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Elsevier BV
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PII: S0952-3278(18)30073-5
DOI: 10.1016/j.plefa.2018.04.002
Reference: YPLEF 1917

To appear in: Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)

Received date: 16 March 2018
Revised date: 18 April 2018
Accepted date: 20 April 2018

Please cite this article as: Jyrki K. Virtanen, Randomized trials of replacing saturated fatty acids with n-6 polyunsaturated fatty acids in coronary heart disease prevention: not the gold standard?, Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA) (2018), doi: 10.1016/j.plefa.2018.04.002

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Highlights

- Replacing saturated fat with polyunsaturated fat is recommended for CHD prevention.
- Several trials in the 1950s-1970s tested this diet-heart hypothesis.
- Recently recovered data from two of the trials challenged the hypothesis.
- Many of the old trials had limitations, which prevents drawing firm conclusions.
Randomized trials of replacing saturated fatty acids with n-6 polyunsaturated fatty acids in coronary heart disease prevention: not the gold standard?

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Conflicts of interest: none.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Abstract

Several trials in the 1950s through 1970s tested the hypothesis that replacing saturated fat in the diet predominantly with n-6 polyunsaturated fat (PUFA) would reduce the incidence of coronary heart disease (CHD), mainly through modifying blood lipid profile. Most of these trials did observe a reduction in serum total cholesterol in the intervention group, but many trials failed to find a significant reduction in the incidence of CHD. However, some meta-analyses have found a reduced incidence of CHD by pooling the results from the trials. Recently, new recovered and reanalyzed data has emerged from two of the old trials. The new findings seemed to counteract the classical diet-heart hypothesis, when they found no cardiovascular benefit and even suggested harm, despite reduction in the serum total cholesterol concentration after replacing saturated fat especially with n-6 PUFA. This has raised criticism regarding the validity of the dietary recommendations that suggest partially replacing saturated fats with n-6 PUFA. This paper introduces the classical diet-heart trials and their main results and how the new findings relate to the overall study data of the cardiovascular effects of the n-6 PUFA. For multiple reasons considered here, it is difficult to draw firm conclusions of the cardiovascular effects of the n-6 PUFA based only on the findings in the old diet-heart trials. A more comprehensive picture emerges when also other lines of evidence is considered. The overall study data, including findings also from prospective cohort studies and from dietary trials with intermediate outcomes, still suggests that replacing saturated fat with n-6 PUFA would rather be beneficial than harmful for the prevention of CHD.

Keywords: polyunsaturated fatty acids; saturated fatty acids; coronary heart disease; prevention; diet-heart hypothesis; clinical trials
1. Introduction

Partial replacement of dietary saturated fat with polyunsaturated fat (PUFA) is a cornerstone of many dietary recommendations for prevention of coronary heart disease (CHD). This replacement has a beneficial impact on the serum lipid profile, especially on the LDL cholesterol concentrations [1]. This so-called diet-heart hypothesis is also supported by many prospective cohort studies that have shown that replacement of saturated fat with PUFA associates with a lower risk of CHD [2,3].

The diet-heart hypothesis was also tested in several randomized trials, most of which started in the late 1950s and early 1960s (Tables 1 & 2). In these trials, the aim was to replace the sources of saturated fat, such as full-fat dairy, butter and fatty meats, with lean meats, low-fat dairy and especially with vegetable oils and margarines that are rich in n-6 PUFA linoleic acid (LA), while keeping the total fat amount similar in both groups. These dietary changes created a large difference in the intakes of saturated fat and n-6 PUFA between the intervention and control groups and, as expected, many of the trials observed a significant reduction in the serum total cholesterol concentrations (Tables 1 & 2). As a side note, at that time the studies only measured serum total cholesterol, not LDL or HDL cholesterol concentrations. However, in spite of the reduction in the serum total cholesterol, many trials did not find a statistically significant effect on CHD incidence (Table 2). Several meta-analyses have pooled the results from these trials in various combinations in an attempt to increase power, with variable findings [4-12].

