Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression

SFigure 1: Flow chart for meta-analysis article selection process.

CHD, coronary heart disease; RCT, randomized controlled trial; SFA, saturated fat;
<table>
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<tr>
<th>Reference</th>
<th>Detailed Dietary Advice</th>
<th>Dietary Assessment</th>
<th>Smoking cessation</th>
<th>Drug intakes</th>
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<tr>
<td>Ball et al. 1965</td>
<td>I: 40g fat daily (14g butter, 84g of meat, 1 egg, 56g cottage cheese, and skimmed milk. The nature of the fat consumed was not altered, nor were any additional unsaturated fats given. The main objections were to the skimmed milk, to the small butter ration which was especially hard on those who took sandwiches to work, and to the restriction on biscuits and cakes. C: Those patients who were overweight were given reducing diets, irrespective of their group. In the control group this was done as far as possible by reducing carbohydrates rather than fats.</td>
<td>Record the weight of all food consumed on a different day each week for the first seven weeks after admission to the trial, and thereafter on the first day of each month. In addition an independent dietitian interviewed a number of patients in each group.</td>
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<td>Burr et al. 1989</td>
<td>I: fat advice, designed to reduce fat intake to 30% of total energy and to increase the PUFA/SFA ratio to 1.0.</td>
<td>The diettian visited and telephoned regularly to reinforce their initial required. Food questionnaires from 7 day weighed intake records.</td>
<td>All smokers were strongly advised to stop smoking and ex-smokers were encouraged not to relapse.</td>
<td>B-blocker: I: 30.6%, C: 28.2%; Other antihypertensive: I: 33.4%, C: 34% Antiangina: I: 47.7%, C: 45.9%; Anticoagulant: I: 6.2%, C: 5.5%; Aspirin/Antiplatelet: I: 10.5%, C: 10%; Digoxin/antiarrhythmic: I: 8.9%, C: 10.2%</td>
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<td>de Lorgeril et al. 1994</td>
<td>I: &lt;35% of energy from total lipids, and &lt;10% SFA. The intake of 18:2 n-6 (linoleic acid) was restricted to ≤4%. Intake of 18:3 n-3 (linolenic acid) was to compose ≥6%, and the PUFA:SFA was to be ≥0.8%. The six dietary commandments: more bread, more vegetables and legumes, more fish, less meat (beef, lamb, pork), and replaced by poultry; no day without fruit; no more butter and cream, to be replaced by a special margarine. In this study, an erucic acid-free (canola) oil-based margarine was supplied, to the families of all subjects of the experimental group. The oils recommended for salads and food preparation were rapeseed without erucic acid and olive oils exclusively. Moderate alcohol consumption, mainly in the form of red wine, was allowed or recommended at meals.</td>
<td>Compliance with the dietary intervention was maintained by checking the amount of margarine consumed by the family, a dietary survey performed at each patient visit (the survey included a 24-h recall and a food frequency questionnaire), and fatty acid analysis of plasma total lipids performed at each visit.</td>
<td>No difference in care I: 7.6% C: 4.9%</td>
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<td>Howard et al. 2006</td>
<td>I: The intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy intake (in kilocalories) by increasing intake of vegetables and fruits to at least 5 servings daily and of grains to at least 6 servings daily. The intervention did not include total energy reduction or weight loss goals. Although not a separate focus of the intervention, it was presumed that by reducing total fat intake to 20% kcal, intake of saturated fat would also be reduced (7% energy intake). The intensive behavioral modification program involved 18 group sessions in the first year and quarterly maintenance sessions thereafter, led by specially trained and certified nutritionists. Each participant was assigned her own fat-gram goal, calculated on the basis of height. Participants self-monitored total fat-gram intake and also servings of vegetables, fruits, and grains. No formal intervention regarding saturated fat, cholesterol, trans fatty acids, or other known atherogenic factors was provided. C: Women in the comparison group received a copy of the Dietary Guidelines for Americans</td>
<td>All participants completed an FFQ designed specifically for the study at baseline and 1 year. Thereafter, one third of the participants completed the FFQ each year in a rotating sample;</td>
<td>No difference in care I: 6.6% C: 6.8%</td>
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<td>Leren et al. 1966</td>
<td>I: Protein (92g), Fat (104g), CHO (269 g) and dietary cholesterol 264 mg; Daily intake of calories was 2387; Calories derived from fat constituted 39%. The sources of fat were: soy bean oil (72%), fish fat (11.6%), animal fat (8.8%), cereal fat (5%), and fat from other sources (2.6%). Of the mean dietary fat, 21.6% was saturated, 25.7% monounsaturated, and 52.7% polyunsaturated.</td>
