 overall, 1.04 in trials with mean follow-up of two years or less, 0.93 in trials with a mean follow-up of more than two years).

This suggests that the effects of dietary fat modification will take time to manifest themselves, and there is little evidence of immediate effects 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.

Degree of lipid lowering

Following the 4S trial it is well established that lipid lowering through use of statins does have a protective effect on people at

high risk of cardiovascular disease. This and more recent statin trials have shown a highly significant 25 per cent fall in coronary heart disease mortality (Ebrahim 1998).

If the protective effect of statins relates to their lipid lowering effect then the extent of lipid lowering within the dietary trials might be important. A summary of the lipid lowering effects of the major intervention trials of statins (Ebrahim 1998) suggests an average reduction of total serum cholesterol of over 20 per cent. Within the set of dietary trials used for this review the mean individual initial total serum cholesterol level was 5.8 mmol/litre, and the average change over the trial was a fall of 0.64 mmol/litre (11.1%). This is a much smaller effect on serum cholesterol than that of the statins, and is similar to the fall provided by bibrates which do not appear to reduce clinical events (Ebrahim 1998).

Rather surprisingly much of the total cholesterol reduction in the dietary trials comes from a low risk trial, the Minnesota Coronary trial, as modified institutional food was provided to a vast number of low risk people over only one year on average, resulting in a large reduction in total cholesterol, but with little change in cardiovascular events and a slight increase in mortality. If the Minnesota Coronary trial is excluded the initial total serum cholesterol level within the dietary trials is 6.46 mmol/litre and the mean change in total cholesterol between the control and intervention groups is a fall of 0.47 mmol/litre (7.3%) in the intervention groups, only a third of the total serum cholesterol fall expected with statin therapy.

This relatively small degree of lipid lowering may be a reason that no significant effect of dietary fat intervention was seen on total or cardiovascular mortality in the short term. The larger number of total cardiovascular events than of deaths provides greater statistical power. There was a suggestion from the meta-regression that a greater degree of reduction of total serum cholesterol resulted in a greater reduction in events.

Participants level of risk

As the rate of events will be higher in high risk groups, it should be possible to see the effect of an intervention more rapidly in a high risk group of participants (Davey Smith 1993). There have been suggestions that randomized 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). It may be very difficult to disprove effectiveness even when such interventions are clinically useless.

In this review a similar level of risk reduction of combined cardiovascular events is seen in both high and low risk groups, but this effect only reaches statistical significance in the high risk participants. This is likely to be due to a relative lack of endpoints in the lower risk population.

When endpoints such as mortality are used the situation becomes more difficult as in low risk groups the proportion of deaths which are unrelated to cardiovascular disease (and 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 rate ratio for total mortality 0.98, for cardiovascular mortality 0.91). Our best estimate is that dietary fat reduction and modification result in a reduction of 9 per cent in deaths due to cardiovascular disease, and a reduction of 2 per cent in total deaths, but the confidence intervals are wide.

The high risk participants in the dietary fat trials all show evidence of cardiovascular disease. Under current guidelines most high risk participants with raised lipid levels should be on statin therapy (Wood 1998). 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 statins remains rationed even for those at high risk the use of low or modified fat diets would appear to be a cost-effective option leading to considerable reductions in cardiovascular events (and so in health budgets) in only a few years.

The low risk participants are unlikely to be on statin therapy under current guidelines. The suggestion of protection of this group from cardiovascular events, with a reduction of roughly 18 per cent of events, by dietary fat modification (even though this does not reach statistical significance, but taking into account the lack of power) would appear to merit continued public health action.

Low fat or modified fat diets

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

The fat interventions included in this review are 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). Whilst these diets have similar effects on total serum cholesterol levels it may be that their effects on cardiovascular disease incidence and mortality are different. For example, low fat, high carbohydrate diets are likely to result in higher triglyceride and lower HDL cholesterol levels than a diet where saturated fats are wholly replaced by

unsaturated fats (Mensink 1992). As only two low fat trial arms with events are included in the meta-analyses, it would not be possible to separate out the effects of the various types of dietary fat changes on mortality and morbidity within this review. But if we aim to achieve best cardiovascular protection (rather than the best cholesterol reduction) we must be clear about exactly what dietary advice is advocated. Further large scale, long term trials with disease end points would be needed to clarify this, but are unlikely to be mounted given the feasibility and cost considerations. However, results of large scale, long term ongoing trials like the Polyp Prevention trial (due to report soon), WINS and Canadian DBCP may help to clarify the effect of low fat diets on total mortality, and also on cardiovascular events in those at low risk of cardiovascular disease.

Improved interventions

Interventions on dietary fat need to result in useful levels of cholesterol reduction and these must be sustained for at least two years to have an impact on levels of cardiovascular events. Systematic reviews of the effect of diet on serum cholesterol levels have suggested that levels of serum cholesterol reduction are much lower in free-living low risk groups than in high risk groups (Ebrahim 1998). We might expect reductions in serum cholesterol of only 3 to 5 per cent even with quite intensive interventions in the general population (Brunner 1997; Tang 1998). Interventions in high risk populations appear to reduce serum cholesterol levels by about ten per cent. This difference is likely to be because of lower levels of motivation and long term dietary compliance in those who have not experienced cardiovascular disease themselves (Tang 1998).

Effective interventions tend to focus specifically on dietary (rather than multiple lifestyle) changes, to incorporate behavioural theories and goals, use active involvement and specific behaviour change strategies, personalise the intervention, provide feedback and multiple contacts and build support through contact with family, colleagues or local leaders. Changing the environment by increasing availability of healthy choices, using simple signs to identify them and/or manipulating food composition without publicising the fact may also be productive (Roe 1997).

There is also confusion about whether low fat or modified fat changes are most effective. 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.

Most of the events analysed in this review come from male participants. It may be that the effect of dietary fats on women's risk of cardiovascular events is distinct from those of men.