In the last few years, new recovered data has emerged from two of the early trials, the Sydney Diet Heart Study [13] and the Minnesota Coronary Survey [14] (Tables 1-3). In addition to presenting the results from the recovered data, both publications presented results from meta-analyses that included the new data. These studies seemed to indicate that replacing saturated fat with only n-6 PUFA might not be such a good idea after all for cardiovascular disease prevention. As expected, these results were received with mixed attitudes among the scientist and understandably may have created confusion and sparked criticism concerning the validity of the dietary recommendations. So what did these two new publications show?
2. The new findings

*Sydney Diet Heart Study*

The Sydney Diet Heart Study was a single-blind, secondary prevention trial among 458 men with a recent coronary event that was conducted between 1966 and 1973 (Table 1) [15]. The study’s aim was to investigate the effects of replacing saturated fat from animal sources with PUFA coming from safflower oil and safflower oil-based margarine. The only PUFA in safflower oil is LA (75% of the fatty acids) [16], so the trial mainly investigated replacement of saturated fat with n-6 PUFA. The intervention period ranged from 2 to 7 years, with the median follow-up being a bit over 3 years. The only previously reported finding from this trial was published in 1978 [15] (Table 3). That paper reported that despite a larger decrease in the serum total cholesterol concentration in the intervention group compared to the control group, the incidence of all-cause mortality was higher in the intervention group [15]. Of the 221 men in the intervention group, 37 men (16.7%) died, whereas of the 237 men in the control group, 28 men (11.8%) died (P<0.01). Ramsden et al. recovered the original data that were stored in magnetic tapes and published the results in 2013. The authors found that participants in the intervention group had 70% increased risk for cardiovascular mortality and 74% increased risk for CHD mortality, in addition to the 62% increased risk for all-cause mortality, compared to those in the control group [13].

The authors then included these results to an updated meta-analysis, where they had separated trials based on whether the intervention had replaced saturated fat with only n-6 PUFA or with both n-6 and n-3 PUFA [17]. The updated analysis, by pooling data from three included trials, showed that replacing saturated fat with only n-6 PUFA was associated with a 33% higher risk of cardiovascular disease mortality and a 27% higher risk of CHD mortality, with both results being borderline statistically significant (P=0.06 and P=0.07, respectively) [13]. Opposite results were obtained from the analyses that pooled four trials where both n-6 and n-3 PUFA (i.e., soybean oil, containing about 10% alpha-linolenic acid) replaced saturated fat. Those analyses showed a 21% lower cardiovascular disease mortality risk (P=0.04) and 19% lower CHD mortality risk (P=0.08).

The results from the Sydney Diet Heart Study have been criticized on the basis that those in the intervention group may have had a significant increase in *trans* fat intake from the high-*trans* fat study margarine [11,18,19]. Therefore, the intervention could have partially replaced saturated fat with the most atherogenic type of fat [11], instead of being only a saturated fat - n-6 PUFA replacement trial. However, although *trans* fats are known to increase serum total and LDL cholesterol concentrations [1], there was a significant 0.8
mmol/L decrease in the total cholesterol concentrations in the intervention group after 12 months (Table 2) [15]. This suggests that the major change would have been the replacement of saturated fat with n-6 PUFA, which decreases total and LDL cholesterol concentrations [1]. Furthermore, intake of trans fats may have differed between the intervention and control groups also in other trials. Due to the manufacturing processes at that time, the common margarines in the 1960s and 1970s contained large amounts of trans fat [21,22], which were not known as a cardiovascular risk factor, yet. In some trials, use of these common margarines was restricted in the intervention group (Table 1). In these trials, PUFA may have thus replaced not only saturated fat but also trans fat in the diet, resulting in lower trans fat intake in the intervention group when compared to the control group. This is suggested by the St. Thomas Atherosclerosis Regression Study, where those in the intervention group were advised to strictly limit margarine use (Table 1). In this trial, trans fat intake was 1.1 percent of energy in the intervention group and 1.8 percent of energy in the control group [20]. Other trials have not reported trans fat intake. Overall, although higher trans fat intake in the intervention group may have affected the results of the Sydney Diet Heart Study, the impact of the possible differences in trans fat intake (either favoring the intervention group or the control group) may not be unique to this trial.

