Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis

World Health Organization

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Abbreviations and acronyms

ApoA-I	apolipoprotein A-I
ApoB	apolipoprotein B
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
cis-MUFA	*cis*-monounsaturated fatty acids
cis-PUFA	*cis*-polyunsaturated fatty acids
CVD	cardiovascular disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
LDL	low-density lipoprotein
NCDs	noncommunicable diseases
NUGAG	WHO Nutrition Guidance Expert Advisory Group
PICO	population, intervention, comparator and outcome
RCT	randomized controlled trial
SFA	saturated fatty acids
TFA	*trans*-fatty acids
WHO	World Health Organization

1. Introduction

1.1 Background

Fats in the diet mainly consist of triglyceride, a molecule composed of three fatty acids and a glycerol backbone. Fatty acids differ in several aspects. First, they are characterized by the number of double bonds. Saturated fatty acids (SFA) have no double bonds, while monounsaturated fatty acids (MUFA) have one double bond and polyunsaturated fatty acids (PUFA) have two or more double bonds. These double bonds have either the *cis* or *trans* configuration. Most unsaturated fatty acids in the diet have the *cis* configuration, but *trans*-fatty acids (TFA) are also present. Second, the position of the double bond varies. Third, fatty acids differ in chain length, though the number of carbon atoms is usually an even number. The most abundant SFA in the diet have 16 (C16:0; palmitic acid) or 18 (C18:0; stearic acid) carbon atoms, while smaller proportions of SFA have 14 (C14:0; myristic acid) or 12 (C12:0; lauric acid) carbon atoms. Some fats (e.g. coconut oil and dairy fat) also contain fatty acids with fewer than 12 carbon atoms. The most abundant *cis*-MUFA is oleic acid (C18:1), and the most abundant *cis*-PUFA are linoleic acid (C18:2n-6) and α-linolenic acid (C18:3n-3). Existing evidence suggests that the intake of fatty acids is a major determinant of the serum lipid and lipoprotein profile.

1.2 Objectives

The aim of this systematic review was to assess the effect of modifying SFA intake on serum lipid and lipoprotein levels by exchanging SFA with *cis*-MUFA, *cis*-PUFA or carbohydrates, in order to inform and contribute to the development of updated WHO recommendations on SFA intake. Effects of TFA were not considered in this analysis.

2. Methods

This systematic review and regression analysis was conducted in accordance with the WHO guideline development process *(1)*. As part of the evidence review, results of the regression analysis were evaluated using the methodology of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group *(2)*. Evidence summaries and GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health, as part of the WHO guideline development process. The PICO (population, intervention, comparator and outcome) questions (**Annex 1**) and priority health outcomes (**Annex 2**) guiding this review were discussed and developed by the NUGAG Subgroup on Diet and Health.

This systematic review and analysis is an update of the results of an earlier published review and analysis *(3)*.

2.1 Criteria for selecting studies to include in this review

2.1.1 Study characteristics

Study design

The review included only studies that were designed to eliminate the effect of nonspecific drifts of the outcome variables with time. Elimination of the effect could be achieved by feeding the different diets side-by-side (parallel design) or by giving the diets to the volunteers in random order (crossover or Latin square design). "Before-and-after" (sequential) designs do not eliminate this effect and were therefore excluded. Dietary periods had to be at least 13 days, because time is otherwise too short for serum lipids and lipoproteins to reach a new steady-state situation *(4, 5)*.

Diets and interventions

Only studies with a thorough daily control of food intake were selected. Protein and alcohol intake had to be constant and fatty acids had to be exchanged for other fatty acids or for carbohydrates. Possible effects of protein and alcohol on the serum lipoprotein profile could therefore not be estimated. Other concomitant interventions (e.g. those targeting weight loss) were not allowed. Daily cholesterol intake between diets within a study had to be comparable (<100 mg difference). Diets that focused on (hydrogenated) very long chain (n-3) PUFA (fish oils) were excluded. Therefore, total PUFA in these studies can be considered to equal PUFA with 18 carbon atoms (linoleic acid plus α-linolenic acid). Studies focusing on medium-chain fatty acids (MCFA) or behenic acid were also excluded, because their number was too limited to allow proper statistical analyses. Only studies with a reported TFA intake of 2% of total energy intake or less were included. If TFA was not reported, it was assumed to be less than 2%. Estimates for the effects of the various fatty acids on serum lipids and lipoproteins were based on within-study comparisons (see **Section 2.2.4**), therefore studies that could only provide one data point based on the inclusion criteria were also excluded.

Participants

Only studies with apparently healthy adult subjects (aged > 17 years), who did not suffer from gross disturbances of lipid metabolism or from diabetes, were considered.

2.1.2 Outcomes

The outcomes assessed in this analysis were serum lipids and lipoproteins, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, LDL cholesterol to HDL cholesterol ratio, total cholesterol to HDL cholesterol ratio, triglyceride to HDL cholesterol ratio, apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB) (**Annex 2**).

2.2 Data collection and analysis

2.2.1 Identification of studies

Search strategy

As indicated in **Section 2**, this analysis is an update of the results of an earlier published analysis *(3)*. For the original analysis, controlled dietary trials published in English between January 1970 and December 1998 were identified through a computer-assisted literature search. Reference lists of identified papers were hand-searched for additional relevant citations. In total, 60 studies were identified that met the inclusion criteria. In 2009, a computer-assisted literature search was performed for articles published between January 1999 and December 2008, which brought the total data set to 83 studies. Finally, in January 2014, a computer-assisted literature search was performed in the PubMed database for articles published between January 2009 and December 2013. Search terms can be found in **Annex 3**. After scanning, an additional eight articles were identified, providing a total of 91 studies.

Selection of studies

A study was excluded if it was evident from the title or abstract that the study did not meet the inclusion criteria (e.g. the study addressed the effects of fish oils only, was not adequately controlled, was not an intervention study, etc.). Full texts of the remaining citations were reviewed for inclusion.

2.2.2 Data extraction and management

For studies meeting the inclusion criteria, data were extracted using standard data extraction forms. Data were then transferred in duplicate to Microsoft Excel. Typographical errors were corrected and the data were analysed for consistency (e.g. sum of fatty acids, sum of percentage of energy from the macronutrients, etc.). Each data point consisted of the fatty acid and carbohydrate composition of a particular diet and the mean serum lipid or lipoprotein concentration or ratio of a group of subjects, as obtained at the end of a dietary period. For parallel designs, serum parameters were adjusted for differences between the intervention groups at baseline.

2.2.3 Assessment of risk of bias in included studies

Risk of bias was assessed for each included study through identification and extraction of relevant information on study design and conduct. The following areas, discussed below, can lead to bias *(6)*, and were included for assessment, each being assigned a *low*, *high* or *unclear* risk of bias:

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- incomplete outcome data
- selective reporting
- other sources of bias.

Random sequence generation

For each included study, it was determined whether randomization was employed and if so, whether the method used to generate the randomization sequence was described in sufficient detail to allow an assessment of whether it would have produced comparable groups. Studies were categorized as one of the following in relation to risk of bias:

- *low* – if a truly random process was used (e.g. random number table or computer random number generator); *or* a crossover study design was used, such that both groups received both the intervention and control treatment, and thus observed differences were unlikely to be a result of group differences;

- *high* – if a non-random process was used (e.g. odd or even date of birth, or hospital or clinic record number), *or* randomization was not used; or
- *unclear* – if the study did not specify whether randomization was used at all, or did not provide enough detail to determine whether the process was truly random.

Allocation concealment

For each included study, it was determined whether the method used to conceal the allocation sequence (in randomized studies) was described in sufficient detail so as to determine whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. Studies were categorized as one of the following in relation to risk of bias:

- *low* – if methods such as telephone or central randomization, consecutively numbered sealed opaque envelopes and so on were used; *or* if the studies had a crossover design or no randomization (in which case, allocation concealment is not relevant and thus does not present a source of bias);
- *high* – if methods such as open allocation, unsealed or non-opaque envelopes, alternation, date of birth and so on were used; or
- *unclear* – if the study did not specify whether allocation concealment was used at all, or did not provide enough detail to determine whether the process was sufficient to prevent knowledge of assignment.

Blinding of participants and personnel

For each included study, the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received, were identified. Studies were judged to be at low risk of bias if they were blinded, or if it was deemed that the lack of blinding was unlikely to have affected the results. Studies were categorized as *low*, *high* or *unclear* risk of bias separately for:

- participants
- personnel
- outcome assessments.

Incomplete outcome data

For each included study, the completeness of data was determined, including attrition and exclusion of data from the analysis. It was further determined whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of participants), reasons for attrition or exclusion (where reported), and whether missing data were balanced across groups or were related to outcomes. Studies were categorized as one of the following in relation to risk of bias:

- *low* – if few drop-outs or losses to follow-up were noted or an intention-to-treat analysis was possible;
- *high* – if there was significant loss to follow-up that was not addressed in terms of comparability across intervention and control groups, or data were not adjusted for missing data, *or* there were wide differences in exclusions between groups, whether or not intention-to-treat analysis was used; or
- *unclear* – if losses to follow up or exclusions were not sufficiently reported to determine whether the process was sufficient.

Selective reporting

For each included study, an attempt was made to determine whether there was selective outcome reporting. Studies were categorized as one of the following in relation to risk of bias:

- *low* – if it was clear that all of the prespecified outcomes and all expected outcomes of interest to the review had been reported;

- *high* – if not all prespecified outcomes had been reported; one or more reported primary outcomes had not been prespecified; outcomes of interest were reported incompletely and so could not be used; *or* results of a key outcome that would have been expected to have been reported were not reported; or
- *unclear* – if the information given was insufficient to judge whether or not outcomes were selectively reported.

Other sources of bias

For each included study, other possible sources of bias were identified, such as potential differences in the groups at baseline, evidence of treatment compliance, residual confounding and other problems that could put it at risk of bias.

2.2.4 Analytical methods

Calculations and conversions

Plasma values for total and HDL cholesterol were multiplied by 1.030 and those for triglyceride by 1.029 to convert them to serum values *(7)*. LDL cholesterol concentrations were calculated using the Friedewald equation *(8)*. For the sake of uniformity, the total cholesterol to HDL cholesterol ratio, the LDL cholesterol to HDL cholesterol ratio, the triglyceride to HDL cholesterol ratio, and the LDL cholesterol concentration for all studies were recalculated, even if these values were reported by the study authors. Plasma values for ApoA-I and ApoB were also multiplied by 1.030 to convert them to serum values.

Dietary fat contains on average 96% by weight as fatty acids; the other 4% are glycerol and other lipids. For publications in which the intakes of the various fatty acid classes had been normalized so as to add up to 100% of total fat, the intakes were converted back into true fatty acid intakes by multiplying them by 0.96.

Statistical analysis

Multiple regression analyses were performed to predict the mean serum lipid or lipoprotein concentration or ratio (the dependent variable) of a group of subjects from the changes in percentage of total energy intake of fatty acids or carbohydrates in the diets (the independent variables). As indicated in **Section 2.1.1**, within each study fatty acids of the experimental diets were exchanged for other fatty acids or for carbohydrates.

In order to estimate the effects on serum lipids of both decreasing SFA intake (via replacement with *cis*-PUFA, *cis*-MUFA or carbohydrates) and increasing SFA intake (via replacement of *cis*-PUFA, *cis*-MUFA or carbohydrates with SFA), four models were generated. A fifth model estimated the effects of individual SFA. All five models used absolute lipid or lipoprotein concentrations or ratios on each diet as dependent variables. A dummy variable for each study was introduced into the model, to ensure that only within-study diet-induced differences were analysed. The estimate for that dummy variable can be envisaged as the mean estimated serum lipid or lipoprotein parameter ("the intrinsic level"), when the participants from that study consumed a standardized fat-free diet. It varies between studies, due to differences in study population (e.g. genetic makeup, age, and body mass index [BMI]), but also by other factors such as the fibre, protein or cholesterol content of the background diet, which was constant within studies, but differed between studies.

In the first model (model 1), SFA served as the reference nutrient and the effects of a mixture of *cis*-PUFA, *cis*-MUFA and carbohydrates, on the dependent variable were estimated. The regression coefficients represent the predicted change in the mean serum lipid or lipoprotein concentration or a ratio when SFA intake decreases by 1% of total energy intake and that of *cis*-PUFA, *cis*-MUFA or carbohydrates increases by the same amount. Diets in which the fatty acid composition of a particular class of fatty acids diverged markedly from that in normal mixed diets, were excluded (e.g. diets specifically enriched in lauric acid or stearic acid). Including these data points would have resulted in less reliable estimates of the effects of a normal mixture of SFA, because evidence indicates that individual SFA have different effects on the serum lipoprotein profile *(9, 10)*.

In the second model (model 2), *cis*-MUFA served as the reference nutrient and the effects of a mixture of *cis*-PUFA, carbohydrates and SFA on the dependent variable were estimated. The regression coefficients in this model now represent the predicted change in the mean serum lipid or lipoprotein concentration or a ratio when *cis*-MUFA intake decreases by 1% of total energy intake and that of *cis*-PUFA, carbohydrates or SFA increases by the same amount.

In the third model (model 3), *cis*-PUFA served as the reference nutrient and the effects of a mixture of *cis*-MUFA, carbohydrates and SFA on the dependent variable were estimated. The regression coefficients in this model now represent the predicted change in the mean serum lipid or lipoprotein concentration or a ratio when *cis*-PUFA intake decreases by 1% of total energy intake and that of *cis*-PUFA, carbohydrates or SFA increases by the same amount.

In the fourth model (model 4), carbohydrate served as the reference nutrient and the effects of a mixture of *cis*-PUFA, *cis*-MUFA and SFA on the dependent variable were estimated. The regression coefficients in this model now represent the predicted change in the mean serum lipid or lipoprotein concentration or a ratio when carbohydrate intake decreases by 1% of total energy intake and that of *cis*-PUFA, *cis*-MUFA or SFA increases by the same amount.

The fifth model (model 5) estimated the effects of individual SFA. The proportions of energy from lauric, myristic, palmitic and stearic acids were used as independent variables, together with the proportions of energy from *cis*-PUFA and *cis*-MUFA. Thus, as in the fourth model above, carbohydrates served as the point of reference. Individual SFA of less than 12 carbon atoms, were not reported in all studies and were therefore not included in the analysis.

The validity of the regression models was examined in several ways. First, normality of the residuals was checked. If the residual was not normally distributed, the most extreme value(s) were excluded. This approach did not change conclusions, but resulted in narrower confidence intervals. Second, the influence of each separate observation on the estimated regression coefficients was assessed using the Cook's distance. Observations with a Cook's distance >0.4 were excluded in the final analysis. Third, visual inspection of plots did not suggest a relationship between residuals and the independent variables. This suggests that the differences between observed and predicted values (i.e. the residuals) did not depend on the absolute level of intake of a particular (class of) fatty acid(s). Results of residuals analysis for SFA intake (model 1) are provided in **Annex 4**. Furthermore, the observed and predicted values for LDL cholesterol concentrations were in excellent agreement (**Annex 5**). Each data point was weighed for the number of participants. All statistical analyses were carried out using SPSS version 23.

Subgroup and sensitivity analyses

Subgroup analyses were performed to examine whether responses to the diets were influenced by baseline lipid and lipoprotein concentrations, gender (by comparing results of studies carried out with only men versus those carried out in men and women or women only) or publication date (by comparing results of studies published before 1993 and in 1993 or later, because it was at approximately that time that the detrimental effects of TFA on the serum lipid and lipoprotein profile became known). Subgroup analysis by type of carbohydrate included in study diets was also planned. Sensitivity analysis was performed in which studies that used liquid formula diets were excluded.

3. Results

3.1 Search results

The initial search for articles published between January 2009 and December 2013 returned 629 potentially eligible articles. After removing citations based on title or abstract, the full texts of 66 articles were assessed for inclusion, and eight were included. Together with the 83 articles from previous searches, a total of 91 dietary trials were identified. Seven of these studies could not be used for the final calculations, because they yielded only one data point (as the intake of TFA in the other diets exceeded 2% of total energy intake) and were therefore excluded, leaving 84 studies. The flow of records through screening, exclusion and inclusion of studies is shown in **Figure 1**.