Other systematic review results

This review aimed to find all relevant dietary intervention trials which reduced or modified dietary fat intake, followed its participants for at least six months and collected mortality or morbidity data, even when the individual trials were not powered to come to any conclusions about mortality or morbidity.

Results of this systematic review are similar to those of a less rigorous systematic review by Ebrahim and Davey Smith (Ebrahim 1996). They examined ten unifactorial dietary trial arms which resulted in serum cholesterol lowering. They found nonsignificant reductions in both total mortality (odds ratio 0.96, 95% CI 0.85 to 1.08) and coronary heart disease mortality (odds ratio 0.98, 95% CI 0.83 to 1.15).

Results of these systematic reviews conflict with a previous systematic review by Truswell on dietary interventions and mortality or morbidity outcomes (Truswell 1994) which found that dietary interventions significantly reduced total mortality (pooled odds ratio 0.94). However his inclusion criteria were very different, including interventions which did not aim to alter dietary fat or serum cholesterol, multifactorial interventions and a non-randomized trial (the Finnish Mental Hospital trial, Miettinen 1972 (1)), and excluding at least one relevant intervention arm (the olive oil arm of the London Corn/Olive trial).

This review is suggestive that dietary fat alteration is protective against combined cardiovascular events. No significant effect on total mortality is seen, probably because the analysis is under powered (with only half of the high risk observation years of the 4S study, less than half of its total cholesterol lowering effect and few participants involved for long enough to see any effect), but the suggestion is a reduction in total mortality in those following a reduced and/or modified fat diet for at least two years. However, it may be that there is no effect of dietary fat reduction and/or modification on total mortality.

AUTHORS' CONCLUSIONS

Implications for practice

Dietary change to reduce or modify dietary fat intake appears to reduce the incidence of combined cardiovascular events. This trend is statistically significant for all trials, but when a trial which also increased omega-3 fat intake in the intervention group is excluded the results are no longer statistically significant. The protective effect is seen almost exclusively in those who continue to modify their diet over at least two years. The extent of this protection appears similar in both high and low risk populations, although the relationship does not achieve statistical significance in low risk participants. Dietary advice to those at high risk of cardiovascular disease (particularly where statins may not be available), and probably also to lower risk population groups, should continue to

include dietary fat modification and it should be stressed that this is a permanent pattern of eating.

There is a suggestion that dietary fat modification has protective effects on total mortality and on cardiovascular mortality when the dietary modification is followed for at least two years, however this trend is not statistically significant. It may be that not enough people were involved in long term trials to show the protective effect of a change in dietary fat, or it may be that there is no such effect.

Implications for research

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.

It is not clear whether there is additional benefit of modifying dietary fat in those at high risk of cardiovascular disease who are on statins to reduce their cholesterol levels. Most of the trials of statins required participants in both control and intervention groups to receive dietary fat advice. Further research to examine the need for maintenance of dietary fat modification whilst on statins would only be feasible using serum cholesterol changes, but the issue is not of major importance.

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 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 a low fat diet, a modified fat diet, or a combination of both is most protective of cardiovascular events. Results from ongoing trials which are assessing the effects of low fat diets on certain cancers may help to clarify the different effects of low and modified fat diets on mortality.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

BDIT Pilot Studies

Methods	"randomly allocated", physician blinding: adequate participant blinding: inadequate systematic difference in care: unclear
Participants	women with mamographic dysplasia (Canada) CVD risk: low control: n= 147 intervention: n= 148 mean years in trial: 7.2 % male: 0 age: mean 45 (all >30)
Interventions	control aims: healthy diet advice, no alteration in dietary fat advised intervention aims: total fat 15%E, replace fat by complex CHO style: diet advice
Outcomes	stated trial outcomes: dietary fat, serum cholesterol data available on total mortality? yes, but in which intervention group is unclear cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

DART

Methods	"randomised", physician blinding: unclear participant blinding: unclear systematic difference in care: no
Participants	men recovering from an MI (UK) risk: high CVD control: n= 1015 intervention: n=1018 mean years in trial: 1.89 % male: 100 age: mean 57 (all <70)
Interventions	control aims: no dietary advice on fat intervention aims: reduce fat intake to 30%E, increase P/S to 1.0 style: diet advice
Outcomes	stated trial outcomes: mortality, reinfarctions data available on total mortality? yes

DART (*Continued*)

	cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths (including stroke deaths) plus non-fatal MI
Notes	

Diet & Gallstones

Methods	"randomly allocated", physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	people with radiolucent gallstones taking UDCA (USA) CVD risk: low control: n= 17 intervention: n= 19 mean years in trial: 0.59 % male: 47 age: mean 53
Interventions	control aims: dietary advice for total fat 38-42%E, dietary chol 500mg/day intervention aims: limit dietary chol to 250mg/day style: diet advice
Outcomes	stated trial outcomes: bile acid kinetics data available on total mortality? yes cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

German Fat Reduced

Methods	"participants assigned to a random number, later numbers sorted & assigned", physician blinding: unclear participant blinding: unclear systematic difference in care: no
Participants	women with BMI 24-29 (Germany) CVD risk: low control: n= 35 intervention: n= 35 mean years in trial: 0.73 % male: 0 age: mean 47 (all 40-60)
Interventions	control aims: advice to buy foods from trial shop, usual fat foods supplied intervention aims: to buy foods from trial shop, low fat foods supplied style: dietary advice & supplement (shop foods)

German Fat Reduced (*Continued*)

Outcomes	stated trial outcomes: weight data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, stroke
Notes	

Glasgow Diet in HT

Methods	"stratified by antihypertensive treatment, randomly allocated", physician blinding: unclear participant blinding: inadequate systematic difference in care: minor
Participants	hypertensives with cholesterol >6.5mmol/L (UK) CVD risk: moderate control: n= 72 intervention: n= 72 mean years in trial:0.46 % male: 49 age: mean 56
Interventions	control aims: no dietary advice intervention aims: reduce serum cholesterol style: diet advice
Outcomes	stated trial outcomes: blood pressure, weight, lipids data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths
Notes	