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<th>Study</th>
<th>Intervention</th>
<th>Adherence measured during</th>
<th>No difference in care</th>
<th>Dietary assessment performed</th>
<th>Statins</th>
<th>β-blockers</th>
<th>ACE-inhibitors</th>
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<td>MRC 1968</td>
<td>I: as far as possible, SFA were removed from the diet. Patients were instructed to take 85g of soya bean oil daily. The oil was chosen because it is highly unsaturated and, when used previously in a similar diet, had been shown to cause satisfactory fall in serum-cholesterol. At least 43g of soya-bean oil daily had to be taken unheated, and it was often drunk with fruit juice. In 10 patients who develop intolerance to the oil, such as nausea and diarrhea, corn oil was substituted. Up to 35g of other fat per day was also allowed. 14g of this was taken as a moderately unsaturated margarine. Foods allowed daily included lean meat (up to 85g), any fish, skimmed milk, and clear soups. Foods forbidden included butter, other margarines, cooking-fat, other oils, fat meat, whole milk, cheese, egg yolk, and most biscuits, and cakes. C: ate the diet they would ordinarily have taken.</td>
<td>of the patients. The degree of adherence was quantified by means of a detailed questionnaire used six times during the period of observation.</td>
<td>No difference in care</td>
<td>Before and after the 1-year period, the patients completed a 7-day record of food intake. Food records were converted into nutrients intake by using the EBIS software dietary analysis program, which is based on the national database of the German nutrition report. The subject’s dietary intake was compared with a validated food frequency questionnaire of the German Institute of Nutrition. For each patient, we compared the calculated intakes of nutrients of both methods.</td>
<td>I: 84.4%, C: 79.2%; β-blockers: I: 75%, 77.3%; ACE-inhibitors: I: 50%, C: 49.5%;</td>
<td>n.d</td>
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<td>Michalsen et al. 2006</td>
<td>I: The intervention for the MG lasted 12 months with decreasing intensity. The program began with a 3-day nonresidential retreat, followed by weekly 3-h meetings for 10 weeks. Thereafter, 2-h meetings took place every other week for 9 months. The meetings were held in groups of 10–13 subjects. The lifestyle program addressed diet and stress management. MG participants were extensively informed about the Mediterranean diet as adapted from the Lyon Diet Heart Study (de Lorgeril et al., 1999) by nutritional information, repetitive group discussions, cooking classes and group meals. If necessary, the dietary instructions were customized in an individual 1-hour-long session, considering the patients’ readiness for behavioural change according to the concept of stages of change (Prochaska and Velicer, 1997). All instructions had to be detailed and compatible with the way of living. The general aim of the dietary recommendations was to provide subjects in the MG with a diet rich in alinolenic acid (ALA), marine n-3 polyunsaturated fatty acids (PUFA), monounsaturated fats (MUFA), phytochemicals, and low in saturated fats (SFA). In brief, the instructions to the MG were to consume at least five portions of fruits and vegetables daily, with an emphasis on root and green vegetables with a high content of ALA, and more than two portions of fatty fish per week. They were further asked to consume preferably whole-grain bread, pasta and rice. The intake of flaxseed and walnuts was strongly recommended. The intakes of meat and sausage should be limited to three servings per week, and beef, lamb and pork were to be replaced by poultry, fish or vegetarian dishes. Both olive oil and canola oil, and, for some dishes, walnut and flaxseed oil, were strongly recommended as the only oils for all food preparations. The intake of margarine was discouraged, with the exception of one margarine based primarily on olive oil and commercially available at that time. (When designing the study, no margarine with a defined high content of ALA was available in Germany). Modest regular alcohol consumption in the form of red wine to the meals was recommended. C: Patients in the AG received only written and less detailed information about the dietary principles of the Mediterranean diet, and some general advice about stress reduction by means of leaflets that were mailed shortly after randomization.</td>
<td>Dietary assessment were performed</td>
<td>No difference in care</td>
<td></td>
<td>I: 8% C: 4%</td>
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<td>n.d</td>
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Plain sponge), etc. Milk, eggs, and butter were restricted. An oil supplement of 80 g/day was prescribed, to be taken in three equal doses at meal-times. The general nature and purpose of treatment were explained, together with the fact that different patients were receiving different kinds of oil.