3.2 Included studies

Characteristics of the 84 included studies are summarized in **Table 1**. The studies yielded 211 diet data points and included 2353 volunteers, of which 65% were men (n=1538) and 34% were women (n=801). For two studies with a total of 14 subjects, the number of men and women was not specified. Forty-six studies were carried out in men only, three studies in women only, and 35 studies in men and women. The diets were fed for 13 to 91 days. Seventy-three studies used a crossover design and 11 studies a parallel design. Forty-seven studies were from the United States of America (USA); eight from the Netherlands; six from Canada; five from Denmark; three from the United Kingdom of Great Britain and Northern Ireland; two each from Israel, Germany, Malaysia, Norway or Spain; and one each from Finland, Italy, New Zealand, Austria and Sweden. Seventeen diets from six studies consisted of liquid formula diets. Seventy-three trials reported the mean age of their participants, which varied between 21 and 72 years (mean 38 years). For 66 studies, BMI values were reported and ranged from 20.0 to 28.6 kg/m^2 (mean 24.2 kg/m^2). For serum total cholesterol (63 studies), mean pre-study levels ranged from 3.7 to 6.7 mmol/L (mean 5.1 mmol/L); for LDL cholesterol (54 studies), from 2.3 to 4.8 mmol/L (mean 3.3 mmol/L); for HDL cholesterol (53 studies), from 0.9 to 1.8 mmol/L (mean 1.2 mmol/L); and for triglyceride (57 studies), from 0.7 to 2.2 mmol/L (mean 1.2 mmol/L).

3.3 Effects of interventions

3.3.1 Analysis of total SFA intake

3.3.1.1 Characteristics of included studies

The 74 trials used to examine the effects of reducing or increasing total SFA intake on serum lipids and lipoproteins yielded 177 total diet data points. The number of diet data points included in the calculations varied from 102 (41 studies) for ApoA-I to 177 (74 studies) for total cholesterol. Mean intake of total fat on these 177 diets was 34.0% of total energy intake (range 4.5–53.0%); of SFA, 9.8% of total energy intake (range 1.6–24.4%); of *cis*-MUFA, 13.6 % of total energy intake (range 1.6–39.8%); and of *cis*-PUFA, 8.4% of total energy intake (range 0.4–28.8%).

3.3.1.2 Effects of reducing SFA intake by replacing SFA with other nutrients

These effects were generated using SFA as the reference nutrient (model 1) as described in **Section 2.2.4**.

Replacement of SFA with cis-PUFA

Results from multiple regression analysis (weighted for N) are summarized in **Table 2** and demonstrate that for each 1% of dietary energy[1] as SFA replaced with an equivalent amount of *cis*–PUFA, there was a

[1] As a percentage of total energy intake

significant decrease[1] in total cholesterol of 0.064 mmol/L (95% CI: −0.070, −0.058), in LDL cholesterol of 0.055 mmol/L (95% CI: −0.061, −0.050), in HDL cholesterol of 0.005 mmol/L (95% CI: −0.006, −0.003), in triglyceride of 0.010 mmol/L (95% CI: −0.014, −0.007), in the total cholesterol to HDL cholesterol ratio of 0.034 (95% CI: −0.040, −0.028), in the LDL cholesterol to HDL cholesterol ratio of 0.034 (95% CI: −0.040, −0.029), in the triglyceride to HDL cholesterol ratio of 0.005 (95% CI: −0.009, −0.002; *P* = 0.004), in ApoA-I of 4.9 mg/dL (95% CI: −7.3, −2.5) and in ApoB of 10.2 mg/dL (95% CI: −12.4, −8.1).

Replacement of SFA with cis-MUFA

Results from multiple regression analysis (weighted for N) are summarized in **Table 2** and demonstrate that for each 1% of dietary energy as SFA replaced with an equivalent amount of *cis*-MUFA, there was a:

- significant decrease[1] in total cholesterol of 0.046 mmol/L (95% CI: −0.051, −0.040), in LDL cholesterol of 0.042 mmol/L (95% CI: −0.047, −0.037), in HDL cholesterol of 0.002 mmol/L (95% CI: −0.004, 0.000; *P* = 0.014), in triglyceride of 0.004 mmol/L (95% CI: −0.007, −0.001; *P* = 0.022), in the total cholesterol to HDL cholesterol ratio of 0.027 (95% CI: −0.033, −0.022), in the LDL cholesterol to HDL cholesterol ratio of 0.029 (95% CI: −0.034, −0.024) and in ApoB of 7.8 mg/dL (95% CI: −9.5, −6.0); and
- non-significant decrease in the triglyceride to HDL cholesterol ratio of 0.002 (95% CI: −0.005, 0.002; *P* = 0.342) and in ApoA-I of 1.8 mg/dL (95% CI: −3.7, 0.1; *P* = 0.064).

Replacement of SFA with carbohydrates

Results from multiple regression analysis (weighted for N) are summarized in **Table 2** and demonstrate that for each 1% of dietary energy as SFA replaced with an equivalent amount of carbohydrates, there was a:

- significant decrease[1] in total cholesterol of 0.041 mmol/L (95% CI: −0.047, −0.035), in LDL cholesterol of 0.033 mmol/L (95% CI: −0.039, −0.027), in HDL cholesterol of 0.010 mmol/L (95% CI: −0.012, −0.008), in the LDL cholesterol to HDL cholesterol ratio of 0.007 (95% CI: −0.013, −0.001; *P* = 0.017), in ApoA-I of 7.0 mg/dL (95% CI: −9.0, −5.1) and in ApoB of 3.6 mg/dL (95% CI: −5.4, −1.7 mg/dL);
- significant increase[1] in triglyceride of 0.011 mmol/L (95% CI: 0.007, 0.014) and the triglyceride to HDL cholesterol ratio of 0.014 (95% CI: 0.010, 0.018); and
- non-significant increase in the total cholesterol to HDL cholesterol ratio of 0.001 (95% CI: −0.006, 0.007; *P* = 0.842).

3.3.1.3 Effects of increasing SFA intake by replacing SFA with other nutrients

These effects were generated using *cis*-PUFA (model 2), *cis*-MUFA (model 3) or carbohydrates (model 4) as the reference nutrients as described in **Section 2.2.4**. (The full results for each analysis are provided in **Annexes 6–8**).

Replacement of cis-PUFA with SFA

Results from multiple regression analysis (weighted for N) are summarized in **Table 3** and demonstrate that for each 1% of dietary energy as *cis*-PUFA replaced with an equivalent amount of SFA, there was a significant increase[1] in total cholesterol of 0.066 mmol/L (95% CI: 0.060, 0.073), in LDL cholesterol of 0.058 mmol/L (95% CI: 0.052, 0.064), in HDL cholesterol of 0.005 mmol/L (95% CI: 0.004, 0.007), in triglyceride of 0.010 mmol/L (95% CI: 0.006, 0.014), in the total cholesterol to HDL cholesterol ratio of 0.034 (95% CI: 0.027, 0.041), in the LDL cholesterol to HDL cholesterol ratio of 0.035 (95% CI: 0.028, 0.041), in the triglyceride to HDL cholesterol ratio of 0.004 (95% CI: 0.001, 0.008; *P* = 0.026), in ApoA-I of 6.3 mg/dL (95% CI: 3.9, 8.7) and in ApoB of 10.3 mg/dL (95% CI: 7.7, 12.8).

Replacement of cis-MUFA with SFA

Results from multiple regression analysis (weighted for N) are summarised in **Table 3** and demonstrate that for each 1% of dietary energy as *cis*-MUFA replaced with an equivalent amount of SFA, there was a:

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[1] *P* < 0.001 unless otherwise noted

- significant increase[1] in total cholesterol of 0.049 mmol/L (95% CI: 0.043, 0.055), in LDL cholesterol of 0.045 mmol/L (95% CI: 0.039, 0.051), in HDL cholesterol of 0.003 mmol/L (95% CI: 0.001, 0.004), in triglyceride of 0.004 mmol/L (95% CI: 0.000, 0.007; P = 0.041), in the total cholesterol to HDL cholesterol ratio of 0.028 (95% CI: 0.021, 0.034), in the LDL cholesterol to HDL cholesterol ratio of 0.030 (95% CI: 0.024, 0.036), in ApoA-I of 2.7 mg/dL (95% CI: 0.7, 4.8) and in ApoB of 8.1 mg/dL (95% CI: 6.1, 10.1); and
- non-significant increase in the triglyceride to HDL cholesterol ratio of 0.001 (95% CI: −0.003, 0.004; P = 0.680).

Replacement of carbohydrates with SFA

Results from multiple regression analysis (weighted for N) are summarized in **Table 3** and demonstrate that for each 1% of dietary energy as carbohydrates replaced with an equivalent amount of SFA, there was a:

- significant increase[1] in total cholesterol of 0.045 mmol/L (95% CI: 0.038, 0.051), in LDL cholesterol of 0.036 mmol/L (95% CI: 0.030, 0.043), in HDL cholesterol of 0.011 mmol/L (95% CI: 0.010, 0.013), in the LDL cholesterol to HDL cholesterol ratio of 0.007 (95% CI: 0.001, 0.014; *P* = 0.033), in ApoA-I of 8.4 mg/dL (95% CI: 6.4, 10.5) and in ApoB of 3.7 mg/dL (95% CI: 1.7, 5.8);
- significant decrease[1] in triglyceride of 0.012 mmol/L (95% CI: −0.015, −0.008) and in the triglyceride to HDL cholesterol ratio of 0.016 (95% CI: −0.020, −0.012); and
- non-significant decrease in the total cholesterol to HDL cholesterol ratio of 0.002 (95% CI: −0.009, 0.005; *P* = 0.553).

3.3.1.4 SFA intake at less than 10% of total energy intake

The population nutrient intake goal for SFA recommended by the joint WHO/FAO expert consultation *(11)* is less than 10% of total energy intake. One of the PICO questions which guided this systematic review was, therefore, designed to look at the effects of SFA consumption above and below 10% of total energy intake. Effects of reducing or increasing SFA intake on serum lipids and lipoproteins were observed across a wide range of SFA intakes, from 1.6 to 24.4% of total energy intake. Of the 177 data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake and 65 included intakes of less than 8%. As noted in **Section 2.2.4**, analysis of the residuals of the regression line indicates that the relationship between a reduction or increase in SFA intake and effect on serum lipids and lipoproteins is linear with a consistent effect on serum lipids and lipoproteins across the entire range of SFA intakes. The results of the regression analysis therefore suggest reducing SFA intake to less than 10% of total energy intake may have additional benefit in terms of improving the overall serum lipoprotein profile when replacing SFA with *cis*-PUFA, *cis*-MUFA – and to a lesser extent carbohydrates – relative to higher intakes. Similarly, the results suggest a negative effect on the overall serum lipoprotein profile when increasing SFA intake from a starting point of less than 10% of total energy intake.

3.3.2 Subgroup and sensitivity analyses for total SFA

Results for subgroup and sensitivity analyses conducted with carbohydrates as the reference nutrient are described below. Results of subgroup and sensitivity analyses with other nutrients serving as the reference nutrient also did not show any significant differences between subgroups or when specified studies were removed for sensitivity analysis.

Subgroup analysis by type of carbohydrate was also planned. However, the number of studies reporting dietary data in sufficient detail to be able to determine with certainty the types of carbohydrates included in the study diets was limited, and therefore subgroup analysis could not be performed.

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[1] *P* < 0.001 unless otherwise noted

3.3.2.1 Baseline levels

As described in **Section 2.2.4**, the estimate for the dummy variable in the regression model can be envisaged as the mean estimated serum lipid level when the participants from that study consumed a standardized fat-free diet. This estimate is a constant within studies, but differs between studies; that is, it can be considered a proxy for baseline lipid concentrations.

To examine whether baseline levels were related to responses, subgroup analyses were performed, in which the studies were split into low and high baseline groups based on the median level as estimated for each parameter based on model 4 in **Section 2.2.4**. The median levels when subjects consumed a standardized fat-free diet were as follows: total cholesterol 4.45 mmol/L, LDL cholesterol 2.89 mmol/L, HDL cholesterol 0.97 mmol/L, triglyceride 1.48 mmol/L, the total cholesterol to HDL cholesterol ratio 4.36, the LDL cholesterol to HDL cholesterol ratio 2.76 and the triglyceride to HDL cholesterol ratio 1.36. These analyses were not performed for ApoB and ApoA-I, because the number of studies in each subgroup was too small to provide reliable estimates for the regression coefficients.

Effect estimates

Effect estimates are presented in **Table 4**. The direction and statistical significance of the estimates did not depend on baseline levels. Effects, however, were in general more pronounced at higher baseline levels.

3.3.2.2 Gender

Thirty-eight studies were carried out in men only, 34 studies in men and women, and two studies in women only. These analyses were not performed for ApoB and ApoA-I, because the number of studies in each subgroup was too small to provide reliable estimates for the regression coefficients.

Effect estimates

Effect estimates are presented in **Table 5**. The direction and statistical significance of the estimates did not depend on gender. For total cholesterol, LDL cholesterol and HDL cholesterol, effects of a mixture of SFA in particular were less pronounced in studies that included men only.

3.3.2.3 Year of publication

In 1990, the detrimental effects of TFA on the serum lipoprotein profile were published for the first time. This may have resulted in an increasing awareness of the need to better analyse and report the intake of TFA of the study diets. Thirty-four studies were published before 1993 and 40 studies in 1993 or later. These analyses were not performed for ApoB and ApoA-I, because the number of studies in each subgroup was too small to provide reliable estimates for the regression coefficients.

Effect estimates

Effect estimates are presented in **Table 6**. The direction and statistical significance of the estimates did not depend on the year of publication. Also, the magnitude of the estimates was in good agreement, although effects of *cis*-PUFA on total cholesterol, LDL cholesterol and the LDL cholesterol to HDL cholesterol ratio were higher for studies published in 1993 or later.

3.3.2.4 Liquid formula diets

Eleven diets from five studies consisted of liquid formula diets. To examine the impact of these diets on the outcomes, analyses were repeated by excluding these studies.

Effect estimates

Effect estimates are presented in **Table 7** and do not suggest that removing studies that employed liquid formula diets substantially changed the results.

3.3.3 Analysis of individual SFA

These effects were generated using carbohydrates as the reference nutrient (model 5) as described in **Section 2.2.4**.

3.3.3.1 Characteristics of included studies

The 52 trials used to examine the effects of the individual SFA on serum lipids and lipoproteins yielded 134 diet data points. The number of diet data points included in the calculations varied from 88 for ApoA-I (34 studies) to 134 (51 studies) for total cholesterol. Mean intake of fat on these 134 diets was 35.6% of total energy intake (range 19.7–53.0%); of SFA, 12.0% of total energy intake (range 1.6–28.9%); of lauric acid (C12:0), 1.2% of total energy intake (range 0.0–16.9%); of myristic acid (C14:0), 1.2% of total energy intake (range 0.0–14.3%); of palmitic acid (C16:0), 5.9% of total energy intake (range 1.0–20.8%); and of stearic acid (C18:0), 2.8% of total energy intake (range 0.3–16.5%).

3.3.3.2 Effect estimates

Results from multiple regression analysis are summarized in **Table 8**. They demonstrate that for each 1% of dietary energy as carbohydrates replaced, there was a:

- significant increase[1] in:
  - total cholesterol when carbohydrates were replaced with lauric acid (0.029 mmol/L; 95% CI: 0.014, 0.045), myristic acid (0.060 mmol/L; 95% CI: 0.042, 0.077) or palmitic acid (0.041 mmol/L; 95% CI: 0.030);
  - LDL cholesterol when carbohydrates were replaced with lauric acid (0.017 mmol/L; 95% CI: 0.003, 0.031; *P* = 0.019), myristic acid (0.044 mmol/L; 95% CI: 0.028, 0.060) or palmitic acid (0.036 mmol/L; 95% CI: 0.026, 0.046);
  - HDL cholesterol when carbohydrates were replaced with lauric acid (0.019 mmol/L; 95% CI: 0.016, 0.023), myristic acid (0.021 mmol/L; 95% CI: 0.017, 0.025) or palmitic acid (0.010 mmol/L; 95% CI: 0.007, 0.013);
  - the LDL cholesterol to HDL cholesterol ratio when carbohydrates were replaced with palmitic acid (0.013; 95% CI: 0.005, 0.021; P = 0.002); and
- significant decrease[1] in:
  - triglyceride when carbohydrates were replaced with lauric acid (–0.015 mmol/L; 95% CI: –0.023, –0.007), myristic acid (–0.011 mmol/L; 95% CI: –0.020, –0.002; *P* = 0.018) or palmitic acid (–0.011 mmol/L; 95% CI: –0.017,–0.006);
  - the total cholesterol to HDL cholesterol ratio (–0.035; 95% CI: –0.048, –0.022) and the LDL cholesterol to HDL cholesterol ratio (–0.024; 95% CI: –0.036, –0.013) when carbohydrates were replaced with lauric acid; and
  - the triglyceride to HDL cholesterol ratio when carbohydrates were replaced with lauric acid (–0.024; 95% CI: –0.032, –0.017), myristic acid (–0.018; 95% CI: –0.027, –0.010) or palmitic acid (–0.015; 95% CI: –0.020,–0.009).