Glasgow Weight Loss

Methods	"medical officer drew coloured straws from a box", physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	healthy women, BMI >25 (UK) CVD risk: low control: n= 53 intervention: n= 57 mean years in trial: 0.43 % male: 0 age: mean 51

Glasgow Weight Loss (*Continued*)

Interventions	control aims: advice - total fat 35%E, CHO 34.5%E, 1200kcal per day intervention aims: total fat 20%E, CHO 58%E, 1200kcal/day style: diet advice
Outcomes	stated trial outcomes: weight loss and cardiovascular risk factors data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths, non fatal MI, stroke
Notes	

Kentucky Low Fat

Methods	"matched on age, gender & cholesterol level, randomly assigned to intervention group using systematic random procedure", physician blinding: adequate participant blinding: inadequate systematic difference in care: minor
Participants	moderately hypercholesterolaemic, non-obese caucasian men and women aged 30-50 years (USA) CVD risk: moderate control: n= 62 intervention: n= 115 mean years in trial: 0.91 % male: 60 age: mean 41 (all 30-50)
Interventions	control aims: no diet intervention intervention aims: 25%E from fats, 20%E from protein, 55%E from CHO, <200mg chol /day (differing amounts of fibre) style: diet advice
Outcomes	stated trial outcomes: diet composition, lipids data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths, fatal and non-fatal MI, stroke
Notes	

Kuopio Fat Modified

Methods	"randomisation stratified for men and women, singles and couples, random number tables", physician blinding: inadequate participant blinding: inadequate systematic difference in care: no

Kuopio Fat Modified (*Continued*)

Participants	free-living people aged 30-60 with serum total cholesterol levels 6.5-8.0mmol/L (Finland) CVD risk: moderate control: n= 37 intervention: n= 41/40/41 mean years in trial: 0.5 % male: 46 age: mean 46 (all 30-60)
Interventions	3 intervention groups control aims: advised total fat 38%E, SFA <18%E, MUFA 15%E, PUFA <5%E, rapeseed oil, butter and semi-skimmed milk provided intervention aims: AHA (low fat, mono) - total fat 30%E (28-30%E, 38%E), SFA <10%E (<14%E, <14%E), MUFA 10%E (10%E, 18%E), PUFA 10%E (4%E, <6%E), sunflower oil (butter, rapeseed oil), sunflower (rapeseed, rapeseed) spread and skimmed milk (all 3 groups) provided style: dietary advice & supplement (food)
Outcomes	stated trial outcomes: lipids and blood pressure data available on total mortality? yes cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

Linoleic Enrichment

Methods	"stratified according to gender, randomised in blocks of 6 using opaque sealed envelopes", physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	type I diabetics with elevated urinary albumin (Netherlands) risk: moderate control: n= 20 intervention: n= 18 mean years in trial: 1.95 % male: 78 age: mean 43 (all 21-65)
Interventions	control aims: usual diet (asked 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 style: diet advice
Outcomes	stated trial outcomes: albuminuria and serum lipoproteins data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, stroke
Notes	

London Corn/Olive

Methods	”sealed envelopes“, physician blinding: inadequate participant blinding: inadequate systematic difference in care: no
Participants	people with angina or following MI (UK) risk: high control: n= 26 intervention: n= 28, 26 mean years in trial: 1.53 % male: (100?) age: mean 55 (all <70)
Interventions	2 intervention groups control aims: usual diet intervention aims: restrict dietary fat, plus 80g/day corn (olive) oil provided style: diet advice & supplement (oil)
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
Notes	

London Low Fat

Methods	”allocated at random to one of two groups at each hospital“, physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	men who have recently recovered from their first MI (UK) CVD risk: high control: n= 129 intervention: n= 123 mean years in trial: 3.0 % male: 100 age: (all <65)
Interventions	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 style: diet advice
Outcomes	stated trial outcomes: reinfarction, death data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths plus non-fatal MI
Notes	

Low Fat in Breast CA

Methods	”stratification by age, randomisation with block size of 2“, physician blinding: unclear participant blinding: inadequate systematic difference in care: minor
Participants	women at high risk of breast cancer (USA) CVD risk: low control: n= 96 intervention: n= 98 mean years in trial: 1.7 % male: 0 age: mean 46 (all 18-67)
Interventions	control aims: asked to maintain usual diet intervention aims: total fat 15%E style: diet advice
Outcomes	stated trial outcomes: feasibility of intervention data available on total mortality? yes, but unclear as to which intervention group they come from cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

Mastopathy Diet

Methods	”randomly allocated“, physician blinding: adequate participant blinding: inadequate systematic difference in care: minor
Participants	women with severe cyclical mastopathy for at least 5 years (Canada) CVD risk: low control: n= 10 intervention: n= 11 mean years in trial: 0.45 % male: 0 age: mean 38
Interventions	control aims: given principles of healthy diet, not counselled to alter fat content intervention aims: total fat 15%E, CHO 65%E style: diet advice
Outcomes	stated trial outcomes: mastopathy symptoms, plasma hormone and lipids data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: none
Notes	

Minnesota Coronary

Methods	”stratified randomisation“, physician blinding: adequate participant blinding: adequate systematic difference in care: no
Participants	institutionalised men and women living in a mental hospital (USA) CVD risk: low control: n= 4516 intervention: n= 4516 mean years in trial: 1.0 % male: 49 age: ranges from <30 to >70
Interventions	control aims: usual institutional diet provided intervention aims: total fat 45%E, PUFA 18-20%E, P/S 2.5, less than 150mg/day dietary chol style: diet provided
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
Notes	