The authors themselves suggested that the higher risk with diets high in LA could be a result of increase in oxidized LA metabolites in LDL and atherosclerotic lesions [13]. They presented additional observational analyses where they showed that the association of increased LA intake with increased risk of cardiovascular mortality in the intervention group was observed especially among smokers and among moderate-to-heavy alcohol drinkers. Cigarette smoking and high alcohol intake are both major sources of oxidative stress [23,24], which, when combined with a very high LA intake, could facilitate the production of oxidized LDL, a risk factor for CHD [25]. The authors had shown in their earlier study that lowering LA intake reduced LA concentration and oxidized LA metabolites in circulation [26]. However, although some of these oxidized LA metabolites have been related to atherosclerosis, they can also have anti-inflammatory and anti-proliferative properties [27]. Overall, there is still limited data on the physiological effects of different LA-derived metabolites [27], so it is difficult to draw firm conclusions of their overall impact on cardiovascular disease progression.
Minnesota Coronary Survey

Minnesota Coronary Survey is the largest trial that has investigated the effects of replacing saturated fat with n-6 PUFA. It was a double-blind trial conducted between 1968 and 1973 and included 4,393 men and 4,664 women aged 20-97 y from 6 mental hospitals and 1 nursing home (Table 1) [14,28,29]. It was mainly a primary prevention trial, because only 392 had electrocardiographic evidence of prior myocardial infarction [14]. Those in the intervention group were served a diet where typical sources of fat in an institutional diet were replaced by corn oil and corn oil-based margarine. Because the food in the institutions was served cafeteria-style, the investigators were able to conduct a double-blinded study.

Due to changes in the discharge policy during the trial that favored early discharge to the community and because the subjects were allowed intermittent stay in the hospitals, the average time in the hospitals was just a bit over one year (384 days) [29]. Only about a quarter of the subjects remained in the trial for at least one year [29]. Of note, there was no control or data on the subjects’ diets that they followed between admissions to the institutions.

An interesting fact about this study is that although it ended in 1973, the results were not published in an academic journal until 1989 [29]. In that publication the authors reported no difference in cardiovascular events or mortality in the whole study population, despite a significant 15% decrease in serum total cholesterol levels in the intervention group (Table 3). A more detailed description of the trial and many subgroup results that were not included in the year 1989 publication were included in a master’s thesis that was published in 1981 [28]. The life-table analyses presented in the thesis suggested an increased mortality risk among those aged ≥65 y in the intervention group. However, these results were never published in an academic journal.

Ramsden et al. recovered some of the original data that were stored in magnetic tapes and as paper documents and in 2016 published the life-table graphs for cumulative mortality in the whole study population and in the prespecified subgroups that had been originally published only in the thesis in 1981 [14]. However, they had not been able to locate the patient-level data for these analyses, so they were not able to determine the statistical significance of the findings. They also presented previously unpublished data regarding the effect of the dietary intervention on coronary and aorta autopsy findings. This data was originally available for 295 subjects, but they were able to recover the data only for 149 subjects. The recovered data showed no statistically significant differences between the intervention and control groups in aortic and coronary atherosclerosis after the median
follow-up of 298 days, but there was evidence for 90% higher incidence rate of myocardial infarction in the autopsy in the intervention group (P=0.035).

In addition to these results, the authors also conducted a meta-analysis where they pooled the findings from the Minnesota Coronary Survey with four other similar but considerably smaller trials [13,30-32], which had replaced saturated fat with n-6 PUFA-rich vegetable oils [14]. The pooled results indicated no impact on CHD or all-cause mortality, despite a mean 8 to 14% greater reduction in serum total cholesterol concentrations in the intervention vs. the control groups.

A major limitation of the trial, as also Ramsden et al. themselves acknowledged, was that only a small part of the recruited subjects stayed in the study for at least one year. For example, the most recent Cochrane review did not include the Minnesota Coronary Survey for this reason [9]. Another limitation is that a half of the original autopsy files remained missing. The autopsy findings are of interest, because post-mortem autopsy data is not commonly available among the diet-heart trials (also the LA Veterans Administration Study has autopsy data [33]). However, as also the authors pointed out, the results from these analyses should be interpreted cautiously because of the small number of subjects with recovered data. Finally, the use of lightly-hydrogenated corn oil margarine, a major source of trans fat, in the intervention group may have affected the results.