No significant associations were observed in:

- the total cholesterol to HDL cholesterol ratio when carbohydrates were replaced with myristic or palmitic acid;
- the LDL cholesterol to HDL cholesterol ratio when carbohydrates were replaced with myristic acid; or
- any serum lipid or ratio when carbohydrates were replaced with stearic acid.

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[1] *P* < 0.001 unless otherwise noted

3.3.4 Subgroup and sensitivity analyses for individual SFA

3.3.4.1 Baseline levels

These analyses were not performed for individual SFA, because the number of studies in each subgroup was too small to provide reliable estimates for the regression coefficients.

3.3.4.2 Liquid formula diets

Twelve diets from four studies consisted of liquid formula diets. To examine the impact of these diets on the outcomes, analyses were repeated by excluding these studies. None of the diets that used liquid formula diets reported ApoB and ApoA-I concentrations; thus these analyses were not performed.

Effect estimates

Effect estimates are presented in **Table 9** and do not suggest that removing studies that employed liquid formula diets substantially changed the results.

3.3.4.3 Gender

These analyses were not performed for individual SFA, because the number of studies in each subgroup was too small to provide reliable estimates for the regression coefficients.

3.3.4.4 Year of publication

These analyses were not performed for individual SFA, because the number of studies in each subgroup was too small to provide reliable estimates for the regression coefficients.

3.4 Quality of the evidence

Some of the trials with parallel design were assessed as having unclear risk of bias in terms of randomization because the randomization procedure was not described adequately. Trials with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have a significant, systematic effect on study results. Blinding was also not deemed to be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some trials may have been able to distinguish between intervention and control diets, this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias. Bias assessments for each study can be found in **Annex 9**.

The assessment of the quality of evidence for priority outcomes is found in the GRADE evidence profiles (**Annex 10**). The quality of evidence for an effect of replacing SFA with *cis*-PUFA, *cis*-MUFA, or carbohydrates on all outcomes was judged to be high, except for ApoA-I and the triglyceride to HDL cholesterol ratio when replacing SFA with *cis*-MUFA and the total cholesterol to HDL cholesterol ratio when replacing SFA with carbohydrates, which were both judged as moderate due to serious imprecision. The quality of evidence for an effect of replacing *cis*-PUFA, *cis*-MUFA or carbohydrates with SFA on all outcomes was judged to be high, except for the triglyceride to HDL cholesterol ratio when replacing *cis*-MUFA with SFA, and the total cholesterol to HDL cholesterol ratio when replacing carbohydrates with SFA, which was judged as moderate due to serious imprecision. The quality of evidence was not assessed for outcomes in the analyses of individual SFA.

4. Strengths and limitations of review

4.1 Strengths

A strength of this study was that a large number of strictly-controlled dietary trials were identified and included in the regression analysis. Most of these studies were of relatively short duration (3–5 weeks), although long enough for serum lipid and lipoproteins concentrations to reach a new steady state. Tight control of dietary intake during the relatively short study period minimized non-compliance and other issues that often affect longer-term behaviour-change studies, increasing confidence in the results of the regression analysis.

Another strength is that the included studies cover a wide range of SFA intakes, from 1.6–24.4% of total energy intake, which increased the likelihood of detecting robust effects. Results are consistent across the entire range of intakes, suggesting that they could apply to a variety of populations with different SFA intakes.

The use of multiple regression allowed for assessment of the differential effects of replacing SFA with various nutrients, rather than simply estimating the effects of reducing or increasing SFA intake without regard to the nature of replacement. This is important, as a number of studies, including the original analysis on which this one is based, have shown that the effect of SFA reduction on serum lipids and lipoproteins is highly dependent on the nature of replacement.

4.2 Limitations

Inclusion of only those studies with strictly controlled diets greatly reduced the chance that dietary factors other than those being studied contributed to the changes observed in serum lipids and lipoproteins. This approach, while valuable in assessing specific effects of modifying SFA intake through exchange of specific nutrients, does not provide a clear picture of what might happen in real world settings in which modification of SFA intake might be accompanied by other changes in diet.

As indicated in **Section 4.1**, and described in the results (**Section 3**), different replacement scenarios have different effects on serum lipids and lipoproteins. Carbohydrate replacements as assessed in this analysis, included a mixture of monosaccharides, disaccharides and polysaccharides. Subgroup analysis by type of carbohydrate could not be performed because of the limited number of number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrates in the diets. Assessment of the effects on the serum lipoprotein profile of replacing SFA with different types of carbohydrates would have been informative, given that a previous meta-analysis has suggested that diets with a low glycaemic index reduced total cholesterol and LDL cholesterol as compared with diets with a high glycaemic index *(12)*. Furthermore, in an analysis of two large cohort studies, isocaloric replacement of SFA by carbohydrates from added sugars or refined carbohydrates was not associated with a change in risk of coronary heart disease, whereas replacement with carbohydrates from whole grains was related to a lower risk *(13)*.

Lastly, although the analysis of individual SFA provided results for four common SFA in the diet, the intakes of lauric and myristic acid in included studies was generally quite low (i.e. mean of 1.2% of total energy intake). Thus, to obtain more insight into the effects of these two SFA on the serum lipoprotein profile at higher intakes, more well-controlled intervention studies at higher intakes are needed. Also, effects of SFA with less than 12 carbon atoms or more than 18 carbon atoms could not be estimated due to lack of information.

5. Conclusion

Results of the multiple regression analysis indicated that effects on the serum lipoprotein profile of reducing SFA intake by replacing a mixture of SFA with *cis*-PUFA (predominantly linoleic acid and α-linolenic acid) or *cis*-MUFA (predominantly oleic acid) were more favourable than replacing SFA with a mixture of carbohydrates. For total and LDL cholesterol and triglycerides in particular, the most favourable effects were observed for *cis*-PUFA. These results are consistent across a wide range of SFA intakes including intakes of less than 10% of total energy intake.

Differences in effects of the individual SFA on the serum lipoprotein profile were observed. Compared with a mixture of carbohydrates, an increased intake of lauric, myristic or palmitic acid raised serum total, LDL and HDL cholesterol levels, and lowered triglyceride levels, while increased intake of stearic acid did not appear to have a significant effect on these or other serum lipid values. Lauric acid alone reduced the total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol ratios as compared with a mixture of carbohydrates.

No significant gender-specific differences were observed regarding SFA intake and effects on serum lipids and lipoproteins, nor were the observed results systematically affected by dates of study publication, or inclusion of liquid diets in studies. In addition, conclusions did not change if subjects were stratified for baseline levels at the start of the study. It was not possible to perform subgroup analysis by type of carbohydrate.

6. Tables

Table 1. Characteristics of included studies

Reference and country	Study design	Composition[1]					Participants		Funding
		Diet	S	M	P	T			
Mensink 1987 *(14)*[2] Mensink 1989 *(15)* The Netherlands	Randomized parallel design with two interventions Experimental period: 35 days	1. 2.	6.7 9.8	9.3 24.0	5.2 5.1		• Initial: 57, final: 48 • Reason for loss: • influenza (n=3), change in smoking habits (n=2), weight loss (n=4)	• Diet 1: 12 men, 12 women • Diet 2: 12 men, 12 women • Mean age: 27 years	• The Commission of the European Communities
Mattson 1985 *(16)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.	19.1 3.3 4.3	15.4 28.2 5.6	3.9 6.9 28.1		• Initial: 12, final: 12 • No dropouts reported	• 12 men • Mean age: 59 years	• Veterans Administration • National Institutes of Health • Moss Heart Foundation
Grundy 1986 A *(17)* USA	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	3.8 6.4	26.9 6.4	7.7 6.4		• Initial: 7, final: 7 • No dropouts reported	• Sex not reported • Mean age: 58 years	• Veterans Administration • National Institutes of Health • Southwestern Medical Foundation • Mead Johnson and Company • Moss Heart Foundation
Brussaard 1980 *(18)* The Netherlands	Randomized parallel design with four interventions Experimental period: 35 days	1. 2. 3. 4.	8.0 10.0 11.0 18.0	10.0 8.0 8.0 16.0	3.0 11.0 19.0 3.0		• Initial: 60, final: 60 • No dropouts reported	• 37 men and 23 women • Diet 1: 16 subjects • Diet 2: 15 subjects • Diet 3: 15 subjects • Diet 4: 14 subjects • Sex distribution not reported. • Age: 18-28 years	• The Netherlands Heart Foundation
Brussaard 1982 *(19)* The Netherlands	Randomized parallel design with two interventions Experimental period: 91 days	1. 2.	9.0 7.0	10.0 8.0	11.0 4.0		• Initial: 35, final: 35 • No dropouts reported	• Diet 1: 11 men and 6 women • Diet 2: 12 men and 6 women • Age: 19-30 years	• The Netherlands Heart Foundation
Mensink 1989 *(20)* The Netherlands	Randomized parallel design with two interventions Experimental period: 35 days	1. 2.	12.9 12.6	15.1 10.8	7.9 12.7		• Initial: 60, final: 58 • No reason for loss reported	• Diet 1: 14 men and 15 women • Diet 2: 13 men and 16 women • Mean age: 25 years	• Netherlands Nutrition Foundation • The Netherlands Heart Foundation • The Netherlands Ministry of Health
Harris 1983 *(21)* USA	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	14.4 6.4	16.4 10.8	7.2 21.6		• Initial: 7, final: 7 • No dropouts reported	• Sex not reported • Mean age: 40 years	• National Heart, Lung, and Blood Institute • Clinical Research Center Grant
Becker 1983 *(22)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.	2.7 4.0 20.3	29.2 15.1 13.7	6.5 17.5 4.1		• Initial: 12, final: 12 • No dropouts reported	• 12 men • Mean age: 32 years	• Clinical Research Center Program • National Institutes of Health • Corn Products

Reference and country	Study design	Composition[1]					Participants		Funding
		Diet	S	M	P	T			
Bonanome 1988 *(23)* USA	Randomized crossover design with three interventions Experimental period: 21 days	1. 2. 3.	19.6 19.9 3.1	14.9 15.2 30.6	3.7 3.2 4.7		• Initial: 11, final: 11 • No dropouts reported	• 11 men • Mean age: 72 years	• Not reported
Grundy 1986 B *(24)* USA	Randomized crossover design with two interventions Experimental period: 60 days	1. 2.	9.6 9.6	12.5 9.6	16.3 9.6		• Initial: 9, final: 9 • No dropouts reported	• 9 men • Mean age: 63 years	• Veterans Administration / National Institutes of Health • Southwestern Medical Foundation • Moss Heart Foundation
Katan 1988 *(25)* The Netherlands	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	23.4 11.6	14.1 11.7	5.2 20.9	1.9 0.5	• Initial: 54, final: 47 • Reason for loss: • illness, weight loss , poor compliance	• 24 men and 23 women • Mean age: 44 years	• The Netherlands Heart Foundation
Grande 1972 *(26)* USA	Randomized crossover design with four interventions Experimental period: 28 days	1. 2. 3. 4.	2.3 3.3 5.2 8.7	1.6 6.5 16.9 7.1	0.6 2.7 6.7 13.3		• Initial: 48, final: 38 • Reason for loss: transport to another institution, illness, poor eating habits	• 38 men • Mean age: 56 years	• Public Health Service Research Grants
Anderson 1976 A *(27)*[3] USA	Randomized crossover design with two interventions Experimental period: 14 days	1. 2.	19.6 4.8	8.4 5.1	5.2 22.7		• Initial: 12, final: 12 • No dropouts reported	• 12 men • Mean age: 21 years	• Public Health Service Research Grants
Anderson 1976 B *(27)*[3] USA	Randomized crossover design with two interventions Experimental period: 14 days	1. 2.	19.4 4.8	8.4 5.1	5.1 22.9		• Initial: 12, final: 12 • No dropouts reported	• 12 men • Mean age: 21 years	• Public Health Service Research Grants
Wolf 1983 *(28)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.	19.2 9.7 14.4	9.5 9.6 7.2	9.7 9.5 7.2		• Initial: 6, final: 6 • No dropouts reported	• 6 men • Mean age: 54 years	• Not reported
Grundy 1988 *(29)* USA	Randomized crossover design with two interventions Experimental period: 42 days	1. 2.	6.7 6.7	25.9 6.7	5.8 5.8		• Initial: 10, final: 10 • No dropouts reported	• 10 men • Mean age: 64 years	• Veterans Administration • National Institutes of Health • Moss Heart Foundation
Reiser 1985 *(30)* USA	Randomized crossover design with three interventions Experimental period: 35 days	1. 2. 3.	9.4 18.8 1.6	10.4 1.1 2.2	0.4 0.3 16.2		• Initial: 19, final: 19 • No dropouts reported	• 19 men • Mean age: 26 years	• National Heart and Blood Vessel Research • National Heart, Lung, and Blood Institute • National Institutes of Health • Clinical Research USDHS Grant • Lipid Research Clinics • National Live Stock and Meat Board • The Texas Cattle Feeders Association • The Standard Meat Co of Fort Worth
Laine 1982 *(31)* USA	Randomized crossover design with four interventions Experimental period: 20 days	1. 2. 3. 4.[4]	8.6 2.6 3.0 2.4	7.7 4.6 4.2 6.1	1.8 11.1 11.1 7.3	2.8	• Initial: 24, final: 24 • No dropouts reported	• 13 men and 11 women • Mean age: 25 years	• American Soy Bean Association • General Clinical Research Centers Program • National Institutes of Health

Lewis 1981 *(32)*[5] Kay 1985 *(33)* United Kingdom	Randomized crossover design with three interventions Experimental period: 35 days	1. 2. 3.	9.6 9.4 13.4	9.2 9.2 13.2	7.2 7.3 11.7		• Initial: 12, final: 12 • No dropouts reported	• 12 men • Mean age: 45 years	• Not reported
McDonald 1989 *(34)* Canada	Randomized crossover design with two interventions Experimental period: 18 days	1. 2.	5.1 6.8	20.2 7.4	10.3 21.6		• Initial: 8, final: 8 • No dropouts reported	• 8 men • Age: 19–32 years	• Canola Council of Canada
Mensink 1990 *(35)* The Netherlands	Randomized crossover design with three interventions Experimental period: 21 days	1. 2.[4] 3.	9.3 9.3 19.4	23.7 13.0 13.6	4.4 4.5 3.0	0.0 10.9 0.7	• Initial: 59, final: 59 • No dropouts reported	• 25 men and 34 women • Mean age: 26 years	• The Netherlands Nutrition Foundation • The Netherlands Ministry of Welfare, Public Health, and Cultural Affairs • The Commission of the European Communities
Valsta 1992 *(36)* Finland	Randomized crossover design with two interventions Experimental period: 25 days	1. 2.	12.4 12.7	16.2 10.2	7.6 13.3		• Initial: 59, final: 59 • No dropouts reported	• 29 men and 30 women • Mean age: 30 years	• Food Research Foundation • The Ministry of Agriculture and Forestry • The Yrjö Jahnsson Foundation • The Academy of Finland • The Finnish Cultural Foundation
Wahrburg 1992 *(37)* Germany	Randomized crossover design with two interventions Experimental period: 23 days	1. 2.	10.2 10.1	16.0 9.9	4.1 10.3		• Initial: 40, final: 38 • Reason for loss: • illness (n=1), genetic anomaly of lipid metabolism (n=1)	• 21 men and 17 women • Mean age: 24 years	• The Commission of the European Communities
Zock 1992 *(38)* The Netherlands	Randomized crossover design with three interventions Experimental period: 21 days	1. 2. 3.[4]	11.0 20.1 10.3	15.7 16.3 15.6	12.5 4.3 4.2	0.1 0.3 7.7	• Initial: 59, final: 56 • Reason for loss: personal (n=1), illness (n=1), pregnancy (n=1)	• 26 men and 30 women • Mean age: 24 years	• Not reported
Wardlaw 1990 *(39)*[6] Kwon 1991 *(40)* USA	Randomized crossover design with two interventions Experimental period: 35 days	1. 2.	6.7 7.7	26.9 13.4	5.8 18.2		• Initial: 22, final: 20 • Reason for loss: not reported	• 20 men • Mean age: 35 years	• SVO Enterprises
Ginsberg 1990 *(41)* USA	Randomized parallel design with two interventions Experimental period: 70 days	1. 2.	9.0 8.8	10.6 17.2	10.0 10.1		• Initial: 39, final: 36 • Reason for loss: allergy (n=1), poor compliance (n=2)	• Diet 1: 12 men • Diet 2: 12 men • Diet 3: 12 men • Mean age: 23 years	• The National Institutes of Heath • Best Foods • Kraft Inc. • Bertolli
Chan 1991 *(42)* Canada	Randomized crossover design with four interventions Experimental period: 18 days	1. 2. 3. 4.	6.5 5.3 7.1 6.4	18.7 18.3 8.4 9.9	7.4 8.5 16.8 16.1		• Initial: 8, final: 8 • One subject dropped out and was replaced	• 8 men • Age: 20-34 years	• Canola Council of Canada • Flax Council of Canada
Wardlaw 1991 *(43)* USA	Randomized parallel design with two interventions Experimental period: 56 days	1. 2.	6.7 6.7	21.1 8.6	10.6 21.1		• Initial: 34, final: 32 • Reason for loss: medication (n=1), unusual lipid values (n=1)	• Diet 1: 16 men • Diet 2: 16 men • Mean age: 33 years	• The Procter & Gamble Company
Berry 1991 *(44)* Israel	Randomized crossover design with two interventions Experimental period: 84 days	1. 2.	8.0 7.1	15.9 6.2	7.5 16.0		• Initial: 26, final: 18 • Reason for loss: drop out (n=4), incomplete blood sampling (n=4)	• 18 men • Mean age: not reported	• The National Institutes of Health