MRC Soya

Methods	”allocated at random“, physician blinding: adequate participant blinding: inadequate systematic difference in care: no
Participants	free-living men who have survived a first MI (UK) CVD risk: high control: n= 194 intervention: n= 199 mean years in trial: 3.7 % male: 100 age: (all <60)
Interventions	control aims: usual diet intervention aims: reduce dietary fat to 35g fat per day, add 84g soya oil per day style: diet advice & supplement (soya oil)
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
Notes	

MSFAT

Methods	”stratified randomisation (according to sex, age, QI index and eating behaviour) by co-ordinating centre“, physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	healthy people aged 20-55 (Netherlands) CVD risk: low control: n= 120 intervention: n= 120 mean years in trial: 0.48 % male: 50 age: 35.8 (all 20-55)
Interventions	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) style: dietary advice & supplements (food provided by trial shop)
Outcomes	stated trial outcomes: weight, vitamin and fatty acid intake, anti-oxidative capacity data available on total mortality? yes cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

National Diet-Heart

Methods	”central stratified randomisation“, physician blinding: adequate participant blinding: adequate systematic difference in care: no
Participants	men living in an institution USA) CVD risk: low control: n= 781 intervention: n= 1475 mean years in trial: varies from 0.58 to 0.96 in different trial arms % male: 100 age: (all 45-54)
Interventions	Faribault First Trial (3 intervention arms) control aims: diet provided 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) style: diet provided Open, First Trial (3 intervention arms) control aims: total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4 intervention aims: B (C,X) total fat 30%E (40%E, 30%E), SFA <9%E (<9%E, <9%E), dietary chol 350-450mg/d (350-450mg/d, 350-450mg/d), PUFA 15%E (18-20%E, 15%E), P/S 1.5 (2.0, 1.5) style: B, C - diet advice (reduce dietary saturated fat and cholesterol) & supplementation (purchase fat modified foods from trial shop), X - diet advice

National Diet-Heart (*Continued*)

	Open, Second Trial (4 intervention arms: BC, F, G, X)) control aims: BC, F, G - total fat 40%E, SFA 16-18%E, dietary chol 650-750mg/d, P/S 0.4, X - advice to continue usual diet intervention aims: BC (F, G, X) total fat 30-40%E (40%E, 40%E, 30%E), SFA reduced (no data, no data, <9%), dietary chol 350-450mg/d (ditto all 3 other groups), increased PUFA (increased, no data, 15%E), P/S 1.5-2.0 (3.0, 10.0, 1.5) style: BC, F, G - dietary advice & supplementation as above, X - diet advice
Outcomes	stated trial outcomes: lipid levels and dietary assesement data available on total mortality? no cardiovascular mortality? yes events available for combined cardiovascular events: fatal and non-fatal MI, peripheral vascular events
Notes	

Oslo Diet-Heart

Methods	”table of random numbers used“, physician blinding: adequate participant blinding: inadequate systematic difference in care: no
Participants	men with previous MI (Norway) CVD risk: high control: n= 206 intervention: n= 206 mean years in trial: 4.3 % male: 100 age: mean 56 (all 30-67)
Interventions	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) style: diet advice & supplement (food)
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
Notes	

Oxford Retinopathy

Methods	"random number sequence, provided and allotted by a separate agency", physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	newly diagnosed non-insulin dependant diabetics (UK) CVD risk: moderate control: n= (125?) intervention: n= (125?) mean years in trial: 9.3 % male: 49 age: mean 47.1 (all <65)
Interventions	control aims: advice, 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 style: diet advice
Outcomes	stated trial outcomes: retinopathy data available on total mortality? yes, but unable to ascertain from which intervention groups cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

Sollentuna Diet

Methods	"blinded drawing of lots by the study physician", physician blinding: unclear participant blinding: inadequate systematic difference in care: minor
Participants	men with moderately raised risk factors for cardiovascular disease (Sweden) CVD risk: moderate control: n= 40 intervention: n= 40 mean years in trial: 0.5 % male: 100 age: mean 46 (all 35-60)
Interventions	control aims: usual diet intervention aims: total fat 30%E, SFA <10%E, MUFA 10-15%E, PUFA up to 10%E, dietary chol<300mg/day style: diet advice
Outcomes	stated trial outcomes: cardiovascular risk factors (waist line, blood pressure, lipids) data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: total MI, cardiovascular deaths, stroke

Sollentuna Diet (*Continued*)

Notes	

Stanford Weight

Methods	”assigned at random“, physician blinding: unclear participant blinding: inadequate systematic difference in care: minor
Participants	sedentary, moderately overweight, non-smoking normotensive men (USA) CVD risk: low control: n= 44 intervention: n= 45 mean years in trial: 0.9 % male: 100 age: (all 25-49)
Interventions	control aims: no dietary advice intervention aims: total fat <30%E, SFA 10%E, total CHO >55%E, <300mg chol/day, with weight reduction style: diet advice
Outcomes	stated trial outcomes: lipoproteins data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths
Notes	

STARS

Methods	”blinded random cards issued centrally by statistician advisor“, physician blinding: unclear participant blinding: inadequate systematic difference in care: no
Participants	men with angina referred for angiography (UK) CVD risk: high control: n= 30 intervention: n= 30 mean years in trial: 3.0 % male: 100 age: mean 51 (all <66)
Interventions	control aims: no diet intervention intervention aims: total fat 27%E, SFA 8-10%E, omega-3 and omega-6 polyunsaturates 8%E, increase in plant-derived soluble fibre, dietary chol 100mg/1000kcal style: diet advice

STARS (*Continued*)

Outcomes	stated trial outcomes: angiography, cardiovascular events and procedures data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths, non-fatal MI, angina, stroke, CABG, angioplasty
Notes	

Sydney Diet-Heart

Methods	"random numbers", physician blinding: adequate participant blinding: inadequate systematic difference in care: no
Participants	men with previous MI (Australia) CVD risk: high control: n= 237 intervention: n= 221 mean years in trial: 4.3 % male: 100 age: mean 49 (all 30-59)
Interventions	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 style: diet advice
Outcomes	stated trial outcomes: cardiovascular mortality data available on total mortality? yes cardiovascular mortality? no events available for combined cardiovascular events: none
Notes	

Toronto Polyp Prev.