3. Discussion

Randomized trials with disease outcomes give the best evidence for causality between exposure and risk of a disease. However, unlike with pharmaceutical agents or with micronutrients like vitamins that can be administered as pills or capsules, placebo-controlled randomized trials that require changes in food intake are very difficult to conduct. Blinding is often impossible, if foods are added or omitted or the structure or taste of a food is changed. The long study duration required to detect an effect on disease incidence means that the subjects need to change their typical dietary habits for several years, which significantly decreases compliance. Indeed, many of the old dietary fat replacement trials were flawed in one way or another, limited for example by a small number of participants, short duration, high drop-out rate, intermitted exposure to study diets, cluster randomization and cross-over design, or possible disproportional intake of trans fatty acids between the intervention and control groups. Due to these limitations, not all trials are included in all meta-analyses that have assessed the impact of replacing saturated fat with n-6 PUFA [4-14]. This has had a rather large impact on whether a meta-analysis has observed a statistically significant
reduction in the CHD incidence. It also highlights the point that the health effects of the n-6 PUFA should not be evaluated based solely on the findings in these old trials.

The dose of n-6 PUFA in many of these trials was much larger than what most dietary guidelines recommend and what is commonly consumed. For example, the Nordic Nutrition Recommendations recommend that PUFA should account for 5-10 percent of energy intake, of which at least 1 percent of energy should come from the n-3 PUFA [34]. In the USA, the Institute of Medicine recommends 5-10 percent of energy as n-6 PUFA [35]. The recommendation by the United Nations Food and Agriculture Organization (FAO) for n-6 PUFA (specifically LA) is 2.5-9 percent of energy, where the higher end of this range is recommended for lowering total and LDL cholesterol concentrations and risk of CHD [36]. In country-specific nutrition surveys, the global average intake of n-6 PUFA has ranged between 1.2 and 12.5 percent of energy, with the mean intake of 5.9 percent of energy [37]. In prospective studies in Western countries, the median LA intake has ranged between 1.5 and 6.4 percent of energy [3]. Notably, in these prospective studies higher LA intake is associated with a lower risk of CHD, whether it replaces saturated fat or carbohydrates in the diet [3]. Of course, observational cohort studies are not free of limitations, either. Major limitations include the residual confounding and that they cannot reliably establish causality between a dietary factor and risk of disease. It is also difficult to accurately estimate dietary intakes, which creates random error, which in turn can attenuate the associations between diet and disease risk. However, for some dietary factors it is also possible to use objective measures of exposure. For example, in the case of LA, circulating or adipose tissue fatty acid levels correlate well with intake [38]. This eliminates problems that are inherent in the subjective methods to assess dietary intakes, like the recall errors in food-frequency questionnaires. Observational studies have observed inverse associations between biomarker LA levels and risk of cardiovascular diseases, thus complementing the findings from studies using dietary intakes as exposure (e.g. [39-41], see also the paper by Wang in this issue about epidemiological evidence of the cardiovascular benefits of n-6 PUFA).

The meta-analyses by Ramsden et al. suggested that there were no cardiovascular benefits in trials that increased only n-6 PUFA (LA) intake, in contrast to the trials where the intervention diet also included n-3 PUFA [13,14]. The n-3 PUFA, both the plant-based alpha-linolenic acid and especially the long-chain n-3 PUFA that are obtained mainly from fish, have known cardiovascular benefits [42,43]. This could indicate that a very high LA intake, as used in many of the old trials (Table 2), may not bring about additional cardiovascular benefits compared to the recommended doses. However, it can also be argued that the lack of
an effect in the trials that increased only LA could be a result of decreased n-3 PUFA intake in the intervention group. In those trials [15,29,30], corn oil or safflower oil or margarine made of these oils replaced not only butter and other sources of saturated fat but also other vegetable oils and margarines. These other oils and margarines, such as those made from soy oil, most likely have contained some n-3 PUFA.

The recovery and re-analysis of the original data from the two studies conducted almost 50 years ago must have been a huge effort and for this the Ramsden’s team should be applauded. These kinds of dietary trials will most likely never be conducted again, because such studies would require a large number of participants who would need to significantly change their dietary habits for several years. The declining cardiovascular disease incidence, increasing use of state-of-the-art medication, and especially the huge costs for successfully conducting such a study, are other reasons why it is good to make the most of these decades old trials. However, because of the many limitations in these trials, their results should not be used as a definite answer to the question: is high n-6 PUFA intake good or bad for the heart? A more comprehensive picture emerges when we also consider the evidence from short-term dietary trials that have found benefits of higher LA intake on, e.g. serum lipid profile and glucose homeostasis [1,44] and from prospective cohort studies that investigate the associations with disease outcomes. An example of a modern approach in epidemiological research are the pooling projects of the individual-level data by the Fatty Acid and Outcomes Research Consortium (FORCE, http://force.nutrition.tufts.edu), an international consortium of observational cohorts with data on fatty acid biomarkers [43,45]. Overall, these studies suggest that higher n-6 PUFA intake would rather be beneficial than harmful for CHD prevention, at least with the doses currently recommended by most organizations.