Reference and country	Study design	Composition[1]					Participants		Funding
		Diet	S	M	P	T			
Berry 1992 *(45)* Israel	Randomized crossover design with two interventions Experimental period: 84 days	1. 2.	6.6 4.7	16.6 6.8	7.5 5.7		• Initial: 26, final: 17 • Reason for loss: not reported	• 17 men • Age: 18–24 years	• The National Institutes of Health, Public Health Service
Kris-Etherton 1993 A *(46)*[7] USA	Randomized crossover design with four interventions Experimental period: 26 days	1. 2. 3. 4.	6.0 20.9 6.3 21.0	27.2 13.2 10.1 10.1	2.3 2.1 17.8 1.7		• Initial: 19, final: 18 • Reason for loss: not reported	• 18 men • Mean age: 26 years	• The American Cocoa Research Institute • The Pennsylvania Agricultural Experimental Station
Kris-Etherton 1993 B *(46)*[7] USA	Randomized crossover design with four interventions Experimental period: 26 days	1. 2. 3. 4.	20.7 21.0 20.5 20.0	12.1 13.3 12.3 10.4	1.8 2.1 1.7 1.6		• Initial: 18, final: 15 • Reason for loss: not reported	• 15 men • Mean age: 27 years	• The American Cocoa Research Institute • The Pennsylvania Agricultural Experimental Station
Tholstrup 1994 *(47)* Denmark	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	16.8 17.5	14.1 14.6	3.6 3.8		• Initial: 59, final: 59 • No dropouts reported	• 12 men • Mean age: 24 years	• Danish Agricultural Ministry • Danish Agricultural and Veterinary Research Council • Danish Technical Research Council
Denke 1992 *(48)* USA	Randomized crossover design with three interventions Experimental period: 21 days	1. 2. 3.	2.6 18.7 18.9	29.1 17.0 15.4	6.0 2.4 3.8		• Initial: 14, final: 14 • No dropouts reported	• 14 men • Mean age: 63 years	• Southwestern Medical Foundation • Moss heart Foundation • Veterans' Affairs • National Heart, Lung, and Blood Institute
Bonanome 1992 *(49)* Italy	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	9.6 9.6	28.8 4.8	4.8 28.8		• Initial: 11, final: 11 • No dropouts reported	• 11 men • Mean age: 22 years	• The European Economic Community
Judd 1994 *(50)* USA	Randomized crossover design with four interventions Experimental period: 42 days	1. 2.[4] 3.[4] 4.	14.0 13.6 13.1 20.1	16.4 14.6 13.5 10.9	5.9 5.7 6.4 5.8	0.7 3.7 6.4 0.7	• Initial: 64, final: 58 • Reason for loss: illness (n=1), no reason reported (n=1), other commitments (n=3), non-compliance (n-1)	• 29 men, 29 women • Mean age: 43 years	• Institute of Shortening and Edible Oils and its member companies
Sundram 1994 *(51)* Malaysia	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	15.0 14.1	11.0 11.6	3.2 3.5		• Initial: 18, final: 17 • Reason for loss: illness of family member (n=1)	• 17 men • Mean age: 21 years	• Not reported
Tholstrup 1994 *(52)* Denmark	Randomized crossover design with three interventions Experimental period: 21 days	1. 2. 3.	15.7 18.1 20.2	15.7 14.3 14.4	2.7 4.3 2.3		• Initial: 15, final: 15 • No dropouts reported	• 15 men • Mean age: 25 years	• Danish Agricultural and Veterinary Research Council • Danish Technical Research Council
Zock 1994 *(53)* The Netherlands	Randomized crossover design with three interventions Experimental period: 21 days	1. 2. 3.	21.3 21.0 10.8	11.2 11.9 21.3	4.1 4.7 4.4	0.8 0.2 0.3	• Initial: 59, final: 59 • No dropouts reported	• 23 men and 36 women • Mean age: 29 years	• Foundation for Nutrition and Health Sciences
Barr 1992 *(54)* USA	Randomized parallel design with two interventions Experimental period: 49 days	1. 2.	9.0 12.2	13.2 10.8	7.8 6.5		• Initial: 51, final: 48 • Reason for loss: illness (n=1), poor compliance (n=2) • 17 men received a diet that was not included in the meta-analysis	• Diet 1: 15 men • Diet 2: 16 men • Mean age: 25 years	• National Institutes of Health • Best Foods, Kraft Inc. • Bertolli

Ginsberg 1994 *(55)* USA	Randomized parallel design with two interventions Experimental period: 42 days	1. 2.	8.9 9.1	8.4 13.2	11.4 6.4		• Initial: 30, final: 30 • No dropouts reported • 12 men received a diet that was not included in the meta-analysis	• Diet 1: 9 men • Diet 2: 9 men • Mean age: 25 years	• National Institutes of Health • Best Foods, Kraft Inc. • Bertolli
Judd 1988 *(56)*8 Marshall 1986 *(57)* USA	Randomized crossover design with two interventions Experimental period: 42 days	1. 2.	6.7 10.6	11.4 10.4	6.5 3.3		• Initial: 24, final: 23 • Reason for loss: personal	• 23 men • Age: 35–60 years	• Not reported
Sundram 1995 *(58)* Malaysia	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	6.0 13.0	17.5 14.3	7.7 4.1		• Initial: 24, final: 23 • Reason for loss: not reported	• 23 men • Mean age: 22 years	• Not reported
Iacono 1991 *(59)* USA	Randomized crossover design with two interventions Experimental period: 40 days	1. 2.	9.5 8.6	9.4 8.7	3.8 10.8		• Initial: 11, final: 11 • No dropouts reported	• 11 men • Mean age: 54 years	• Not reported
Lichtenstein 1993 *(60)*[9] Lichtenstein 1994 *(61)* Lichtenstein 1994 *(62)* USA	Randomized crossover design with five interventions Experimental period: 32 days	1. 2. 3. 4. 5.	5.4 6.9 6.9 12.1 7.4	14.5 9.0 17.0 11.3 10.8	6.7 11.2 3.9 3.4 8.8		• Initial: 15, final: 14 • Reason for loss: scheduling problems (n=1)	• 6 men and 8 women • Mean age: 63 years	• US Department of Agriculture • National Institutes of Health • Uncle Bens, Inc
Dougherty 1995 *(63)* USA	Randomized crossover design with two interventions Experimental period: 40 days	1. 2.	10.8 9.1	9.5 9.5	7.9 7.0	0.6 1.0	• Initial: 10, final: 10 • No dropouts reported	• 10 men • Mean age: 37 years	• Not reported
Marckmann 1992 *(64)* Denmark	Randomized crossover design with two interventions Experimental period: 14 days	1. 2.	15.4 13.5	11.8 8.2	6.0 4.7		• Initial: 13, final: 13 • No dropouts reported	• 6 men and 17 women • Mean age: 26 years	• The Danish Heart Foundation • The Danish Health Insurance Foundation • The Danish Agricultural and Veterinary Research Council
Howard 1995 *(65)* USA	Randomized crossover design with four interventions Experimental period: 42 days	1. 2. 3. 4.	8.2 8.0 9.4 9.5	14.2 12.1 8.5 5.7	3.1 4.8 7.2 12.5		• Initial: 77, final: 63 • Reason for loss: employment obligations (n=4), poor compliance (n=9), loss of blood samples (n=1)	• 30 men and 33 women • Mean age: 46 years	• National Heart, Lung, and Blood Institute • Best Foods
Fielding 1995 A *(66)*[10] USA	Randomized parallel design with two interventions Experimental period: 28 days	1. 2.	10.3 15.3	16.5 15.4	8.5 5.8		• Initial: 48, final: 42 • Reason for loss: not reported (n=5), incomplete data (n=1)	• 42 men • Diet 1: 21 men • Diet 2: 21 men • Mean age: 29 years	• National Institutes of Health • Arteriosclerosis SCOR • National Dairy Promotion and Research Board
Fielding 1995 B *(66)*[10] USA	Randomized parallel design with two interventions Experimental period: 28 days	1. 2.	10.0 16.7	14.9 12.7	9.9 4.7		• Initial: 48, final: 42 • Reason for loss: not reported (n=5), incomplete data (n=1)	• 42 men • Diet 1: 20 men • Diet 2: 22 men • Mean age: 29 years	• National Institutes of Health • Arteriosclerosis SCOR • National Dairy Promotion and Research Board
Park 1996 *(67)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1.[4] 2.[4] 3.[4]	15.2 13.7 13.5	17.0 18.1 16.8	6.9 6.6 8.2		• Initial: 18, final: 17 • Reason for loss: not reported	• 17 men • Mean age: 26 years	• The National Live Stock and Meat Board • The Ohio Agricultural Experimental Station
Cater 1997 *(68)* USA	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	23.3 5.7	18.4 39.8	6.0 4.9		• Initial: 9, final: 9 • No dropouts reported	• 9 men • Mean age: 66 years	• NIH Endocrinology and Metabolism Training Grant • NIH-NHLBI Clinical Investigator Award • National Institutes of Health

Reference and country	Study design	Composition[1]					Participants		Funding
		Diet	S	M	P	T			
Tholstrup 1998 *(69)* Denmark	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	19.1 24.4	11.6 7.7	4.5 5.2	1.6 0.1	• Initial: 18, final: 18 • No dropouts reported	• 18 men • Mean age: 25 years	• The Danish Dairy Research Foundation • The Danish Research Development Program for Food Technology
Mazier 1997 *(70)* Canada	Randomized crossover design with two interventions Experimental period: 13 days	1. 2.	11.0 10.9	24.0 9.2	4.1 17.9		• Initial: 9, final: 9 • No dropouts reported	• 9 men • Mean age: 26 years	• The Heart and Stroke Foundation of British Columbia and Yukon
Ginsberg 1998 *(71)* USA	Randomized crossover design with three interventions Experimental period: 56 days	1. 2. 3.	14.4 8.6 5.8	12.5 12.5 12.5	5.8 5.8 5.8		• Initial: 118, final: 103 • Reason for loss: not reported	• 46 men and 57 women • Mean age: 38 years	• National Heart, Lung, and Blood Institute • National Center for Research Resources
Müller 1998 *(72)* Norway	Randomized crossover design with three interventions Experimental period: 17 days	1. 2.[4] 3.	12.5 6.3 7.3	11.4 10.3 11.4	5.5 5.3 9.8	0.1 6.7 0.2	• Initial: 30, final: 27 • Reason for loss: not reported (n=2), poor compliance (n=1)	• 27 women • Mean age: 27 years	• The Nordic Industrial Fund • Mills DA
Hunter 2000 *(72)* United Kingdom	Randomized crossover design with three interventions Experimental period: 14 days	1. 2. 3.	17.6 6.8 7.3	13.9 25.0 14.4	4.5 4.5 14.4		• Initial: 9, final: 6 • Reason for loss: not reported	• 6 men • Mean age: 28 years	• Ministry of Agriculture, Food and Fisheries • Scottish Executive Rural Affairs Department
Judd 2002 *(74)*[11] Baer 2004 *(75)* USA	Randomized crossover design with six interventions Experimental period: 35 days	1. 2. 3.[4] 4.[4] 5. 6.	12.8 12.6 12.8 16.9 20.9 20.8	10.5 17.6 10.6 10.6 10.5 10.5	3.8 3.8 4.0 4.3 4.4 4.2	0.2 0.1 8.3 4.2 0.3 0.2	• Initial: 54, final: 50 • Reason for loss: not reported (n=3), poor compliance (n=1)	• 50 men • Mean age: 42 years	• Technical Committee on Dietary Lipids, International Life Sciences Institute
Vega-López 2006 *(76)*	Randomized crossover design with two interventions Experimental period: 35 days	1. 2.	14.8 6.4	10.9 15.4	3.5 8.7	0.6 1.0	• Initial: 15, final: 15 • No dropouts reported	• 5 men and 10 women • Mean age: 64 years	• National Institutes of Health / US Department of Agriculture
Lichtenstein 1999 *(77)* USA	Randomized crossover design with five interventions Experimental period: 35 days	1. 2. 3.[4] 4.[4] 5.[4]	7.3 8.6 8.4 8.6 8.5	8.1 8.1 8.0 9.9 8.5	12.5 13.5 11.1 8.1 6.3	0.6 0.9 3.3 4.2 6.7	• Initial: 36, final: 36 • No dropouts reported	• 18 men and 18 women • Mean age: 63 years	• National Institutes of Health • US Department of Agriculture
Lovejoy 2002 *(78)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.[4]	5.9 10.9 7.2	14.7 8.8 7.6	6.3 6.4 4.0	0.0 0.0 7.0	• Initial: 31, final: 25 • Reason for loss: not reported	• 12 men and 13 women • Mean age: 28 years	• US Department of Agriculture
Berglund 2007 *(79)* USA	Randomized crossover design with three interventions Experimental period: 49 days	1. 2. 3.	15.0 8.4 7.7	13.8 20.0 14.9	5.6 6.0 5.3		• Initial: 110, final: 85 • Reason for loss: not reported	• 52 men and 33 women • Mean age: 36 years	• National Institutes of Health
Binkoski 2005 *(80)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.	10.8 8.0 7.6	14.3 16.5 13.6	7.5 4.1 7.4		• Initial: 31, final: 31 • No dropouts reported	• 12 men and 19 women • Mean age: 46 years	• National Institutes of Health • National Sunflower Association
Castro 2000 *(81)* Spain	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	9.4 8.6	24.3 24.8	4.3 4.7		• Initial: 22, final: 21 • Reason for loss: illness (n=1)	• 21 men • Mean age: 23 years	• Investigaciones de la Seguridad Social • Koype Co