Methods	"stratification by physician, gender, age, randomisation by research associate, centrally, using random numbers generated by computer", physician blinding: adequate participant blinding: inadequate systematic difference in care: minor
Participants	people after adenomatous colorectal polypectomy (Canada) CVD risk: low control: n= 102 intervention: n= 99 mean years in trial: 2.0 % male: 55

Toronto Polyp Prev. (*Continued*)

	age: mean 58 (all <85)
Interventions	control aims: advice for nutritionally balanced diet (optional low fibre supplement with added calcium and iron) intervention aims: total fat <20%E, at least 50g fibre daily (optional fibre supplement with added calcium and iron) style: dietary advice & supplement (food)
Outcomes	stated trial outcomes: recurrence of neoplastic polyps data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: none
Notes	

Turku Weight

Methods	"randomised according to gender, age and overweight", physician blinding: unclear participant blinding: inadequate systematic difference in care: yes
Participants	adults 30-50% overweight (Finland) CVD risk: low control: n= 44 intervention: n= 46, 46 mean years in trial: 0.9 % male: 26 age: (all 25-50)
Interventions	2 intervention arms control aims: usual diet intervention aims: mixed (vegetarian) - total fat 25-30%E (20-25%E), 1200kcal/day (1200kcal/day), low in sugar, high in fibre and vegetables, moderate meat, fish & eggs (no meat, fish or eggs) style: diet advice
Outcomes	stated trial outcomes: weight, blood pressure, lipids data available on total mortality? yes cardiovascular mortality? yes events available for combined cardiovascular events: cardiovascular deaths, total MI, andinga, stroke, heart failure, angioplasty or CABG
Notes	

Veterans Admin

Methods	”table of random numbers used“, physician blinding: adequate participant blinding: adequate systematic difference in care: no
Participants	men living at the Veterans Administration Centre (USA) CVD risk: low control: n= 422 intervention: n= 424 mean years in trial: 3.66 % male: 100 age: mean 65 (all 54-88)
Interventions	control aims: provided, total fat 40%E intervention aims: total fat 40%E, 2/3 of SFA replaced by unsaturated fats, dietary chol reduced style: diet provided
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
Notes	

Veterans Skin CA

Methods	”list of randomly generated numbers“, physician blinding: adequate participant blinding: inadequate systematic difference in care:minor
Participants	people with non-melanoma skin cancer (USA) CVD risk: low control: n= 67 intervention: n= 66 mean years in trial: 1.9 % male: 60 age: mean 52
Interventions	control aims: no dietary advice intervention aims: total fat 20%E, protein 15%E, CHO 65%E style: diet advice
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
Notes	

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

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

Study	Reason for exclusion
Anon 1979 (4)	
Anon 1984 (2)	
Anon 1986 (4)	
Anon 1992 (4)	
Anon 1993 (2)	
Anon 1995 (3)	
Appel 1997 (6)	
Arntzenius 1985 (2)	
Aro 1990 (6)	
Baer 1993 (1)	
Bakx 1997 (4)	
Barndt 1977 (2)	
Baron 1990 (4)	
Barr 1990 (6)	
Barratt 1994 (1)	
Baumann 1982 (6)	
Beckmann 1988 (1)	
Beckmann 1995 (3)	

(*Continued*)

Beresford 1992 (6)	
Beresford 1997 (7)	
Bergstrom 1967 (6)	
Berry 1992 (6)	
Bierenbaum 1963 (2)	
Bloemberg 1991 (7)	
Bloomgarden 1987 (4)	
Bonnema 1995 (2)	
Bosaeus 1992 (6)	
Boyar 1988 (1)	
Brensike 1982 (2)	
Brown 1984 (2)	
Bruce 1994 (2)	
Bruno 1983 (4)	
Butcher 1990 (6)	
Butowski 1998 (1)	
Byers 1995 (2)	
Caggiula 1996 (2)	
Cerin 1993 (6)	
Chan 1993 (6)	
Chapman 1950 (6)	
Charbonnier 1975 (6)	
Chiostri 1988 (6)	
Chlebowski 1987 (6)	

(*Continued*)

Choudhury 1984 (6)	
Christakis 1966 (1)	
Clark 1997 (4)	
Clifton 1992 (6)	
Cobb 1991 (6)	
Cohen 1991 (3)	
Cole 1988 (6)	
Colquhoun 1990 (6)	
Colquhoun 1997 (2)	
Consolazio 1946 (6)	
Cox 1996 (4)	
Croft 1986 (3)	
Crouch 1986 (1)	
Daniel 1986 (6)	
Davis 1989 (3)	
de Boer 1983 (6)	
de Bont 1981 (2)	
de Lorgeril 1994 (3)	
DeBusk 1994 (4)	
Delius 1969 (3)	
Demark 1990 (6)	
Dengel 1995 (2)	
Denke 1994 (6)	
Ding 1992 (6)	

(*Continued*)

Dobs 1991 (2)	
Dornelas 1998 (4)	
Duffield 1982 (4)	
Dullaart 1997 (1)	
Dyson 1997 (2)	
Ehnholm 1982 (6)	
Ehnholm 1984 (6)	
Eisenberg 1990 (6)	
Ellegard 1991 (6)	
Farinaro 1977 (1)	
Fielding 1995 (6)	
Fielding 1995A (4)	
Fisher 1981 (6)	
Fortmann 1988 (3)	
Gambera 1995 (6)	
Ginsberg 1988 (6)	
Ginsberg 1995 (6)	
Gjone 1972 (6)	
Glasgow 1997 (1)	
Glatzel 1966 (2)	
Goble 1997 (4)	
Goodpaster 1999 (2)	
Grundy 1986 (6)	
Harris 1990 (6)	