References


37. R. Micha, S. Khatibzadeh, P. Shi, et al., Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: A systematic analysis including 266 country-specific nutrition surveys, BMJ 348 (2014) g2272.


Table 1

Description of the diet-heart trials that are commonly included in meta-analyses

<table>
<thead>
<tr>
<th>Study name, country</th>
<th>Study start year</th>
<th>Study duration</th>
<th>Study population</th>
<th>Preventive n</th>
<th>Sources of PUFA in the intervention group</th>
<th>Control diet</th>
<th>Intervention diet also contained additional n-3 PUFA?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose Corn Oil Trial, UK [30]</td>
<td>Not reported</td>
<td>2 y</td>
<td>54 free-living subjects, aged &lt;70 y (gender not reported)</td>
<td>Secondary y</td>
<td>A total of 80 g of corn oil taken 3 times/d with meals. Additional advice: fried foods, fatty meats, sausages, pastry, ice cream, cheese, cakes, etc. were to be avoided. Milk, butter and eggs were restricted</td>
<td>No dietary advice</td>
<td>No</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Duration</td>
<td>Participants</td>
<td>Randomization</td>
<td>Diet Advice</td>
<td>Additional Advice</td>
<td></td>
</tr>
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</tr>
<tr>
<td>Oslo Diet-Heart Study, Norway [46,47]</td>
<td>1958</td>
<td>5 y</td>
<td>412 free-living men, aged 30-64 y (mean 56 y)</td>
<td>No</td>
<td>Yes</td>
<td>0.5 L/wk soy oil either used in food preparation or “taken as medicine”. Dietary advice, but multivitamin tablets provided. (EPA and DHA from fish, alpha-linolenic acid from soy oil) Additional advice: fish, shellfish, whale meat and poultry instead of beef, mutton and pork (canned sardines in cod liver oil provided); lard, shortenings, margarine, whole milk, cream, butter and fatty cheeses restricted, olive oil use discouraged</td>
<td></td>
</tr>
<tr>
<td>Study Location</td>
<td>Year</td>
<td>Duration (y)</td>
<td>Participants</td>
<td>Diets Provided</td>
<td>Typical Institutional Diet</td>
<td>Yes/No (α-Linolenic Acid)</td>
<td></td>
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</tr>
<tr>
<td>Finnish Mental Hospital Study, Finland</td>
<td>1959</td>
<td>6+6 y</td>
<td>922 men aged 34-64 and 713 women aged 44-64</td>
<td>Soy oil blended with milk, &quot;soft&quot; margarine high in PUFA instead of &quot;ordinary&quot; margarine and butter</td>
<td>Yes</td>
<td>(α-Linolenic acid from soy oil)</td>
<td></td>
</tr>
<tr>
<td>Los Angeles Veterans Administration Study, USA</td>
<td>1959</td>
<td>8 y</td>
<td>846 semi-institutionalized men aged 54-88 y (mean 65 y)</td>
<td>Soy oil, corn oil, safflower oil, cottonseed oil provided</td>
<td>Typical institutional diet modified to resemble</td>
<td>Yes</td>
<td>(α-Linolenic acid from soy oil)</td>
</tr>
</tbody>
</table>
within the institutional diet in place of fats of animal origin. The oils were incorporated in the diet as blended in skim milk, imitation ice cream, “unsaturated” margarine, special sausage products, and filled cheeses and also used liberally in cooking and baking. Meat fat minimized by using trimmed lean cuts of meat. Egg
| Medical Research Council Soy Oil Study, UK [32] | 1960 | 2-7 y | 393 free-living men, aged <60 y | 85 g/d soy oil, of which at least half to be taken unheated (mainly drunk with fruit juice). In ten men, corn oil was substituted because of nausea and diarrhea. Additional advice: 14 g/d margarine allowed; butter, other oils and cooking fats, fatty meat, whole milk, cheese, egg yolks restricted to 7/wk | No | Yes (alpha-linolenic acid from soy oil) |
yolk, and most biscuits and cakes forbidden