Kris-Etherton 1999 *(82)* USA	Randomized crossover design with four interventions Experimental period: 24 days	1. 2. 3. 4.	6.7 6.7 6.7 7.7	11.5 20.2 16.3 17.3	5.8 5.8 8.6 9.6		• Initial: 26, final: 22 • Reason for loss: poor compliance (n=2), moved outside the area (n=2)	• 9 men and 13 women • Mean age: 34 years	• The Peanut Institute
Müller 2003 *(83)* Norway	Randomized crossover design with three interventions Experimental period: 22 days	1. 2. 3.	28.9 13.7 5.7	3.9 2.6 13.3	2.8 1.8 14.8	0.3 0.1 0.2	• Initial: 31, final: 25 • Reason for loss: not reported	• 25 women • Mean age: 31 years	• The Norwegian Research Council • Mills DA
Nielsen 2002 *(84)* Denmark	Randomized crossover design with three interventions Experimental period: 21 days	1. 2. 3.	10.5 11.5 11.5	14.5 16.9 7.6	6.5 2.3 11.7		• Initial: 18, final: 18 • No dropouts reported	• 18 men • Mean age: 24 years	• Not reported
Poppitt 2002 *(85)* New Zealand	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	19.2 14.4	5.8 7.7	13.4 15.4		• Initial: 20, final: 20 • No dropouts reported	• 20 men • Mean age: Not reported	• New Zealand Dairy Board • Auckland Uniservices • Maurice & Phyllis Paykel Trust
Rajaram 2001 *(86)* USA	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	8.2 8.8	11.0 18.9	6.3 10.7		• Initial: 24, final: 23 • Reason for loss: not reported	• 14 men and 9 women • Mean age: Not reported	• National Pecan Sellers Association
Sanders 2003 *(87)* United Kingdom	Randomized crossover design with three interventions Experimental period: 14 days	1.[4] 2. 3.	9.1 9.8 10.5	11.8 19.9 12.3	5.9 6.3 6.1	9.2 0.1 0.1	• Initial: 36, final: 29 • Reason for loss: personal reasons (n=7)	• 29 men • Mean age: 24 years	• Ministry of Agriculture, Food and Fisheries • The Medical Research Council
Wagner 2001 *(88)* Austria	Randomized crossover design with two interventions Experimental period: 14 days	1. 2.	8.5 8.4	9.8 14.5	11.5 6.9		• Initial: 28, final: 28 • No dropouts reported	• 28 men • Mean age: 24 years	• Not reported
Kratz 2002 *(89)* Germany	Randomized parallel design with three interventions Experimental period: 28 days	1. 2. 3.	9.1 10.7 10.0	19.3 23.3 8.7	9.0 3.4 18.5		• Initial: 69, final: 58 • Reason for loss: illness (n=6), poor compliance (n=5)	• Diet 1: 10 men and 8 women • Diet 2: 11 men and 9 women • Diet 3: 10 men and 10 women • Mean age: 26 years	• Central Marketing Agency of the German Agricultural Industry • The German Union for the Promotion of Oil and Protein Plants • The Austrian Science Foundation • The Brökelmann Ölmühle Company
Lichtenstein 2006 *(90)* USA	Randomized crossover design with five interventions Experimental period: 35 days	1. 2. 3. 4. 5.[4]	6.5 4.9 5.8 6.8 7.3	6.3 6.1 18.8 6.7 8.1	12.3 14.1 2.3 13.2 8.1	0.6 0.6 0.3 0.5 2.4	• Initial: 42 (including 10 replacers), final: 30 • Reason for loss: time constraints (n=3), poor compliance (n=4), change in medical status (n=2), loss of medical insurance (n=1), moved out of the state (n=1), or dislike of the food (n=1)	• 14 men and 16 women • Mean age: 63 years	• The National Institutes of Health • US Department of Agriculture
Motard-Belanger 2008 *(91)* Canada	Randomized crossover design with four interventions Experimental period: 28 days	1. 2. 3.[4] 4.[4]	18.5 18.3 19.4 18.0	11.8 11.8 10.0 10.1	4.6 4.4 3.5 4.0	0.8 1.5 3.7 3.7	• Initial: 48, final: 38 • Reason for loss: not reported	• 38 men • Mean age: 33 years	• Dairy Farmers of Canada • Novalait Inc • Natural Sciences and Engineering Research Council of Canada
Rajaram 2009 *(92)* USA	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	9.4 8.0	9.4 8.0	4.3 10.8	1.0 0.8	• Initial: 27, final: 25 • Reason for loss: time constraints (n=2)	• 14 men and 11 women • Age: 23–65 years	• California Walnut Commission

Reference and country	Study design	Composition[1]					Participants		Funding
		Diet	S	M	P	T			
Gillingham 2011 *(93)* Canada	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.	11.2 5.6 6.1	16.1 22.9 15.9	6.5 5.7 12.3		• Initial: 39, final: 36 • Reason for loss: relocation of residence (n=2), work-related issues (n=1)	• 13 men and 23 women • Mean age: 48 years	• Flax Canada 2015 • Canola Council of Canada • Agri-Food Research & Development Initiative
Iggman 2011 *(94)* Sweden	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	19.6 7.9	11.1 17.4	3.9 9.6		• Initial: 20, final: 20 • No dropouts reported	• 14 men and 6 women • Mean age: 51 years	• Not reported
Marin 2011 *(95)* Spain	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	8.8 8.8	13.0 23.4	5.0 4.6		• Initial: 59, final: 59 • No dropouts reported	• 31 men and 28 women • Mean age: 21 years	• Ministerio de Ciencia e Innovacion / Spanish Ministry of Health • CIBER Fisiopatologia de la Obesidad y Nutricion • Consejeria de Innovacion • Consejeria de Salud
Roussell 2012 *(96)* USA	Randomized crossover design with two interventions Experimental period: 35 days	1. 2.	6.0 6.0	9.0 11.0	8.0 7.0		• Initial: 42, final: 36 • Reason for loss: job change (n=1), illness (n=1), poor compliance (n=4)	• 15 men and 21 women • Mean age: 50 years	• Beef Checkoff Program • National Institutes of Health
Zhao 2004 *(97)* USA	Randomized crossover design with three interventions Experimental period: 42 days	1. 2. 3.	12.7 8.5 8.2	13.2 12.2 12.3	8.7 16.4 17.2		• Initial: 23, final: 23 • No dropouts reported	• 20 men and 3 women • Mean age: 50 years	• California Walnut Commission • Walnut Marketing Board
Sabaté 2003 *(98)* USA	Randomized crossover design with three interventions Experimental period: 28 days	1. 2. 3.	8.2 8.0 7.7	12.1 16.5 19.4	6.2 7.5 8.7		• Initial: 27, final: 25 • Reason for loss: poor compliance (n=2)	• 14 men and 11 women • Mean age: 41 years	• Almond Board of California
Curb 2000 *(99)* USA	Randomized crossover design with three interventions Experimental period: 30 days	1. 2. 3.	13.4 8.6 8.6	11.5 14.4 19.2	8.6 6.7 5.8		• Initial: 34, final: 30 • Reason for loss: not reported	• 15 men and 15 women • Age: 18-53 years	• US Army Medical Research Acquisition Activity
Cater 2001 *(100)* USA	Randomized crossover design with two interventions Experimental period: 21 days	1. 2.	23.1 2.9	15.1 37.5	3.3 2.2		• Initial: 7, final: 7 • No dropouts reported	• 7 men • Mean age: 66 years	• National Institutes of Health
Lacroix 2012 *(101)* Canada	Randomized crossover design with two interventions Experimental period: 28 days	1. 2.	9.9 10.3	14.2 12.8	5.9 5.8	0.6 1.8	• Initial: 72, final: 61 • Reason for loss: protocol too demanding (n=8), change of menopausal status (n=2), missing data (n=1)	• 61 women • Mean age: 64 years	• Dairy Farmers of Canada • Dairy Australia • Agriculture and Agri-Food Canada • The Canadian Dairy Commission

S, saturated fatty acids; M, *cis*-monounsaturated fatty acids; P, *cis*-polyunsaturated fatty acids; T, *trans*-fatty acids

[1] The fatty acid composition of the diets is reported as a percentage of total energy intake
[2] Both publications reported data from the same study; the study is referred to as "Mensink 1987" in the table in risk of bias figures in **Annex 8**
[3] Two separate studies were reported in a single publication; the studies are referred to as "Anderson 1976 A" and "Anderson 1976 B" in the table and risk of bias figures in **Annex 8**
[4] Studies were not used, because the intake of *trans*-fatty acids was > 2% of energy
[5] Both publications reported data from the same study; the study is referred to as "Lewis 1981" in the table and risk of bias figures in **Annex 8**
[6] Both publications reported data from the same study; the study is referred to as "Wardlaw 1991" in the table and risk of bias figures in **Annex 8**
[7] Two separate studies were reported in a single publication; the studies are referred to as "Kris-Etherton 1993 A" and "Kris-Etherton 1993 B" in the table and risk of bias figures in **Annex 8**
[8] Both publications reported data from the same study; the study is referred to as "Judd 1988" in the table and risk of bias figures in **Annex 8**
[9] All three publications reported data from the same study; the study is referred to as "Lichtenstein 1993" in the table and risk of bias figures in **Annex 8**
[10] Two separate studies were reported in a single publication; the studies are referred to as "Fielding 1995 A" and "Fielding 1995 B" in the table and risk of bias figures in **Annex 8**
[11] Both publications reported data from the same study; the study is referred to as "Judd 2002" in the table and risk of bias figures in **Annex 8**

Table 2. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from SFA is replaced isocalorically by carbohydrates, *cis*-MUFA or *cis*-PUFA

Lipid or lipoprotein	Unit	Change per 1% of energy replaced			No[1]
		SFA → Carb	SFA → MUFA	SFA → PUFA	
ΔTotal cholesterol	mmol/L	–0.041	–0.046	–0.064	177/74
95% CI[2]		–0.047 to –0.035	–0.051 to –0.040	–0.070 to –0.058	
P-value		<0.001	<0.001	<0.001	
ΔLDL cholesterol	mmol/L	–0.033	–0.042	–0.055	165/69
95% CI		–0.039 to –0.027	–0.047 to –0.037	–0.061 to –0.050	
P-value		<0.001	<0.001	<0.001	
ΔHDL cholesterol	mmol/L	–0.010	–0.002	–0.005	163/68
95% CI		–0.012 to –0.008	–0.004 to 0.000	–0.006 to –0.003	
P-value		<0.001	0.014	<0.001	
ΔTriglyceride	mmol/L	0.011	–0.004	–0.010	172/72
95% CI		0.007 to 0.014	–0.007 to –0.001	–0.014 to –0.007	
P-value		<0.001	0.022	<0.001	
ΔTotal to HDL cholesterol ratio		0.001	–0.027	–0.034	159/66
95% CI		–0.006 to 0.007	–0.033 to –0.022	–0.040 to –0.028	
P-value		0.842	<0.001	<0.001	
ΔLDL to HDL cholesterol ratio		–0.007	–0.029	–0.034	161/67
95% CI		–0.013 to –0.001	–0.034 to –0.024	–0.040 to –0.029	
P-value		0.017	<0.001	<0.001	
ΔTriglyceride to HDL cholesterol ratio		0.014	–0.002	–0.005	161/67
95% CI		0.010 to 0.018	–0.005 to 0.002	–0.009 to –0.002	
P-value		<0.001	0.342	0.004	
ΔApoA-I	mg/dL	–7.0	–1.8	–4.9	102/41
95% CI		–9.0 to –5.1	–3.7 to 0.1	–7.3 to –2.5	
P-value		<0.001	0.064	<0.001	
ΔApoB	mg/dL	–3.6	–7.8	–10.2	104/42
95% CI		–5.4 to –1.7	–9.5 to –6.0	–12.4 to –8.1	
P-value		<0.001	<0.001	<0.001	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

Table 3. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates, *cis*-MUFA or *cis*-PUFA is replaced isocalorically by SFA

Lipid or lipoprotein	Unit	Change per 1% of energy replaced			No[1]
		Carb → SFA	MUFA → SFA	PUFA → SFA	
ΔTotal cholesterol	mmol/L	0.045	0.049	0.066	177/74
95% CI[2]		0.038 to 0.051	0.043 to 0.055	0.060 to 0.073	
P-value		<0.001	<0.001	<0.001	
ΔLDL cholesterol	mmol/L	0.036	0.045	0.058	165/69
95% CI		0.030 to 0.043	0.039 to 0.051	0.052 to 0.064	
P-value		<0.001	<0.001	<0.001	
ΔHDL cholesterol	mmol/L	0.011	0.003	0.005	163/68
95% CI		0.010 to 0.013	0.001 to 0.004	0.004 to 0.007	
P-value		<0.001	0.001	<0.001	
ΔTriglyceride	mmol/L	-0.012	0.004	0.010	172/72
95% CI		−0.015 to −0.008	0.000 to 0.007	0.006 to 0.014	
P-value		<0.001	0.041	<0.001	
ΔTotal to HDL cholesterol ratio		−0.002	0.028	0.034	159/66
95% CI		−0.009 to 0.005	0.021 to 0.034	0.027 to 0.041	
P-value		0.553	<0.001	<0.001	
ΔLDL to HDL cholesterol ratio		0.007	0.030	0.035	161/67
95% CI		0.001 to 0.014	0.024 to 0.036	0.028 to 0.041	
P-value		0.033	<0.001	<0.001	
ΔTriglyceride to HDL cholesterol ratio		−0.016	0.001	0.004	161/67
95% CI		−0.020 to −0.012	−0.003 to 0.004	0.001 to 0.008	
P-value		<0.001	0.680	0.026	
ΔApoA-I	mg/dL	8.4	2.7	6.3	102/41
95% CI		6.4 to 10.5	0.7 to 4.8	3.9 to 8.7	
P-value		<0.001	0.008	<0.001	
ΔApoB	mg/dL	3.7	8.1	10.3	104/42
95% CI		1.7 to 5.8	6.1 to 10.1	7.7 to 12.8	
P-value		0.001	<0.001	<0.001	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

Table 4. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by SFA: impact of baseline levels

Lipid or lipoprotein	Unit	Change per 1% of energy replaced	No	Change per 1% of energy replaced	No[1]
		Below median[2]		Above median	
ΔTotal cholesterol	mmol/L	0.035	82/37	0.050	95/37
95% CI[3]		0.023 to 0.048		0.043 to 0.057	
P-value		<0.001		<0.001	
ΔLDL cholesterol	mmol/L	0.029	79/35	0.041	86/34
95% CI		0.020 to 0.039		0.032 to 0.049	
P-value		<0.001		<0.001	
ΔHDL cholesterol	mmol/L	0.008	81/34	0.013	82/34
95% CI		0.005 to 0.011		0.011 to 0.016	
P-value		<0.001		<0.001	
ΔTriglyceride	mmol/L	–0.011	83/36	–0.013	89/36
95% CI		–0.015 to –0.006		–0.019 to –0.007	
P-value		<0.001		<0.001	
ΔTotal to HDL cholesterol ratio		0.002	76/33	–0.006	83/33
95% CI		–0.008 to 0.012		–0.016 to 0.004	
P-value		0.695		0.246	
ΔLDL to HDL cholesterol ratio		0.007	78/34	0.006	83/33
95% CI		–0.002 to 0.016		–0.004 to 0.017	
P-value		0.103		0.218	
ΔTriglyceride to HDL cholesterol ratio		–0.012	78/34	–0.019	83/33
95% CI		–0.016 to –0.008		–0.026 to –0.013	
P-value		<0.001		<0.001	

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The median level when subjects consumed a standardized fat-free diet was for total cholesterol 4.45 mmol/L, for LDL cholesterol 2.89 mmol/L, for HDL cholesterol 0.97 mmol/L, for triglyceride 1.48 mmol/L, for the total to HDL cholesterol ratio 4.36, for the LDL cholesterol to HDL cholesterol ratio 2.76 and for the for the triglyceride to HDL cholesterol ratio 1.36
[3] The 95% CIs refer to the regression coefficients on the line directly above

Table 5. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by SFA: impact of gender

Lipid or lipoprotein	Unit	Change per 1% of energy replaced	No	Change per 1% of energy replaced	No[1]
		Men only		Women only or men and women	
ΔTotal cholesterol	mmol/L	0.037	85/38	0.049	92/36
95% CI[2]		0.028 to 0.047		0.041 to 0.057	
P-value		<0.001		<0.001	
ΔLDL cholesterol	mmol/L	0.026	73/33	0.041	92/36
95% CI		0.014 to 0.038		0.033 to 0.048	
P-value		<0.001		<0.001	
ΔHDL cholesterol	mmol/L	0.007	71/32	0.013	92/36
95% CI		0.004 to 0.010		0.011 to 0.016	
P-value		<0.001		<0.001	
ΔTriglyceride	mmol/L	–0.014	82/37	–0.010	90/35
95% CI		–0.020 to –0.008		–0.015 to –0.005	
P-value		<0.001		<0.001	
ΔTotal to HDL cholesterol ratio		0.002	71/32	–0.004	88/34
95% CI		–0.014 to 0.018		–0.011 to 0.003	
P-value		0.808		0.216	
ΔLDL to HDL cholesterol ratio		0.008	71/32	0.007	90/35
95% CI		–0.006 to 0.021		–0.001 to 0.014	
P-value		0.269		0.088	
ΔTriglyceride to HDL cholesterol ratio		–0.012	71/32	–0.017	90/35
95% CI		–0.020 to –0.005		–0.022 to –0.012	
P-value		0.002		<0.001	

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

Table 6. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by SFA: impact of year of publication