(*Continued*)

Hartman 1993 (2)	
Hartwell 1986 (2)	
Hashim 1960 (6)	
Haynes 1984 (3)	
Heber 1991 (6)	
Heller 1993 (7)	
Hildreth 1951 (2)	
Hjermann 1980 (4)	
Hood 1965 (1)	
Horlick 1957 (6)	
Horlick 1960 (6)	
Houtsmuller 1979 (2)	
Howard 1977 (6)	
Howard 1997 (6)	
Hunninghake 1990 (6)	
Hutchison 1983 (2)	
Iacono 1981 (6,1)	
Ishikawa 1995 (1)	
Iso 1991 (2)	
Ives 1993 (4)	
Jalkanen 1991 (4)	
Jepson 1969 (1)	
Jolliffe 1963 (1)	
Jula 1990 (4)	

(*Continued*)

Karmally 1990 (6)	
Karvetti 1992 (4)	
Kather 1985 (6)	
Katzel 1995 (1)	
Katzel 1995A (3)	
Kawamura 1993 (6)	
Keidar 1988 (6)	
Kempner 1948 (2)	
Keys 1952 (1)	
Keys 1957 (6)	
Keys 1957A (6)	
Keys 1957B (6)	
Kingsbury 1961 (6)	
Knopp 1989 (2)	
Knutsen 1989 (4)	
Kohler 1986 (1)	
Koopman 1990 (6)	
Kris 1994 (6)	
Kristal 1997 (4)	
Kromhout 1987 (2)	
Laitinen 1993 (4)	
Laitinen 1994 (4)	
Lewis 1958 (6)	
Lewis 1981 (6)	

(*Continued*)

Lewis 1985 (4)	
Linko 1957 (6)	
Little 1990 (6)	
Little 1991 (1)	
Lottenberg 1996 (6)	
Macdonald 1972 (6)	
MacLennan 1995 (7)	
Mansel 1990 (3)	
Marckmann 1993 (1)	
Mattson 1985 (6)	
McCarron 1997 (6)	
McNamara 1981 (6)	
Mensink 1987 (6)	
Mensink 1989 (6)	
Mensink 1990 (6)	
Mensink 1990A (6)	
Miettinen 1972 (1)	
Miettinen 1994 (6)	
Millar 1973 (2)	
Miller 1998 (6)	
Milne 1994 (2)	
Mokuno 1988 (6)	
Moreno 1994 (1)	
Morrison 1950 (1)	

(*Continued*)

Morrison 1951 (1)	
Morrison 1960 (1)	
Mortensen 1983 (6)	
Murray 1990 (2)	
Mutanen 1997 (6)	
Natvig 1968 (2)	
Neil 1995 (2)	
Neverov 1997 (4)	
Nordoy 1971 (6)	
O'Brien 1976 (6)	
Pan 1997 (3)	
Pascale 1995 (4)	
Rabast 1979 (6)	
Rabkin 1981 (6)	
Radack 1990 (6)	
Rasmussen 1995 (6)	
Renaud 1986 (1)	
Retzlaff 1997 (7)	
Roderick 1997 (7)	
Rose 1987 (2)	
Sandstrom 1992 (1)	
Schaefer 1995 (6)	
Schaefer 1995A (6)	
Schectman 1996 (4)	

(*Continued*)

Schlierf 1995 (4)	
Seppanen-Laakso (6)	
Singh 1990 (1)	
Singh 1991 (4)	
Singh 1992 (2)	
Sirtori 1992 (6)	
Sorensen 1992 (7)	
Sorensen 1996 (4)	
Starmans 1995 (6)	
Steinbach 1996 (4)	
Stevenson 1988 (2)	
Taylor 1991 (1)	
Tilley 1995 (7)	
Towle 1994 (6)	
Turner 1996 (2)	
Turpeinen 1960 (1)	
Urbach 1952 (2)	
Uusitupa 1993 (4)	
Vavrikova 1958 (6)	
Wass 1981 (6)	
Wassertheil 1985 (3)	
Watts 1988 (6)	
Weintraub 1992 (2)	
Weststrate 1998 (6)	

(*Continued)*

Whelton 1997 (3)	
Wilke 1974 (6)	
Williams 1990 (3)	
Williams 1992 (3)	
Williams 1994 (3)	
Wilmot 1952 (2)	
Wing 1998 (2)	
Wood 1988 (3)	
Zock 1995 (6)	

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 ongoing studies *[ordered by study ID]*

Canadian DBCP

Trial name or title	
Methods	
Participants	women with mamographic densities >50% breast area (Canada CVD risk: low % men: 0 age: (all 30-65)
Interventions	control: self-selected diet (no advice) intervention: total fat 15%E, protein 20%E, CHO 65%E style: diet advice
Outcomes	Stated trial outcomes: incidence of breast cancer
Starting date	1994?
Contact information	NF Boyd, Division of Epidemiology and Statistics, Ontario Cancer Institute, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9

Canadian DBCP (*Continued*)

Notes	

CARMEN

Trial name or title	
Methods	
Participants	people with BMI 26-34 (Europe) CVD risk: low
Interventions	control: no advice or shop, no intervention or shop to attain national "normal" intake intervention: Dietary advice and trial shop aims: total fat 10%E with varying ratios of refined to complex CHO style: dietary advice & supplement (shop)
Outcomes	Stated trial outcomes: weight, body composition, lipids
Starting date	1996?
Contact information	WHM Saris, Department of Human Biology, University of Maastricht, PO Box 616, NL-6200 MD, The Netherlands
Notes	