| Diet and Reinfarction Trial, UK [51,52] | Dietary advice | No specific dietary advice, except for a “sensible eating sheet”, which did not include dietary advice on any of the intervention components. | No foods provided for the subjects. | Mean EPA intake 0.25 g/d in the intervention group and 0.21 g/d in the control group. |
| 1983 2 y 2033 free-living men, aged <70 y (mean 56 y) | No specific dietary advice | Dietary advice recommending thin spreading of a PUFA margarine on bread; skimmed milk instead of fattier milk; fried or roasted foods limited and cooked only in polyunsaturated oil; fatty cheese intake limited to 3 oz/wk and eggs to 2/wk; lean meats | Dietary advice | EPA intake 0.25 g/d in the intervention group and 0.21 g/d in the control group. |
(poultry, white fish, very lean beef) instead of fattier meats; cakes pastries, biscuits pies, crisps, chocolates and toffee limited; fat suggested to be replaced by bread, potatoes, rice and pasta

St. Thomas Atherosclerosis Regression Study, UK [20,53] 1987 3.3 y 55 free-living men, aged <66 y (mean age 54 y in the intervention group, 49 y in the control group) Dietary advice to strictly limit animal protein (e.g. meat, cheese, fish), margarine, and oils, No dietary advice Higher intake of EPA and DHA in the intervention group (0.48 g/d) compare
and to avoid processed foods (e.g., cookies, pastry, cakes, safflower oil and safflower oil-enriched foods) as well as vegetables, fruits and legumes, and oats. Relatively large quantities of starchy, low-fat foods (e.g., pasta, potatoes, bread, and rice) and fruits (particularl
Safflower oil used in place of animal fats, common margarines and shortening in cooking oils, salad dressings, baked goods, and other products, and also taken as a supplement.

| Minnesota Coronary Survey, USA [14,29] | 1968 | 4.5 y (mean) | 4393 men and 4664 women from 6 mental hospitals | Mainly primary (392 subjects had electro- | Corn oil in place of usual hospital cooking fats | Typical institutional diet | No |
and 1 nursing home, aged 20-97 y (mean 48 y). Cardiographic evidence of myocardial infarction also added to numerous food items (e.g. salad dressings, filled beef, filled milk, filled cheeses).

Soft corn oil polyunsaturated margarine used in place of butter.

PUFA, polyunsaturated fat; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
### Table 2

Main findings in the diet-heart trials

<table>
<thead>
<tr>
<th>Study name, country</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Change in plasma total cholesterol concentration during study (mmol/L)</th>
<th>Main results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose Corn Oil Trial, UK [30]</td>
<td>Not reported</td>
<td>Not reported</td>
<td>-0.5</td>
<td>No statistically significant differences in CHD events</td>
<td></td>
</tr>
<tr>
<td>Oslo Diet-Heart Study, Norway [46,47]</td>
<td>8.5 / 20.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not assessed</td>
<td>-1.4</td>
<td>Lower incidence of major CHD events, mainly fatal myocardial infarction, in the intervention group</td>
<td>Rather a multifactorial trial, because several dietary factors were changed in the intervention group</td>
</tr>
<tr>
<td>Finnish Mental Hospital Study,</td>
<td>8.6 / 12.7</td>
<td>17.2 / 4.3</td>
<td>-1.1 in men, -0.9 in women&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Lower incidence of total and fatal CHD</td>
<td>This study is not included in most meta-</td>
</tr>
</tbody>
</table>
Finland [48,49] during the experimental diet period analyses. The main reasons are that the two hospitals instead of the patients were randomized (cluster randomization with n=2). Other reasons include the cross-over design without a washout period and the disproportionate use of a cardiotoxic drug in one control arm.