Lipid or lipoprotein	Unit	Change per 1% of energy replaced	No	Change per 1% of energy replaced	No[1]
		Published before 1993		Published in 1993 or later	
ΔTotal cholesterol	mmol/L	0.045	77/34	0.045	100/40
95% CI[2]		0.035 to 0.054		0.036 to 0.054	
P-value		<0.001		<0.001	
ΔLDL cholesterol	mmol/L	0.035	69/31	0.038	96/38
95% CI		0.024 to 0.046		0.030 to 0.046	
P-value		<0.001		<0.001	
ΔHDL cholesterol	mmol/L	0.011	67/30	0.012	96/38
95% CI		0.007 to 0.014		0.010 to 0.014	
P-value		<0.001		<0.001	
ΔTriglyceride	mmol/L	–0.014	72/32	–0.010	100/40
95% CI		–0.019 to –0.009		–0.015 to –0.004	
P-value		<0.001		0.002	
ΔTotal to HDL cholesterol ratio		0.003	65/29	–0.004	94/37
95% CI		–0.008 to 0.015		–0.013 to 0.005	
P-value		0.543		0.344	
ΔLDL to HDL cholesterol ratio		0.010	65/29	0.007	96/38
95% CI		0.000 to 0.020		–0.002 to 0.015	
P-value		0.048		0.143	
ΔTriglyceride to HDL cholesterol ratio		–0.014	65/29	–0.017	96/38
95% CI		–0.020 to –0.009		–0.023 to –0.012	
P-value		<0.001		<0.001	

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

Table 7. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by SFA: exclusion of studies using liquid formula diets

Lipid or lipoprotein	Unit	Change per 1% of energy replaced	No[1]
		Carb → SFA	
ΔTotal cholesterol	mmol/L	0.046	166/69
95% CI[2]		0.039 to 0.052	
P-value		<0.001	
ΔLDL cholesterol	mmol/L	0.037	154/64
95% CI		0.031 to 0.044	
P-value		<0.001	
ΔHDL cholesterol	mmol/L	0.011	152/63
95% CI		0.010 to 0.013	
P-value		<0.001	
ΔTriglyceride	mmol/L	–0.012	163/68
95% CI		–0.016 to –0.008	
P-value		0.001	
ΔTotal to HDL cholesterol ratio		–0.002	150/62
95% CI		–0.009 to 0.004	
P-value		0.485	
ΔLDL to HDL cholesterol ratio		0.007	152/63
95% CI		0.000 to 0.014	
P-value		0.040	
ΔTriglyceride to HDL cholesterol ratio		–0.016	152/63
95% CI		–0.020 to –0.012	
P-value		<0.001	
ΔApoA-I	mg/dL	8.4	100/40
95% CI		6.4 to 10.5	
P-value		<0.001	
ΔApoB	mg/dL	3.7	102/41
95% CI		1.6 to 5.8	
P-value		0.001	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

Table 8. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0) or stearic acid (C18:0)

Lipid or lipoprotein	Unit	Change per 1% of energy replaced				No[1]
		Carb → C12:0	Carb → C14:0	Carb → C16:0	Carb → C18:0	
ΔTotal cholesterol	mmol/L	0.029	0.060	0.041	–0.006	134/52
95% CI[2]		0.014 to 0.045	0.042 to 0.077	0.030 to 0.052	–0.019 to 0.007	
P-value		<0.001	<0.001	<0.001	0.384	
ΔLDL cholesterol	mmol/L	0.017	0.044	0.036	–0.003	130/50
95% CI		0.003 to 0.031	0.028 to 0.060	0.026 to 0.046	–0.015 to 0.009	
P-value		0.019	<0.001	<0.001	0.606	
ΔHDL cholesterol	mmol/L	0.019	0.021	0.010	0.000	132/51
95% CI		0.016 to 0.023	0.017 to 0.025	0.007 to 0.013	–0.003 to 0.003	
P-value		<0.001	<0.001	<0.001	0.853	
ΔTriglyceride	mmol/L	–0.015	-0.011	–0.011	–0.005	135/53
95% CI		–0.023 to –0.007	–0.020 to –0.002	–0.017 to –0.006	–0.012 to 0.001	
P-value		<0.001	0.018	<0.001	0.110	
ΔTotal to HDL cholesterol ratio		–0.035	–0.009	0.006	–0.002	125/48
95% CI		–0.048 to –0.022	–0.023 to 0.006	–0.003 to 0.015	–0.013 to 0.009	
P-value		<0.001	0.244	0.180	0.676	
ΔLDL to HDL cholesterol ratio		–0.024	0.000	0.013	–0.001	130/50
95% CI		–0.036 to –0.013	–0.013 to 0.014	0.005 to 0.021	–0.011 to 0.009	
P-value		<0.001	0.941	0.002	0.831	
ΔTriglyceride to HDL cholesterol ratio		–0.024	–0.018	–0.015	–0.003	131/51
95% CI		–0.032 to –0.017	–0.027 to –0.010	–0.020 to –0.009	–0.009 to 0.004	
P-value		<0.001	<0.001	<0.001	0.407	
ΔApoA-I	mg/dL	19.2	6.8	6.5	–1.4	88/34
95% CI		14.6 to 23.7	0.5 to 13.1	3.8 to 9.3	–4.4 to 1.7	
P-value		<0.001	0.034	<0.001	0.374	
ΔApoB	mg/dL	–1.3	2.0	3.3	–1.8	91/35
95% CI		–6.8 to 4.2	–2.9 to 6.9	–0.2 to 6.9	–5.7 to 2.1	
P-value		0.627	0.417	0.065	0.368	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

Table 9. Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0) or stearic acid (C18:0): exclusion of studies using liquid formula diets

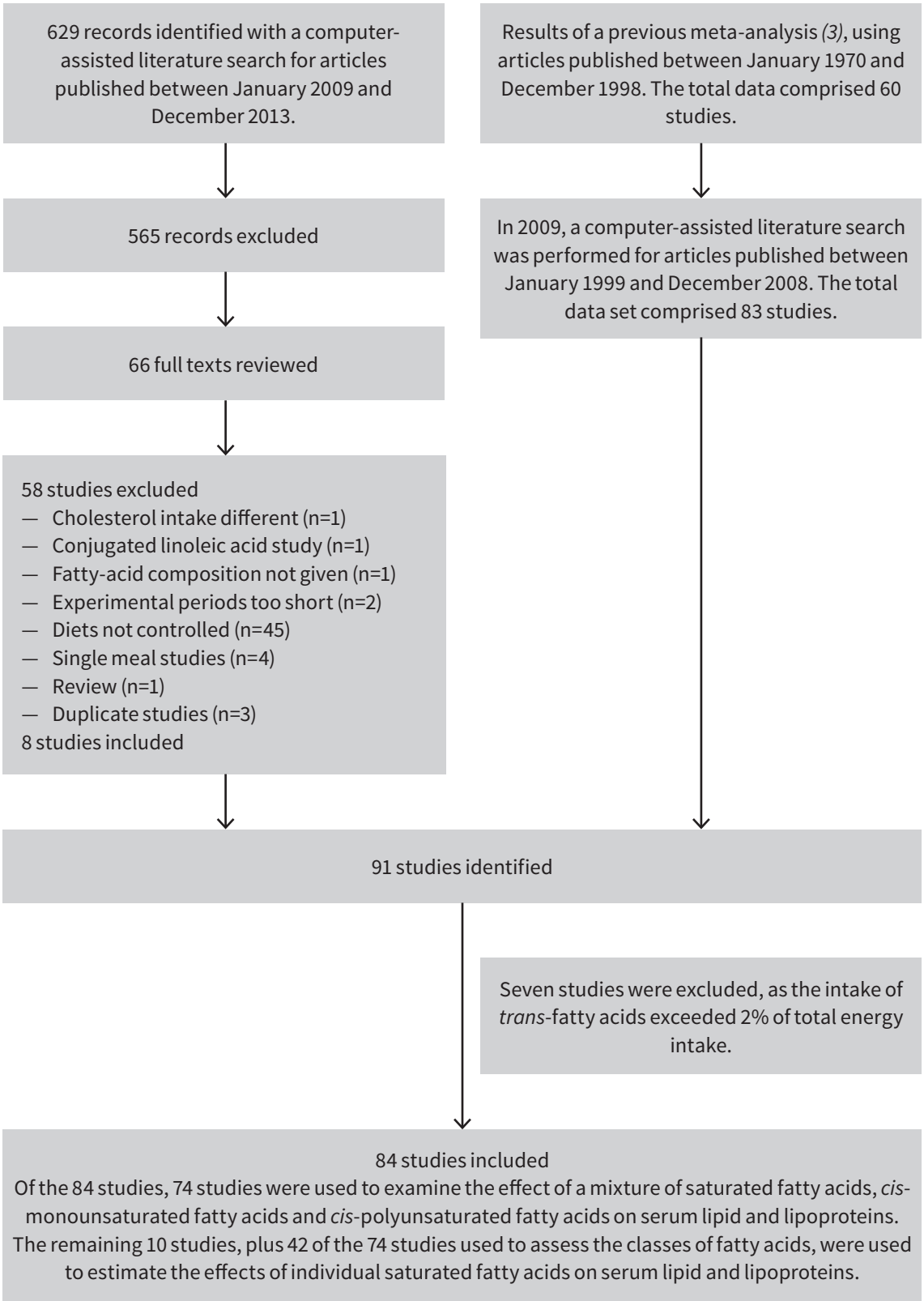
Lipid or lipoprotein	Unit	Change per 1% of energy replaced				No[1]
		Carb → C12:0	Carb → C14:0	Carb → C16:0	Carb → C18:0	
ΔTotal cholesterol	mmol/L	0.033	0.058	0.041	–0.003	122/48
95% CI[2]		0.014 to 0.052	0.039 to 0.076	0.028 to 0.053	–0.017 to 0.012	
P-value		0.001	<0.001	<0.001	0.717	
ΔLDL cholesterol	mmol/L	0.019	0.042	0.036	0.000	118/46
95% CI		0.002 to 0.036	0.026 to 0.059	0.025 to 0.048	–0.013 to 0.013	
P-value		0.031	<0.001	<0.001	0.977	
ΔHDL cholesterol	mmol/L	0.021	0.020	0.010	–0.001	120/47
95% CI		0.017 to 0.026	0.016 to 0.025	0.007 to 0.012	–0.004 to 0.003	
P-value		<0.001	<0.001	<0.001	0.684	
ΔTriglyceride	mmol/L	–0.016	–0.011	–0.012	–0.005	123/49
95% CI		–0.025 to –0.006	–0.020 to –0.002	–0.018 to –0.006	–0.012 to 0.002	
P-value		0.001	0.023	<0.001	0.177	
ΔTotal to HDL cholesterol ratio		–0.033	–0.009	0.006	0.002	116/45
95% CI		–0.048 to –0.019	–0.023 to 0.006	–0.003 to 0.016	–0.010 to 0.013	
P-value		<0.001	0.223	0.188	0.779	
ΔLDL to HDL cholesterol ratio		–0.022	0.000	0.013	0.003	118/46
95% CI		–0.035 to –0.009	–0.013 to 0.013	0.005 to 0.022	–0.007 to 0.013	
P-value		0.001	0.994	0.003	0.604	
ΔTriglyceride to HDL cholesterol ratio		–0.025	–0.018	–0.014	–0.002	120/47
95% CI		–0.034 to –0.016	–0.026 to –0.009	–0.020 to –0.008	–0.009 to 0.005	
P-value		<0.001	<0.001	<0.001	0.539	

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

7. Figures

Figure 1. Flow diagram of study selection



ANNEX 1.

PICO questions

1. What is the effect in the population of reduced percentage of total energy intake from saturated fatty acids (SFA) relative to higher intake for reduction in risk of noncommunicable diseases (NCDs)?
2. What is the effect in the population of consuming less than 10% of total energy as SFA relative to more than 10% total energy as SFA for reduction in risk of NCDs?
3. What is the effect in the population of a reduction in percentage of total energy intake from SFA from 10% in gradual increments relative to higher intake for reduction in risk of NCDs?
4. What is the effect in the population of reduced percentage of total energy intake from long-chain SFA, very long-chain SFA and medium-chain SFA relative to higher intake for reduction in risk of NCDs?
5. What is the effect in the population of reduced percentage of total energy intake from lauric acid, myristic acid, palmitic acid or stearic acid relative to higher intake for reduction in risk of NCDs?
6. What is the effect in the population of replacing SFA with carbohydrates (refined vs. unrefined), *cis*-monounsaturated fatty acids (*cis*-MUFA), *cis*-polyunsaturated fatty acids (*cis*-PUFA), protein or trans-fatty acids (TFA) relative to no replacement for reduction in risk of NCDs?

ANNEX 2.

Priority outcomes

1. All-cause mortality
2. Coronary heart disease (CHD) incidence, CHD mortality, and CHD morbidity
3. Cardiovascular disease (CVD) incidence (as a composite indicator defined by study authors), CVD mortality, and CVD morbidity
4. Stroke including stroke incidence (type of stroke), stroke mortality, and stroke morbidity
5. Blood lipids including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, LDL cholesterol to HDL cholesterol ratio, total cholesterol to HDL cholesterol ratio, triglyceride to HDL cholesterol ratio and lipoprotein (a)
6. Adverse effects reported by study authors

ANNEX 3.

Search strategy

PubMed

((((((((“comparative study”[Publication Type]) OR “randomized controlled trial”[Publication Type]) OR “controlled clinical trial”[Publication Type]))

AND

((((“cholesterol/blood”[MeSH Terms]) OR “cholesterol, ldl/blood”[MeSH Terms]) OR “lipids/blood”[MeSH Terms]) OR “lipoproteins/blood”)))

AND

“humans”[MeSH Terms]))

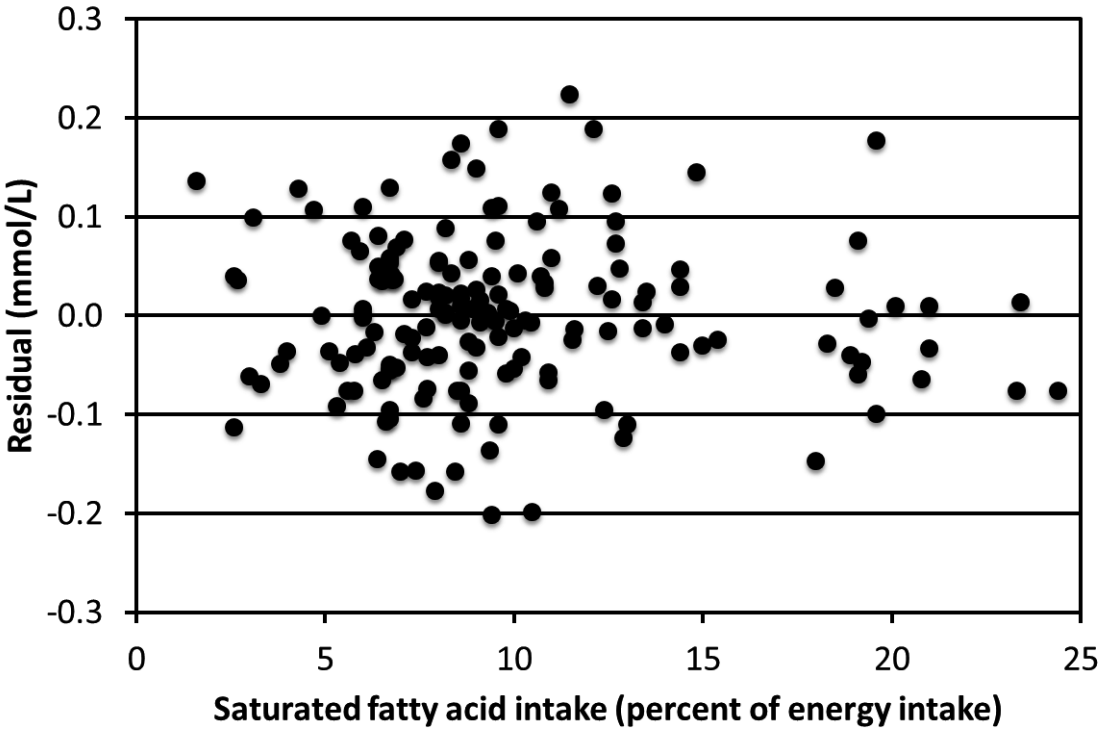
AND

((dietary fat*[MeSH Terms]) OR (((((palmitic acid*[MeSH Terms]) OR stearic acid*[MeSH Terms]) OR myristic acid*[MeSH Terms])) OR lauric acid*[MeSH Terms]))

ANNEX 4.

Residuals analysis

Scatterplot of the relationship between SFA intake (model 1 in **Section 2.2.4**) and the difference between observed and predicted serum LDL cholesterol concentrations (residuals). Each point refers to one of the 165 diets from the 69 studies as used for the calculations (see **Table 1**). "Predicted" values were calculated as the intrinsic level of the group under study plus the predicted change induced by the experimental diet.