Polyp Prevention

Trial name or title	
Methods	
Participants	people with at least one adenomatous polyp of the large bowel removed (USA) CVD risk: low % male: 65 age: mean 65 (all at least 35)
Interventions	control: general dietary guidelines intervention: total fat 20%E, 18g fibre/1000kcal, 5-8 servings fruit and veg daily style: diet advice
Outcomes	Stated trial outcomes: recurrence of polyps
Starting date	1991
Contact information	A Schatzkin, Department of Health and Human Services, Public Health Service, NIH, National Cancer Institute, Bethesda MD 20892, USA

Polyp Prevention (*Continued*)

Notes	

WINS

Trial name or title	
Methods	
Participants	women with localised breast cancer (USA) CVD risk: low % men: 0 age: mean 61 (all post-menopausal)
Interventions	control: minimal nutritional counselling focussed on nutritional adequacy intervention: total fat 15-20%E style: dietary advice
Outcomes	Stated trial outcomes: dietary fat intake, total cholesterol, weight and waist
Starting date	1990?
Contact information	DP Rose, Division of Nutrition and Endocrinology, American Health Foundation, 1 Dana Road, Valhalla, NY 10595 USA
Notes	

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Outcome data from included trials [data as 'control / intervention']

Included arm	Initial CVD risk	Person-yrs obs.	No. randomized	Total mortality	CVD mortality	Comb. CVD event	Events included
BDIT Pilot Studies	low	1138/986	147/148	3 (randomization uncertain)			
DART	high	1917/1925	1015/1018	113/111	100/101	147/136	CV deaths (inc. stroke) plus non-fatal MI
Diet & Gallstones	low	10.3/10.9	17/19	0/0			
German Fat Reduced	low	25.1/26.3	35/35	0/0	0/0	0/0	CV deaths, non-fatal MI, stroke
Glasgow Diet in HT	moderate	33.8/33.2	72/72	0/0	0/0	0/0	CV deaths
Glasgow Weight Loss	low	22.4/24.4	53/57	0/0	0/0	0/0	CV deaths, non fatal MI, stroke
Kentucky Low Fat	moderate	56.5/105	62/115	0/0	0/0	0/0	CV deaths, fatal and non-fatal MI, stroke
Kuopio Fat Modified (AHA)	moderate	6.2/20.5	12.3/41	0/0			
Kuopio Fat Mod. (low fat)	moderate	6.2/20.0	12.3/40	0/0			
Kuopio Fat Modified (mono)	moderate	6.2/20.5	12.3/41	0/0			

Table 1. Outcome data from included trials [data as 'control / intervention'] (*Continued*)

Linoleic Enrichment	moderate	40/34	20/18	0/0	0/0	0/0	CV deaths, non-fatal MI, stroke
London Corn /Olive (Corn)	high	21.8/41.3	13/28	0.5/5	0.5/5	5.5/15	CV deaths, non-fatal MI, angina, stroke
London Corn /Olive (Olive)	high	21.8/38.0	13/26	0.5/3	0.5/3	5.5/11	CV deaths, non-fatal MI, angina, stroke
London Low Fat	high	393.5/373.9	129/123	24/20	20/17	42/38	CV deaths plus non-fatal MI
Low Fat in Breast CA	low	171/170	96/98	(at least 2 deaths, randomization uncertain)			
Mastopathy Diet	low	4.5/5.0	10/11	0/0	0/0	0/0	CV deaths
Minnesota Coronary	low	4715/4823	4516/4516	248/269	157/157	129/134	total MI plus sudden death plus stroke
MRC Soya	high	715/751	194/199	31/28	25/27	74/62	cardiovascular deaths and fatal or non-fatal MI
MSFAT	low	55.9/59.4	120.5/120.5	0/0			
National diet-heart (Faribault 1st, B)	low	18.2/52.5	19/56		0/0	0/0	fatal and non-fatal MI, PV events
National diet-heart (Faribault 1st, C)	low	18.2/49.0	19/54		0/0	0/0	fatal and non-fatal MI, PV events
National diet-heart (Faribault 1st, E)	low	18.2/53.5	19/57		0/0	0/0	fatal and non-fatal MI, PV events

Table 1. Outcome data from included trials [data as 'control / intervention'] (*Continued*)

National diet-heart (open 1st, B)	low	120.5/358.5	127.3/385		0/0	0.3/0	fatal and non-fatal MI, PV events
National diet-heart (open 1st, C)	low	120.5/361.0	127.3/390		0/0	0.3/4	fatal and non-fatal MI, PV events
National diet-heart (open 1st, X)	low	120.5/50.0	127.3/54		0/0	0.3/1	fatal and non-fatal MI, PV events
National diet-heart (open 2nd, BC)	low	58.8/112.5	101.3/194		0/0	1.3/0	fatal and non-fatal MI, PV events
National diet-heart (open 2nd, F)	low	58.8/73.7	101.3/127		0/0	1.3/1	fatal and non-fatal MI, PV events
National diet-heart (open 2nd, G)	low	58.8/69.6	101.3/120		0/0	1.3/0	fatal and non-fatal MI, PV events
National diet-heart (open 2nd, X)	low	22/22	38/38		0/0	0/0	fatal and non-fatal MI, PV events
Oslo Diet-Heart	high	885/895	206/206	65/48	52/38	91/66	total MI, sudden death, stroke, angina
Oxford Retinopathy	moderate	1160/1160	125/125	(34 deaths, randomization uncertain)			
Sollentuna Diet	moderate	19.5/20.0	40/40	0/0	0/0	0/0	total MI, CV deaths, stroke
Stanford Weight	low	42/42	44/45	0/0	0/0	0/0	CV deaths
STARS	high	87.8/91.0	30/30	3/1	3/1	20/8	CV deaths, non-fatal MI, angina, stroke, CABG, angioplasty

Table 1. Outcome data from included trials [data as 'control / intervention'] (*Continued*)

