Effects of *trans*-fatty acid intake on blood lipids and lipoproteins: a systematic review and meta-regression analysis

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World Health Organization

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Abbreviations and acronyms

ApoA-I	apolipoprotein A-I
ApoB	apolipoprotein B
cis-MUFA	*cis*-monounsaturated fatty acids
cis-PUFA	*cis*-polyunsaturated fatty acids
CHD	coronary heart disease
CI	confidence interval
CLA	conjugated linoleic acid
CVD	cardiovascular disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
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

Cardiovascular disease (CVD) is one of the major causes of death globally, and accounts for a significant portion of premature deaths (i.e. death before the age of 70) *(1)*. A diet with a high intake of industrial *trans*-fatty acids (TFA) has been shown to elevate low-density lipoprotein (LDL) cholesterol and modify other blood lipids and lipoproteins *(2–4)*, and is associated with increased risk of CVD *(5–8)*.

TFA are unsaturated fatty acids with at least one double bond in the *trans* configuration. They can be divided into two groups, depending on their origin. Industrial TFA are formed by partial hydrogenation of vegetable or fish oils, whereas ruminant TFA are formed by biohydrogenation in the rumen of cows and sheep *(9, 10)*. The same isomers are present in both industrial and ruminant TFA, but the proportions differ *(11, 12)*.

This document summarizes the evidence for the effect of TFA intake, of both industrial and ruminant origin, on risk factors for CVD. The evidence is based on a systematic review and meta-regression analysis that took into account only controlled intervention studies conducted in humans.

1.2 Objectives

The aim of this review and meta-regression analysis was to assess the effect of modifying TFA intake on blood lipid and lipoprotein levels by exchanging TFA with *cis*-monounsaturated fatty acids (*cis*-MUFA), *cis*-polyunsaturated fatty acids (*cis*-PUFA), saturated fatty acids (SFA) or carbohydrates, in order to inform and contribute to the development of updated WHO recommendations on TFA intake.

2. Methods

This systematic review and meta-regression analysis were conducted in accordance with the WHO guideline development process *(13)*. As part of the evidence review, results of the meta-regression analysis were evaluated using the methodology of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group *(14)*. Results of the systematic review and meta-regression analysis and GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health, as part of WHO's 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.

2.1 Criteria for selecting studies to include in this review

2.1.1 Study characteristics

Study design

Included were randomized controlled trials (RCTs) with at least one intervention group with either increased industrial TFA or ruminant TFA intake, compared to a control group or control diet, including parallel and crossover or Latin square designs. The review excluded before-and-after (sequential) designs that lacked a control group, and studies that only compared one type of TFA to another.

The review included only strictly controlled dietary studies, based on the following inclusion criteria:

- food intake had to be fully controlled and thoroughly described, with dietary fatty acids as the sole variable; and
- cholesterol intake had to be constant (otherwise it would be difficult to reliably identify the independent effects of fatty acids or dietary cholesterol because, generally, animal fats high in SFA are high in dietary cholesterol, and vegetable oils high in unsaturated fatty acids are low in cholesterol) and, if necessary, cholesterol intake was kept constant by using eggs or egg yolk, or by adding crystalline cholesterol to the diets.

Participants

Subjects included adults (aged >17 years) of either gender from the general population. Studies in apparently healthy populations that did not have disturbances of lipid metabolism or diabetes were considered, as were studies in individuals with chronic conditions such as overweight or obesity, as long as they maintained a stable weight during the study. Studies targeting those who were pregnant, acutely ill or had chronic infections such as human immunodeficiency virus (HIV) were excluded.

Interventions

Interventions included those that were aimed at modifying TFA intake directly via provision of food and that reported an outcome of interest. Treatment periods had to be at least 13 days, because that is the minimum period to achieve a new steady-state concentration of plasma lipids and lipoproteins *(15, 16)*. Trials in which subjects lost or gained significant amounts of weight (because this would have an effect on blood lipids and lipoproteins independent of dietary composition) *(2, 17)*, those that aimed for weight loss in one arm but not the other, and those with multifactorial interventions were excluded.

In line with chemical nomenclature, this review designates all fatty acids with at least one double bond in the *trans* configuration as TFA. In the calculation of dietary TFA intakes per diet or dietary group, all TFA (i.e. total TFA) were included, irrespective of the source (industrial or ruminant). For each study, the difference in total TFA intake between the intervention and control diet was determined by subtracting the total TFA intake in the control diet from the total TFA intake in the treatment diet.

2.1.2 Outcomes

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

2.2 Data collection and analysis

2.2.1 Identification of studies

Search strategy

The basis for this review was the 2010 quantitative review of Brouwer et al. (*3*). The search was repeated in 2014, and was limited to original research papers of human studies published in English from 1990 and later. The search terms are found in **Annex 3**.

Databases

The database searched was PubMed (from January 1990 to September 2014).

Additional resources

Reference lists of identified papers were hand-searched for additional, relevant citations.

2.2.2 Data extraction and management

Workflow

For studies meeting the inclusion criteria, data were extracted using standard forms. A sample data extraction form is provided in **Annex 4**.