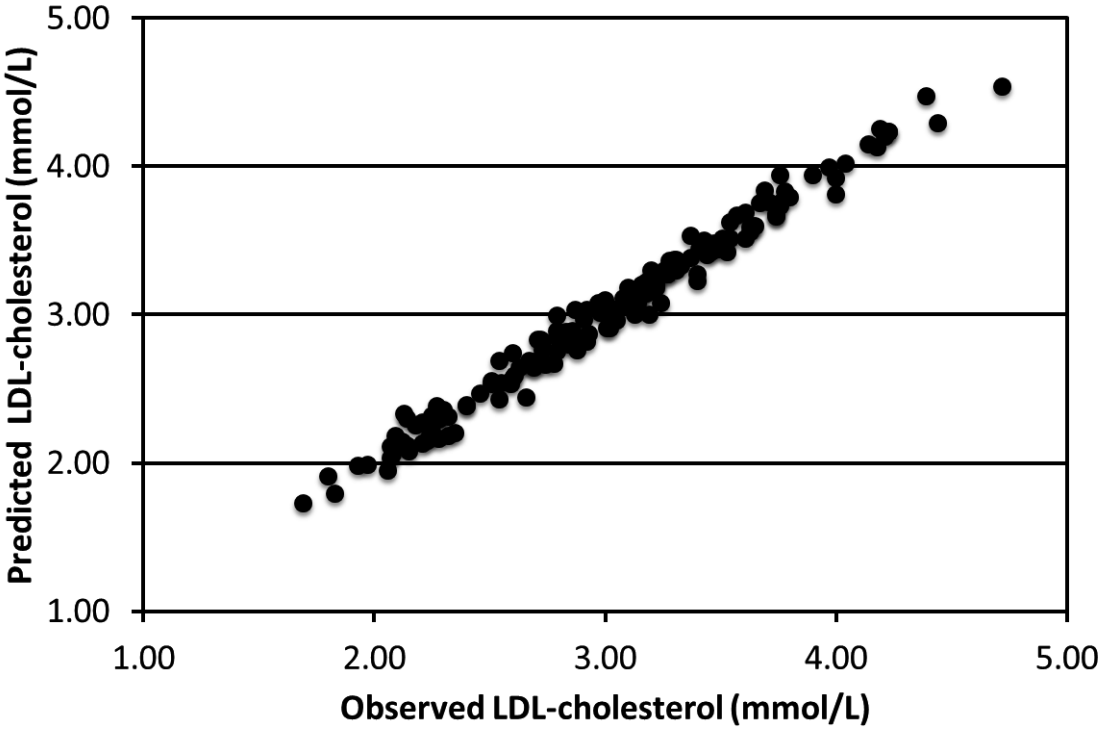


SFA, saturated fatty acids; LDL, low-density lipoprotein

ANNEX 5.

Relationship between observed and predicted serum LDL cholesterol concentrations

Each point refers to one of the 165 diets from the 69 studies as used for the calculations in regression model 1 (see **Section 2.2.4 and Table 2**). "Predicted" values were calculated as the intrinsic level of the group under study plus the predicted change induced by their experimental diet



ANNEX 6.

Results of *cis*-PUFA replacement

Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from *cis*-PUFA in the diet is replaced isocalorically by carbohydrates, SFA or *cis*-MUFA.

Lipid or lipoprotein	Unit	Change per 1% of energy replaced			No[1]
		PUFA → Carb	PUFA → SFA	PUFA → MUFA	
ΔTotal cholesterol	mmol/L	0.019	0.066	0.016	177/74
95% CI[2]		0.013 to 0.025	0.060 to 0.073	0.011 to 0.022	
P-value		<0.001	<0.001	<0.001	
ΔLDL cholesterol	mmol/L	0.019	0.058	0.012	165/69
95% CI		0.012 to 0.025	0.052 to 0.064	0.007 to 0.017	
P-value		<0.001	<0.001	<0.001	
ΔHDL cholesterol	mmol/L	–0.005	0.005	0.003	163/68
95% CI		–0.007 to –0.004	0.004 to 0.007	0.001 to 0.004	
P-value		<0.001	<0.001	<0.001	
ΔTriglyceride	mmol/L	0.020	0.010	0.006	172/72
95% CI		0.016 to 0.024	0.006 to 0.014	0.003 to 0.009	
P-value		<0.001	<0.001	<0.001	
ΔTotal to HDL cholesterol ratio		0.032	0.034	0.005	159/66
95% CI		0.025 to 0.039	0.027 to 0.041	0.000 to 0.011	
P-value		<0.001	<0.001	0.053	
ΔLDL to HDL cholesterol ratio		0.024	0.035	0.004	161/67
95% CI		0.017 to 0.031	0.028 to 0.041	–0.001 to 0.009	
P-value		<0.001	<0.001	0.104	
ΔTriglyceride to HDL cholesterol ratio		0.018	0.004	0.003	161/67
95% CI		0.014 to 0.022	0.001 to 0.008	0.000 to 0.006	
P-value		<0.001	0.026	0.040	
ΔApoA-I	mg/dL	–1.8	6.3	3.4	104/42
95% CI		–4.0 to 0.3	3.9 to 8.7	1.6 to 5.3	
P-value		0.097	<0.001	0.001	
ΔApoB	mg/dL	5.7	10.3	1.8	102/41
95% CI		3.3 to 8.1	7.7 to 12.8	–0.2 to 3.8	
P-value		<0.001	<0.001	0.074	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

ANNEX 7.

Results of *cis*-MUFA replacement

Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from *cis*-MUFA is replaced isocalorically by carbohydrates, SFA or by *cis*-PUFA.

Lipid or lipoprotein	Unit	Change per 1% of energy replaced			No[1]
		MUFA → Carb	MUFA → SFA	MUFA → PUFA	
ΔTotal cholesterol	mmol/L	0.003	0.049	-0.018	177/74
95% CI[2]		–0.002 to 0.008	0.043 to 0.055	–0.023 to –0.013	
P-value		0.227	<0.001	<0.001	
ΔLDL cholesterol	mmol/L	0.007	0.045	–0.013	165/69
95% CI		0.002 to 0.012	0.039 to 0.051	–0.018 to –0.009	
P-value		0.012	<0.001	<0.001	
ΔHDL cholesterol	mmol/L	–0.008	0.003	–0.002	163/68
95% CI		–0.009 to –0.006	0.001 to 0.004	–0.004 to –0.001	
P-value		<0.001	0.001	0.002	
ΔTriglyceride	mmol/L	0.014	0.004	–0.007	172/72
95% CI		0.011 to 0.018	0.000 to 0.007	–0.010 to –0.004	
P-value		<0.001	0.041	<0.001	
ΔTotal to HDL cholesterol		0.026	0.028	–0.008	159/66
95% CI		0.020 to 0.032	0.021 to 0.034	–0.013 to –0.002	
P-value		<0.001	<0.001	0.005	
ΔLDL cholesterol to HDL cholesterol		0.020	0.030	–0.006	161/67
95% CI		0.014 to 0.026	0.024 to 0.036	–0.011 to –0.001	
P-value		<0.001	<0.001	0.018	
ΔTriglyceride to HDL cholesterol		0.015	0.001	–0.004	161/67
95% CI		0.012 to 0.019	–0.003 to 0.004	–0.007 to –0.001	
P-value		<0.001	0.680	0.009	
ΔApoA-I	mg/dL	–5.0	2.7	–3.0	102/41
95% CI		–6.9 to –3.1	0.7 to 4.8	–5.0 to–1.0	
P-value		<0.001	0.008	0.004	
ΔApoB	mg/dL	3.7	8.1	–2.7	104/42
95% CI		1.7 to 5.7	6.1 to 10.1	–4.7to –0.8	
P-value		0.001	<0.001	0.007	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

ANNEX 8.

Results of carbohydrate replacement

Estimated multiple regression equations for the mean changes in serum lipids and lipoproteins when 1% of energy in the diet from carbohydrates is replaced isocalorically by SFA, *cis*-MUFA or *cis*-PUFA.

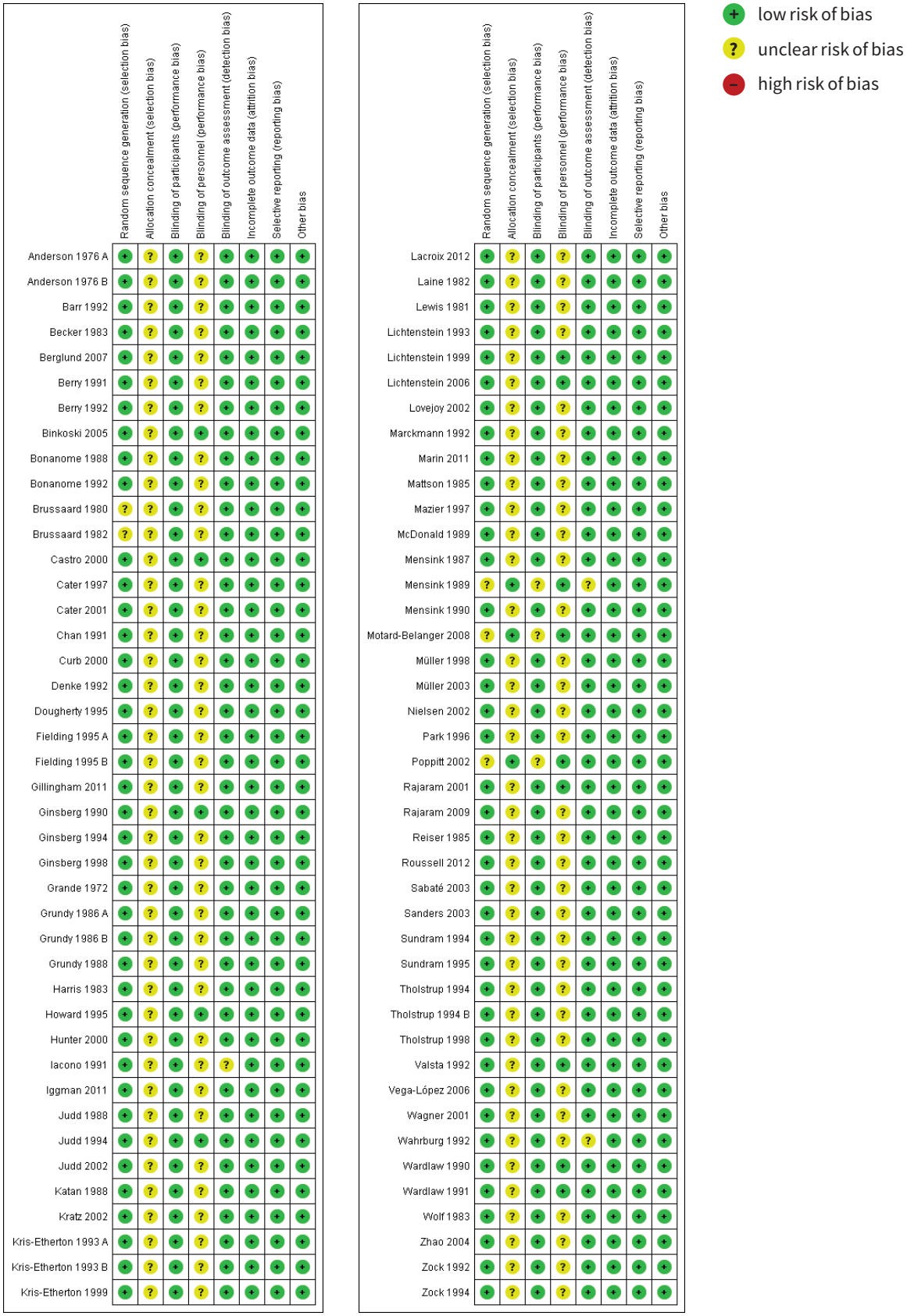
Lipid or lipoprotein	Unit	Change per 1% of energy replaced			No[1]
		Carb → SFA	Carb → MUFA	Carb → PUFA	
ΔTotal cholesterol	mmol/L	0.045	–0.004	–0.022	177/74
95% CI[2]		0.038 to 0.051	–0.010 to 0.001	–0.028 to –0.016	
P-value		<0.001	0.097	<0.001	
ΔLDL cholesterol	mmol/L	0.036	–0.009	–0.022	165/69
95% CI		0.030 to 0.043	–0.014 to –0.003	–0.028 to –0.015	
P-value		<0.001	0.002	<0.001	
ΔHDL cholesterol	mmol/L	0.011	0.008	0.006	163/68
95% CI		0.010 to 0.013	0.007 to 0.010	0.004 to 0.008	
P-value		<0.001	<0.001	<0.001	
ΔTriglyceride	mmol/L	–0.012	–0.015	–0.021	172/72
95% CI		–0.015 to –0.008	–0.018 to –0.011	–0.025 to –0.017	
P-value		<0.001	<0.001	<0.001	
ΔTotal to HDL cholesterol		–0.002	–0.029	–0.036	159/66
95% CI		–0.009 to 0.005	–0.035 to –0.023	–0.043 to –0.029	
P-value		0.553	<0.001	<0.001	
ΔLDL cholesterol to HDL cholesterol		0.007	–0.022	–0.027	161/67
95% CI		0.001 to 0.014	–0.028 to –0.016	–0.034 to –0.021	
P-value		0.033	<0.001	<0.001	
ΔTriglyceride to HDL cholesterol		–0.016	–0.016	–0.020	161/67
95% CI		–0.020 to –0.012	–0.020 to –0.013	–0.024 to –0.016	
P-value		<0.001	<0.001	<0.001	
ΔApoA-I	mg/dL	8.4	5.5	2.3	104/42
95% CI		6.4 to 10.5	3.7 to 7.3	0.1 to 4.6	
P-value		<0.001	<0.001	0.042	
ΔApoB	mg/dL	3.7	–4.4	–6.9	102/41
95% CI		1.7 to 5.8	–6.3 to –2.4	–9.1 to –4.6	
P-value		0.001	<0.001	<0.001	

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; Carb, carbohydrates; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids

[1] Number of diets/number of studies
[2] The 95% CIs refer to the regression coefficients on the line directly above

ANNEX 9.

Risk of bias assessment



ANNEX 10.

GRADE evidence profiles

GRADE evidence profile 1

Question: What is the effect of replacing saturated fatty acids in the diet of adults with *cis*-polyunsaturated fatty acids?[1]
Population: General adult population

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.064 (−0.070, −0.058)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.055 (−0.061, −0.050)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.005 (−0.006, −0.003)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.010 (−0.014, −0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	−0.034 (−0.040, −0.028)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.034 (−0.040, −0.029)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.005 (−0.009, −0.002)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	−4.9 (−7.3, −2.5)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−10.2 (−12.4, −8.1)	⊕⊕⊕⊕ HIGH	IMPORTANT

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RCT, randomized controlled trial

[1] A mixture of dietary saturated fatty acids (SFA) was replaced with *cis*-polyunsaturated fatty acids (*cis*-PUFA) consisting of linoleic acid plus α-linolenic acid.

[2] Number of data points (diet groups) are provided in parentheses. Each data point contains mean dietary information on SFA, *cis*-PUFA and *cis*-monounsaturated fatty acid (*cis*-MUFA) intake as well as an associated change in a given serum lipid or lipoprotein for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the analysis.

[3] All studies were strictly controlled, dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization as the randomization procedure was not described adequately. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have an significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.

[4] This analysis was conducted as a multiple regression in which data points (see Footnote 2) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner is not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, indicate that any inconsistency is unlikely to decrease confidence in the results of the multiple regression analysis and is therefore not considered to be serious.

[5] All studies directly assessed the effect of modifying dietary fat intake such that models could be derived, which provide estimates of the effects of exchanging SFA with other nutrients on serum lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating review. All studies were conducted in the population of interest (adults without disturbances of lipid metabolism or diabetes).

[6] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of reducing SFA intake on a particular serum lipid or lipoprotein and the 95% CI is a measure of variability of that effect.. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has not been downgraded for serious imprecision.

[7] Publication bias was not formally assessed.

[8] Total number of participants. Data points containing dietary information on SFA, *cis*-PUFA and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein were directly extracted from all study groups from included trials without distinction between intervention and control groups.

[9] The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-PUFA.

GRADE evidence profile 2

Question: What is the effect of replacing saturated fatty acids in the diet of adults with *cis*-monounsaturated fatty acids?[1]
Population: General adult population

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.046 (−0.051, −0.040)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.042 (−0.047, −0.037)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.002 (−0.004, 0.000)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.004 (−0.007, −0.001)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	−0.027 (−0.033, −0.022)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.029 (−0.034, −0.024)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	2010	−0.002 (−0.005, 0.002)	⊕⊕⊕O MODERATE	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	1425	−1.8 (−3.7, 0.1)	⊕⊕⊕O MODERATE	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−7.8 (−9.5, −6.0)	⊕⊕⊕⊕ HIGH	IMPORTANT

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RCT, randomized controlled trial

[1] A mixture of dietary saturated fatty acids (SFA) is replaced with *cis*-monounsaturated fatty acids (*cis*-MUFA) consisting primarily of oleic acid.
[2] Number of data points (diet groups) are provided in parentheses. Each data point contains mean dietary information on SFA, *cis*-polyunsaturated fatty acids (*cis*-PUFA) and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the analysis.
[3] All studies were strictly controlled, dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization as the randomization procedure was not described adequately. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have an significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not

expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias. The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-MUFA.