Sydney Diet-Heart	high	1011/939	237/221	28/39			
Toronto Polyp Prevention	low	204/198	102/99	0/0	0/0	0/0	CV deaths
Turku Weight (mixed)	low	21.5/41.5	22/46	0/0	0/0	0/0	CV deaths, total MI, angina, stroke, heart failure, angioplasty or CABG
Turku Weight (vegetarian)	low	21.5/38.5	22/46	0/0	0/0	0/0	CV deaths, total MI, angina, stroke, heart failure, angioplasty or CABG
Veterans Administration	low	1544/1588	422/424	177/174	59/44	122/97	sudden death, definite MI, definite stroke, angina, PV events
Veterans Diet & Skin CA	low	125/123	67/66	2/1	2/0	2/0	CV deaths
Total, all trials		15,096/15,806 (30,902)	8647/9549 (18,196)	692/699 (1430)	419/393 (812)	643/573 (1216)	
Total, high risk trials		5053/5054 (10,107)	1837/1851 (3688)	265/255 (520)	201/192 (393)	385/336 (721)	

Table 2. Results of random effects meta-analyses and subgrouping

Analysis described	Outcome	Rate ratio	95% C.I.	Effect significant?	Heterogeneity?
Meta-analysis	total mortality	0.98	0.86 to 1.12	no	not significant (chi-square = 11.9 on 10 degrees of freedom, p=0.298)
Meta-analysis	cardiovascular mortality	0.91	0.77 to 1.07	no	not significant (chi-square = 10.4 on 9 degrees of freedom, p=0.319)

Table 2. Results of random effects meta-analyses and subgrouping (*Continued*)

Meta-analysis	combined cardiovascular events	0.84	0.719 to 0.986	yes, significant protective effect of the intervention	not significant (chi-square = 20.4 on 15 degrees of freedom, p=0.159)
Meta-analysis, subgroup 'mean follow-up 2 years or less'	total mortality	1.04	0.90 to 1.21	no	not significant (chi-square = 4.1 on 4 degrees of freedom, p=0.396)
Meta-analysis, subgroup 'mean follow-up more than 2 years'	total mortality	0.93	0.75 to 1.15	no	not significant (chi-square = 6.8 on 5 degrees of freedom, p=0.237)
Meta-analysis, subgroup 'low cardiovascular risk'	total mortality	1.01	0.89 to 1.16	no	not significant (chi-square = 1.0 on 2 degrees of freedom, p=0.602)
Meta-analysis, subgroup 'high cardiovascular risk'	total mortality	0.97	0.76 to 1.25	no	not significant (chi-square = 10.6 on 7 degrees of freedom, p=0.155)
Meta-analysis, subgroup 'diet advice only'	total mortality	1.03	0.79 to 1.34	no	not significant (chi-square = 4.7 on 4 degrees of freedom, p=0.324)
Meta-analysis, subgroup 'diet advice plus supplement'	total mortality	0.92	0.57 to 1.50	no	not significant (chi-square = 4.9 on 3 degrees of freedom, p=0.177)
Meta-analysis, sub-group 'diet provided'	total mortality	1.02	0.89 to 1.16	no	not significant (chi-square = 0.6 on 1 degree of freedom, p=0.451)
Meta-analysis, subgroup 'mean follow-up 2 years or less'	combined cardiovascular events	0.96	0.75 to 1.23	no	not significant (chi-square = 12.3 on 10 degrees of freedom, p=0.269)
Meta-analysis, subgroup 'mean follow-up more than 2 years'	combined cardiovascular events	0.76	0.65 to 0.90	yes, significant protective effect of the intervention	not significant (chi-square = 4.0 on 4 degrees of freedom, p=0.405)
Meta-analysis, subgroup 'low cardiovascular risk'	combined cardiovascular events	0.82	0.56 to 1.20	no	not significant (chi-square = 13.0 on 8 degrees of freedom, p=0.113)

Table 2. Results of random effects meta-analyses and subgrouping (*Continued*)

Meta-analysis, subgroup 'high cardiovascular risk'	combined cardiovascular events	0.84	0.70 to 0.99	yes, significant protective effect of the intervention	not significant (chi-square = 7.2 on 5 degrees of freedom, p=0.300)
Meta-analysis, subgroup 'diet advice only'	combined cardiovascular events	0.79	0.51 to 1.23	no	not significant (chi-square = 8.5 on 4 degrees of freedom, p=0.074)
Meta-analysis, subgroup 'diet advice plus supplement'	combined cardiovascular events	0.79	0.62 to 1.00	no	not significant (chi-square = 8.5 on 8 degrees of freedom, p=0.383)
Meta-analysis, sub-group 'diet provided'	combined cardiovascular events	0.89	0.68 to 1.16	no	not significant (chi-square = 2.2 on 1 degree of freedom, p=0.136)

Table 3. Results of random effects meta-regression (rate ratio versus change in factor)

Analysis described	Slope	95% C.I.	Effect significant?
ln (rate ratio for total mortality) versus difference in percentage energy from fat	0.015	-0.009 to 0.039	no
ln (rate ratio for total mortality) versus difference in serum total cholesterol	0.297	-0.141 to 0.734	no
ln (rate ratio for combined cardiovascular events) versus difference in percentage energy from fat	0.004	-0.012 to 0.021	no
ln (rate ratio for combined cardiovascular events) versus difference in serum total cholesterol	0.296	-0.094 to 0.687	no

WHAT'S NEW

Last assessed as up-to-date: 31 January 2000.

Date	Event	Description
9 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 2000

Date	Event	Description
1 February 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All co-reviewers were active in the design of the review and in providing critical revisions of the manuscript. Julian Higgins also performed the statistical analyses, Rachel Thompson duplicated the inclusion / exclusion and data extraction of all studies and Rudolph Riemersma arbitrated on study inclusion where necessary. Shah Ebrahim and Carolyn Summerbell were primary advisors. Lee Hooper originated and was primarily responsible for planning and carrying out the review and was the principal author.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- University of Manchester, UK.

External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Aged; Humans; Middle Aged