<p>| Los Angeles Veterans Administration Study, USA [31,33,50] | Not reported | Not reported | -1.1 | -0.9 | No statistically significant difference in CHD events, but lower incidence of |</p>
<table>
<thead>
<tr>
<th>Study Description</th>
<th>S/P Ratio</th>
<th>Δ S/P</th>
<th>Δ P</th>
<th>Δ CHD Events</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council Soy Oil Study, UK [32]</td>
<td>Not reported</td>
<td>-0.9</td>
<td>-0.1</td>
<td>No statistically significant difference in CHD events</td>
<td></td>
</tr>
<tr>
<td>Diet and Reinfarction Trial, UK [51]</td>
<td>11.2 / 9.5</td>
<td>14.9 / 6.7</td>
<td>-0.2</td>
<td>-0.1</td>
<td>No statistically significant difference in CHD events</td>
</tr>
<tr>
<td>Low compliance in the intervention group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. Thomas Atherosclerosis Regression Study, UK [20,53]</td>
<td>8.9 / 7.3</td>
<td>17.1 / 4.7</td>
<td>-1.0</td>
<td>-0.1</td>
<td>Less progression of coronary atherosclerosis and lower incidence of total cardiac events in the intervention group, but no statistically significant difference in</td>
</tr>
<tr>
<td>In this study the total fat intake was significantly lower and carbohydrate and fiber intakes significantly higher in the intervention group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CHD events

**Re-analyzed studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>CHD Events</th>
<th>Total Mortality</th>
<th>Cardiovascular Disease</th>
<th>CHD Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sydney Diet Heart Study, Australia [13,15]</td>
<td>9.8 / 15.1 13.5 / 8.9</td>
<td>-0.8e -0.5e</td>
<td>Higher incidence of all-cause, cardiovascular disease and CHD mortality in the intervention group</td>
<td></td>
</tr>
<tr>
<td>Minnesota Coronary Survey, USA [14,29]</td>
<td>9.2 / 14.7 18.3 / 5.2</td>
<td>-0.7d -0.1d</td>
<td>No difference in CHD events or total mortality in the whole cohort. Possible increased mortality risk in those ≥65 y of age</td>
<td></td>
</tr>
</tbody>
</table>

LA, linoleic acid; CHD, coronary heart disease; PUFA, polyunsaturated fat; S/P, saturated/polyunsaturated.

aData based on 7-14-day diet records of only 17 subjects.
\[ \text{Because of the crossover design, the results are only reported as the mean difference in serum cholesterol concentrations in the two hospitals between the experimental-diet and normal-diet periods.} \]

\[ \text{\textsuperscript{c}Measured from 371 subjects after 12 months of follow-up.} \]

\[ \text{\textsuperscript{d}Calculated from the data for 2355 subjects who stayed at the study for at least one year [14].} \]
Table 3

Comparison of the primary and secondary analyses of the Sydney Diet Heart Study and the Minnesota Coronary Survey

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary study</th>
<th>Secondary analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Saturated fat replaced with n-6 polyunsaturated fat</td>
<td></td>
</tr>
<tr>
<td>Cohort analyzed</td>
<td>458 men</td>
<td>458 men</td>
</tr>
<tr>
<td>Outcomes presented</td>
<td>Incidence of all-cause mortality</td>
<td>Incidence of all-cause, CVD and CHD mortality</td>
</tr>
<tr>
<td>Findings</td>
<td>Higher all-cause mortality in the intervention group</td>
<td>Higher all-cause, CVD and CHD mortality in the intervention group</td>
</tr>
<tr>
<td><strong>Minnesota Coronary Survey</strong></td>
<td>Frantz et al. (1989) [29]</td>
<td>Ramsden et al. (2016) [14]</td>
</tr>
<tr>
<td>Intervention</td>
<td>Saturated fat replaced with n-6 polyunsaturated fat</td>
<td></td>
</tr>
<tr>
<td>Cohort analyzed</td>
<td>9057 men and women</td>
<td>9423 men and women in the analyses with incident events, a 149 subjects with recovered autopsy data</td>
</tr>
<tr>
<td>Outcomes presented</td>
<td>Incidence of myocardial infarction, sudden death and all-cause mortality</td>
<td>Incidence of all-cause mortality; coronary atherosclerosis and myocardial infarction detected at autopsy</td>
</tr>
<tr>
<td>Findings</td>
<td>No evidence of benefit for cardiovascular events or mortality in the intervention group</td>
<td>No evidence of benefit for mortality or for the autopsy findings in the intervention group. Possible increased mortality risk in those ≥65 y of age</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; CVD, cardiovascular disease.

aThe number of subjects reported also in the master’s thesis [28].