[4] This analysis was conducted as a multiple regression in which data points (see Footnote 2) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner is not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, indicate that any inconsistency is unlikely to decrease confidence in the results of the multiple regression analysis and is therefore not considered to be serious.

[5] All studies directly assessed the effect of modifying dietary fat intake such that models could be derived, which provide estimates of the effects of exchanging SFA with other nutrients on serum lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating review. All studies were conducted in the population of interest (adults without disturbances of lipid metabolism or diabetes).

[6] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of reducing SFA intake on a particular serum lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has not been downgraded for serious imprecision.

[7] Publication bias was not formally assessed.

[8] Total number of participants. Data points containing dietary information on SFA, *cis*-PUFA and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein were directly extracted from all study groups from included trials without distinction between intervention and control groups.

[9] The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-MUFA.

[10] The 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.

GRADE evidence profile 3

Question: What is the effect of replacing saturated fatty acids in the diet of adults with carbohydrates?[1]
Population: General adult population

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
Total cholesterol (units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.041 (−0.047, −0.035)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.033 (−0.039, −0.027)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.010 (−0.012, −0.008)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	0.011 (0.007, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious Imprecision[10]	None	1990	0.001 (−0.006, 0.007)	⊕⊕⊕O MODERATE	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.007 (−0.013, −0.001)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.014 (0.010, 0.018)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	−7.0 (−9.0, −0.51)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−3.6 (−5.4, −1.7)	⊕⊕⊕⊕ HIGH	IMPORTANT

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RCT, randomized controlled trial

[1] A mixture of dietary saturated fatty acids (SFA) was replaced with a mixture of carbohydrates (mono-, di- and polysaccharides), however, the number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrate used in the studies was limited.

[2] Number of data points (diet groups) are provided in parentheses. Each data point contains mean dietary information on SFA, *cis*-polyunsaturated fatty acid (*cis*-PUFA) and *cis*-monounsaturated fatty acid (*cis*-MUFA) intake as well as an associated change in a given serum lipid or lipoprotein for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the analysis.

[3] All studies were strictly controlled, dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization as the randomization procedure was not described adequately. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have an significant, systematic effect on study results. Blinding was not deemed to

be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias. The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of carbohydrates.

[4] This analysis was conducted as a multiple regression in which data points (see Footnote 2) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner is not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, indicate that any inconsistency is unlikely to decrease confidence in the results of the multiple regression analysis and is therefore not considered to be serious.

[5] All studies directly assessed the effect of modifying dietary fat intake such that models could be derived, which provide estimates of the effects of exchanging SFA with other nutrients on serum lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating review. All studies were conducted in the population of interest (adults without disturbances of lipid metabolism or diabetes).

[6] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of reducing SFA intake on a particular serum lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has not been downgraded for serious imprecision.

[7] Publication bias was not formally assessed.

[8] Total number of participants. Data points containing dietary information on SFA, *cis*-PUFA and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein were directly extracted from all study groups from included trials without distinction between intervention and control groups.

[9] The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of carbohydrates.

[10] Imprecision was assessed as indicated in Footnote 6. The 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.

GRADE evidence profile 4

Question: What is the effect of a reduction in saturated fatty acids intake in adults with intakes greater than 10% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations7				
By replacing SFA specifically with *cis*-PUFA?[10]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.064 (−0.070, −0.058)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.055 (−0.061, −0.050)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.005 (−0.006, −0.003)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.010 (−0.014, −0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	−0.034 (−0.040, −0.028)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.034 (−0.040, −0.029)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.005 (−0.009, −0.002)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	−4.9 (−7.3, −2.5)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−10.2 (−12.4, −8.1)	⊕⊕⊕⊕ HIGH	IMPORTANT

By replacing SFA specifically with *cis*-MUFA?[11]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.046 (−0.051, −0.040)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.042 (−0.047, −0.037)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.002 (−0.004, 0.000)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.004 (−0.007, −0.001)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	−0.027 (−0.033, −0.022)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.029 (−0.034, −0.024)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	2010	−0.002 (−0.005, 0.002)	⊕⊕⊕O MODERATE	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	1425	−1.8 (−3.7, 0.1)	⊕⊕⊕O MODERATE	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−7.8 (−9.5, −6.0)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing SFA specifically with carbohydrates?[13]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.041 (−0.047, −0.035)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.033 (−0.039, −0.027)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.010 (−0.012, −0.008)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	0.011 (0.007, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations7				
Total cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	1990	0.001 (–0.006, 0.007)	⊕⊕⊕O MODERATE	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	–0.007 (–0.013, –0.001)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.014 (0.010, 0.018)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	–7.0 (–9.0, –0.51)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	–3.6 (–5.4, –1.7)	⊕⊕⊕⊕ HIGH	IMPORTANT

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RCT, randomized controlled trial; SFA, saturated fatty acids

[1] Effects of decreasing SFA intake on serum lipids and lipoproteins by replacement with *cis*-PUFA, *cis*-MUFA or carbohydrates were observed across a wide range of saturated fatty acids intake, from 1.6 to 24.4% of total energy intake and residuals analysis indicates that the relationship between SFA intake and effect on serum lipids and lipoproteins is consistent across the entire range of SFA intakes. Of the 177 data points used in the multiple regression, 61 included an SFA intake component of more than 10% of total energy intake.

[2] Number of data points (diet groups) are provided in parentheses. Each data point contains mean dietary information on SFA, *cis*-MUFA and *cis*-PUFA intake as well as an associated change in a given serum lipid or lipoprotein for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the analysis.

[3] All studies were strictly controlled, dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization as the randomization procedure was not described adequately. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have an significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias. The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-PUFA, *cis*-MUFA or carbohydrates.

[4] This analysis was conducted as a multiple regression in which data points (see Footnote 2) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner is not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, indicate that any inconsistency is unlikely to decrease confidence in the results of the multiple regression analysis and is therefore not considered to be serious.

[5] All studies directly assessed the effect of modifying dietary fat intake such that models could be derived, which provide estimates of the effects of exchanging SFA with other nutrients on serum lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating review. All studies were conducted in the population of interest (adults without disturbances of lipid metabolism or diabetes).

[6] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of reducing SFA intake on a particular serum lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has not been downgraded for serious imprecision.

[7] Publication bias was not formally assessed.

[8] Total number of participants. Data points containing dietary information on SFA, *cis*-PUFA and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein were directly extracted from all study groups from included trials without distinction between intervention and control groups.

[9] The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-PUFA, *cis*-MUFA or carbohydrates as indicated in the blue subheadings.

[10] The *cis*-PUFA used as isocaloric replacement for SFA in individual studies assessing serum lipid and lipoprotein outcomes were linoleic acid and α-linolenic acid.

[11] The *cis*-MUFA used as isocaloric replacement for SFA in individual studies assessing serum lipid and lipoprotein outcomes was predominantly oleic acid.

[12] The 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.

[13] The carbohydrates used as isocaloric replacement for SFA in individual studies assessing serum lipid outcomes were a mixture of mono-, di- and polysaccharides, however, the number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrates used in the studies was limited.

GRADE evidence profile 5

Question: What is the effect of a reduction in saturated fatty acids intake in adults to less than 10% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
By replacing SFA specifically with *cis*-PUFA?[10]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.064 (−0.070, −0.058)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.055 (−0.061, −0.050)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.005 (−0.006, −0.003)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.010 (−0.014, −0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)5	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	−0.034 (−0.040, −0.028)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.034 (−0.040, −0.029)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.005 (−0.009, −0.002)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	−4.9 (−7.3, −2.5)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−10.2 (−12.4, −8.1)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing SFA specifically with *cis*-MUFA?[11]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.046 (−0.051, −0.040)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.042 (−0.047, −0.037)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.002 (−0.004, 0.000)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.004 (−0.007, −0.001)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	−0.027 (−0.033, −0.022)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.029 (−0.034, −0.024)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	2010	−0.002 (−0.005, 0.002)	⊕⊕⊕O MODERATE	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	1425	−1.8 (−3.7, 0.1)	⊕⊕⊕O MODERATE	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−7.8 (−9.5, −6.0)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing SFA specifically with carbohydrates?[13]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	−0.041 (−0.047, −0.035)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	−0.033 (−0.039, −0.027)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	−0.010 (−0.012, −0.008)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	0.011 (0.007, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT

Total cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	1990	0.001 (−0.006, 0.007)	⊕⊕⊕O MODERATE	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.007 (−0.013, −0.001)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.014 (0.010, 0.018)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	−7.0 (−9.0, −0.51)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	−3.6 (−5.4, −1.7)	⊕⊕⊕⊕ HIGH	IMPORTANT

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RCT, randomized controlled trial; SFA, saturated fatty acids

[1] Effects of decreasing SFA intake on serum lipids and lipoproteins by replacement with *cis*-PUFA, *cis*-MUFA or carbohydrates were observed across a wide range of saturated fatty acids intake, from 1.6 to 24.4% of total energy intake and residuals analysis indicates that the relationship between SFA intake and effect on serum lipids and lipoproteins is consistent across the entire range of SFA intakes. Of the 177 data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake; 65 data points included intakes of less than 8%.

[2] Number of data points (diet groups) are provided in parentheses. Each data point contains mean dietary information on SFA, *cis*-MUFA and *cis*-PUFA intake as well as an associated change in a given serum lipid or lipoprotein for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the analysis.

[3] All studies were strictly controlled, dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization as the randomization procedure was not described adequately. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have an significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias. The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-PUFA, *cis*-MUFA or carbohydrates.

[4] This analysis was conducted as a multiple regression in which data points (see Footnote 2) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner is not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, indicate that any inconsistency is unlikely to decrease confidence in the results of the multiple regression analysis and is therefore not considered to be serious.

[5] All studies directly assessed the effect of modifying dietary fat intake such that models could be derived, which provide estimates of the effects of exchanging SFA with other nutrients on serum lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating review. All studies were conducted in the population of interest (adults without disturbances of lipid metabolism or diabetes).

[6] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of reducing SFA intake on a particular serum lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has not been downgraded for serious imprecision.

[7] Publication bias was not formally assessed.

[8] Total number of participants. Data points containing dietary information on SFA, *cis*-PUFA and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein were directly extracted from all study groups from included trials without distinction between intervention and control groups.

[9] The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-PUFA, *cis*-MUFA or carbohydrates as indicated in the blue subheadings.

[10] The *cis*-PUFA used as isocaloric replacement for SFA in individual studies assessing serum lipid and lipoprotein outcomes were linoleic acid and α-linolenic acid.

[11] The *cis*-MUFA used as isocaloric replacement for SFA in individual studies assessing serum lipid and lipoprotein outcomes was predominantly oleic acid.

[12] The 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.

[13] The carbohydrates used as isocaloric replacement for SFA in individual studies assessing serum lipid outcomes were a mixture mono-, di- and polysaccharides, however, the number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrates used in the studies was limited.

GRADE evidence profile 6

Question: What is the effect of an increase in saturated fatty acids intake in adults with a starting intake of less than 10% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
By replacing *cis*-PUFA with SFA?[10]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	0.066 (0.060, 0.073)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	0.058 (0.052, 0.064)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	0.005 (0.004, 0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	0.010 (0.006, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	0.034 (0.027, 0.041)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.035 (0.028, 0.041)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.004 (0.001, 0.008)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	6.3 (3.9, 8.7)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	10.3 (7.7, 12.8)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing *cis*-MUFA with SFA?[11]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	0.049 (0.043, 0.055)	⊕⊕⊕⊕ HIGH	IMPORTANT

LDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	0.045 (0.039, 0.051)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	0.003 (0.001, 0.004)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	0.004 (0.000, 0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1990	0.028 (0.021, 0.034)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.030 (0.024, 0.036)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (follow-up 13–91 days; unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	2010	0.001 (−0.003, 0.004)	⊕⊕⊕O MODERATE	IMPORTANT
ApoA-I (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	2.7 (0.7, 4.8)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (follow-up 14–91 days; units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	8.1 (6.1, 10.1)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing carbohydrates with SFA?[13]										
Total cholesterol (follow-up 13–91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
74 (177)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2172	0.045 (0.038, 0.051)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2026	0.036 (0.030, 0.043)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (units mmol/L per 1% energy exchange; better indicated by higher values)										
68 (163)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2017	0.011 (0.010, 0.013)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride (units mmol/L per 1% energy exchange; better indicated by lower values)										
72 (172)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2156	−0.012 (−0.015, −0.008)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
66 (159)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[12]	None	1990	−0.002 (−0.009, 0.005)	⊕⊕⊕O MODERATE	IMPORTANT

Quality assessment							No. of participants[8]	Effect[9] (95% CI)	Quality	Importance
No. of studies[2]	Design	Risk of bias[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other considerations[7]				
LDL cholesterol to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	0.007 (0.001, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglyceride to HDL cholesterol ratio (unitless; better indicated by lower values)										
67 (161)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2010	−0.016 (−0.020, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (units mg/dL per 1% energy exchange; better indicated by higher values)										
41 (102)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1425	8.4 (6.4, 10.5)	⊕⊕⊕⊕ HIGH	IMPORTANT
Apo-B (units mg/dL per 1% energy exchange; better indicated by lower values)										
42 (104)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1486	3.7 (1.7, 5.8)	⊕⊕⊕⊕ HIGH	IMPORTANT

ApoA-I, apolipoprotein A-I; Apo-B, apolipoprotein B; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, *cis*-polyunsaturated fatty acids; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RCT, randomized controlled trial; SFA, saturated fatty acids

[1] Effects of increasing SFA intake on serum lipids and lipoproteins by replacing *cis*-PUFA, *cis*-MUFA or carbohydrates with a mixture of SFA, were observed across a wide range of SFA intakes, from 1.6 to 24.4% of total energy intake and residuals analysis indicates that the relationship between SFA intake and effect on serum lipids and lipoproteins is consistent across the entire range of SFA intakes. Of the 177 data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake; 65 data points included intakes of less than 8%.

[2] Number of data points (diet groups) are provided in parentheses. Each data point contains mean dietary information on SFA, *cis*-MUFA and *cis*-PUFA intake as well as an associated change in a given serum lipid or lipoprotein for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the analysis.

[3] All studies were strictly controlled, dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization as the randomization procedure was not described adequately. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, as all participants were intended to receive all treatments and thus it is unlikely that any differences at baseline would have an significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias as all interventions consisted of food provision and though it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias. The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as *cis*-PUFA, *cis*-MUFA or carbohydrates is replaced with an isocaloric amount of SFA.

[4] This analysis was conducted as a multiple regression in which data points (see Footnote 2) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner is not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, indicate that any inconsistency is unlikely to decrease confidence in the results of the multiple regression analysis and is therefore not considered to be serious.

[5] All studies directly assessed the effect of modifying dietary fat intake such that models could be derived, which provide estimates of the effects of exchanging SFA with other nutrients on serum lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating review. All studies were conducted in the population of interest (adults without disturbances of lipid metabolism or diabetes).

[6] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of reducing SFA intake on a particular serum lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has not been downgraded for serious imprecision.

[7] Publication bias was not formally assessed.

[8] Total number of participants. Data points containing dietary information on SFA, *cis*-PUFA and *cis*-MUFA intake as well as an associated change in a given serum lipid or lipoprotein were directly extracted from all study groups from included trials without distinction between intervention and control groups.

[9] The reported effect is the regression coefficient resulting from multiple regression. It is interpreted as the change in a particular serum lipid or lipoprotein when 1% of total energy intake as SFA is replaced with an isocaloric amount of *cis*-PUFA, *cis*-MUFA or carbohydrates as indicated in the blue subheadings.

[10] The *cis*-PUFA being isocalorically exchanged with SFA in individual studies assessing serum lipid and lipoprotein outcomes were linoleic acid and α-linolenic acid.

[11] The *cis*-MUFA being isocalorically exchanged with SFA in individual studies assessing serum lipid and lipoprotein outcomes was predominantly oleic acid.

[12] The 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.

[13] The carbohydrates being isocalorically exchanged with SFA in individual studies assessing serum lipid outcomes were a mixture mono-, di- and polysaccharides, however, the number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrates used in the studies was limited.

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