C: No advice on dietary fat was given to control patients.

Dietary intake before admission to hospital was estimated in both groups by taking a detailed history of pre-study food intake from patients and using the 24-hour recall method. Every patient had to describe the intake of foods and beverages for the past 24 hours, and the dietary advice was adjusted individually and repeated every third month. The patients were asked at every control session to prepare a written 4-day diary of foods and beverages consumed. They were asked not to weight the foods but to describe in ordinary words the size of the single ingredients (eg, a small, medium, or large apple) or size of portions of food; furthermore, they were asked to describe in detail fat percentages, especially in dairy produce and minced meat. Also, the patients were asked to note their hot meals. The food diaries were returned to the study nurse, who

<p>| Singh et al. 1992 | I+ C: In both diets meat, eggs, hydrogenated oils, butter, and clarified butter were replaced with vegetarian meat substitutes and soya bean, sunflower, and ground nut oils so as to provide a prudent diet reflecting the recommendations of the American Heart Association. Group A patients were also advised to eat fruit, vegetables, pulses, nuts, and fish. The goal was to provide at least 400 g/day of fruits and vegetables. In both groups, patients had a mainly vegetarian diet, eating eggs 4-5 times a week and meat 1-2 times a week. Other health related advice, such as stopping smoking, reducing alcohol intake, counseling to relieve mental stress and on physical activity, was given to both groups. However, though patients in group A had the advice regularly reinforced, those in group B were left to usual care after the initial advice. | No difference in care: I: 36% C: 35% | Propranolol: I: 46%, C: 44%; Verpamil: I: 25%, C: 27%; Nitrates: I: 98%, C: 97%; Frusemide: I: 14%, C: 18%; |
| Sondergaard et al. 2003 | I: was given dietary advice by a master of science in clinical nutrition and a specially trained research nurse. In general, the patients were advised to eat at least 600 grams of fruits and vegetables daily, to modify the intake of fat, especially saturated fat from meat and dairy produce, to eat fatty fish at least once a week and preferably several times a week, to eat plenty of bread and cereals, and to replace refined, hard, animal margarine products with vegetable oils, preferably canola oil. The first session was performed as a thorough interview lasting for at least 1 hour and using the 24-hour recall method. C: The control group was offered booklets about heart-healthy diets that are usually delivered to patients in the coronary care unit. They were also offered a single visit to a dietitian who was not participating in the study. The patients were examined every third month at clinical control sessions, but without follow-up on dietary advice. The control group was asked to perform a single diary after 1 year, and the results were entered and analyzed in the same database. | No difference in care: I: 43% C: 52% | 8-blockers: I: 56%; C: 68%; Calcium antagonists: I: 22%, C: 17%; ACE inhibitors: I: 15%, C: 22%; Long-acting nitrates: I: 6%, C: 19% (significant difference between groups; p=0.04) |</p>
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<th>Study</th>
<th>Intervention arm</th>
<th>Specific Study Characteristics</th>
<th>Follow-up</th>
<th>Outcome Measures</th>
<th>n.d</th>
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<td>Watts et al. 1992</td>
<td>I:</td>
<td>Total fat intake was reduced to 27% of dietary energy, SFA content 8-10%, and dietary cholesterol to 100mg/1000 kcal; omega-6 and omega-3 PUFA were increased to 8%, and plant derived soluble fiber (chiefly pectin) intake was increased to the equivalent of 3.6g polygalacturonate/1000 kcal. Intake of alcohol was permitted at the patient’s habitual level. Patients were instructed by a dietitian after a detailed history was obtained as a guide to energy requirements; choice of food was adapted to individual preferences. For patients with a BMI below 25 kg/m² an isocaloric diet was prescribed; overweight patients were prescribed a diet that contained 1000-1200 kcal daily to achieve a BMI of 25 kg/m². C: received, in common with both intervention groups, cardiological supervision and treatment, repeated counseling against smoking, and antihypertensive treatment if appropriate. All participants were advised about a suitable level of daily exercise. Patients in the control group with a BMI above 25 kg/m² were advised to lose weight but did not receive formal dietary counseling.</td>
<td>At each follow-up visit the clinician inquired about dietary compliance and provided encouragement.</td>
<td>No difference I: 26.9% C: 29.2%</td>
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<td>Woodhill et al. 1978</td>
<td>I:</td>
<td>were advised and tutored individually to reduce SFA intake to approximately 10% and dietary cholesterol to 300 mg or less per day. They were encouraged to use food containing PUFA to 15% or more of daily calories.</td>
<td>The diets of all participants were assessed by interview and/or food log three times during the first year and twice yearly thereafter.</td>
<td>No difference in care I+C: 38%</td>
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Table 1: Specific study characteristics
Figure S2. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 2 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S3. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 3 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S4. Forest plot showing pooled relative risks (RRs) with 95% CI for combined cardiovascular events for 3 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S5. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 3 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.
Figure S6. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 6 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S7. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 6 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S8. Forest plot showing pooled relative risks (RRs) with 95% CI for combined cardiovascular events for 6 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.
Figure S9. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 5 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S10. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 8 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S11. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 9 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.
Figure S12. Forest plot showing pooled relative risks (RRs) with 95% CI for total cardiovascular events for 9 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

Figure S13. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 9 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.
Figure S14. Bubble plot showing the association between % energy change from SFA and all-cause mortality

Figure S15. Bubble plot showing the association between % energy change from PUFA and all-cause mortality
Figure S16. Bubble plot showing the association between % energy change from MUFA and all-cause mortality

Figure S17. Bubble plot showing the association between % energy change from LA and all-cause mortality
Figure S18. Bubble plot showing the association between % energy change from SFA and cardiovascular mortality.

Figure S19. Bubble plot showing the association between % energy change from PUFA and cardiovascular mortality.
Figure S20. Bubble plot showing the association between % energy change from MUFA and cardiovascular mortality.

Figure S21. Bubble plot showing the association between % energy change from LA and cardiovascular mortality.
Figure S22. Bubble plot showing the association between % energy change from SFA and cardiovascular events.

Figure S23. Bubble plot showing the association between % energy change from PUFA and cardiovascular events.
Figure S24. Bubble plot showing the association between % energy change from MUFA and cardiovascular events.
Figure S25. Bubble plot showing the association between % energy change from LA and cardiovascular events

Figure S26. Bubble plot showing the association between % energy change from SFA and myocardial infarction
Figure S27. Bubble plot showing the association between % energy change from PUFA and myocardial infarction

Figure S28. Bubble plot showing the association between % energy change from MUFA and myocardial infarction
Figure S29. Bubble plot showing the association between % energy change from LA and myocardial infarction.

Figure S30. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 6 randomized controlled trials (PUFA vs. SFA).
Figure S31. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 6 randomized controlled trials (PUFA vs. SFA).

Figure S32. Forest plot showing pooled relative risks (RRs) with 95% CI for total cardiovascular events for 6 randomized controlled trials (PUFA vs. SFA).

Figure S33. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 6 randomized controlled trials (PUFA vs. SFA).

Figure S34. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 3 randomized controlled trials (fish advice vs. no fish advice).
Figure S35. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 3 randomized controlled trials (fish advice vs. no fish advice).

Figure S36. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular events for 3 randomized controlled trials (fish advice vs. no fish advice).

Figure S37. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for all-cause mortality. SE = Standard error
Figure S38. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for cardiovascular mortality. SE = Standard error

Figure S39. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for combined cardiovascular events. SE = Standard error
Figure S40. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for myocardial infarction. SE = Standard error