Analysis

The intakes of industrial and ruminant TFA varied widely across studies, and the association between TFA intake and change in blood lipids and lipoproteins is highly dose-dependent. Therefore, the data were analysed via meta-regression rather than pooling mean differences across studies. It was reasoned that meta-regression would give a clearer, more informative picture of the relationship between TFA intake and blood lipids and lipoproteins. It was further thought that assessing the effects of different replacement nutrients would be facilitated by use of regression analysis as described in **Calculation of effect size** below.

Sources of TFA

The main body of evidence on the effects of TFA intake on blood lipids and lipoproteins comes from studies of industrial TFA intake, with a limited number of studies involving interventions to modify intake of ruminant TFA. Studies in which the intervention consisted of modifying industrial TFA intake were analysed separately from those in which the intervention consisted of modifying ruminant TFA intake. Results of these analyses and visual inspection of the regression lines indicated that, for most outcomes, the small number of ruminant TFA studies provided similar results to those of studies of industrial TFA. Previous analysis had also suggested that the effects on blood lipids and lipoproteins were similar between ruminant and industrial TFA *(3)*. Therefore, in addition to separate analyses for studies of industrial TFA and ruminant TFA, a combined analysis of all TFA studies was undertaken.

Calculation of effect size

In the studies included in the meta-regression analyses, differences in TFA intake were achieved by replacing other nutrients with isocaloric amounts of TFA. The other nutrients were *cis*-MUFA, *cis*-PUFA and SFA, or a combination of the three. To compare studies, *cis*-MUFA was chosen as the common reference nutrient. Hence, all dietary intake values were converted to *cis*-MUFA equivalents using formulae developed from the work of Mensink *(18)*, which provides regression coefficients estimating the change in serum lipids and lipoproteins when SFA (total, and separately for lauric, myristic, palmitic and stearic acids), *cis*-MUFA or *cis*-PUFA are exchanged isocalorically with carbohydrates.

Once the values had been converted to *cis*-MUFA equivalents, they were used as independent variables (in the form of percentage of TFA replaced isocalorically by *cis*-MUFA) in meta-regression, with changes in blood lipids and lipoproteins as dependent variables. Employing the same formulae used to create *cis*-MUFA equivalents, dietary intake information was converted to carbohydrates, *cis*-PUFA and SFA, such that comparisons of replacing TFA with isocaloric amounts of each of these nutrients could be made. As with *cis*-MUFA, meta-regression was performed with the other nutrients (in the form of percentage of TFA isocalorically replaced by the nutrient) as independent variables, and changes in blood lipids and lipoproteins as dependent variables.

The model developed by regression analysis also allows assessment of the effects on blood lipids and lipoproteins when *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates are isocalorically replaced with TFA. The regression coefficients are the opposite of those obtained for analysis of replacing TFA with *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates, and provide estimates of the effect on a given blood lipid or lipoprotein when 1% of total energy intake from the other nutrients is isocalorically replaced with TFA.

To maintain uniformity, the LDL cholesterol to HDL cholesterol ratio was recalculated from mean LDL cholesterol and HDL cholesterol levels for all studies, as was the total cholesterol to HDL cholesterol ratio, even where ratios had been reported in the studies. If energy intake values were provided, these were used to determine energy percentage of TFA intake. Studies were weighted for size using the number of participants (N) with weighted least square regression. Regression lines were forced through the origin because a zero change in diet should produce a zero change in blood lipids. Study points and regression lines that are not weighted for study size are presented as figures. Microsoft Excel, IBM SPSS version 22.0, Prism GraphPad and RevMan 5.1 were used to perform the calculations, conduct the analyses and produce the figures.

The validity of the model was tested by residuals analysis for the main outcome parameter, LDL cholesterol, when replaced with *cis*-MUFA.

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 *(19)*, 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 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.

Publication bias

Publication bias was assessed by funnel plot analysis for all outcomes.

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 the study at risk of bias. We also considered potential areas of bias unique to crossover study designs, including suitability of study design and conduct, selection of study participants and formation of treatment groups and intervention implementation.

3. Results

3.1 Search results

The basis for this review was the 2010 quantitative review of Brouwer et al. *(3)*, which identified 28 papers. The search was repeated in 2014, and identified six new papers on ruminant TFA. Eighteen studies were not included in the meta-regression because they did not fulfil our inclusion criteria (**Table 2**). This review included 16 studies, of which 13 investigated effects of industrial TFA (18 comparisons) and four investigated effects of ruminant TFA (five comparisons); one study *(20)* investigated the effects of both industrial and ruminant TFA (**Figure 1** and **Table 1**).

3.2 Included studies

Characteristics of included studies are described in detail below and summarized in **Table 1**.

3.2.1 Settings

All included studies were conducted in developed countries in Europe or North America. Five of the industrial TFA studies were performed in the United States of America (USA) *(21–25)*, four in the Netherlands *(26–29)*, two in Scandinavia *(30, 31)*, one in Canada *(20)* and one in the United Kingdom of Great Britain and Northern Ireland *(32)*. Three of the ruminant TFA studies were performed in Canada *(20, 33, 34)* and one in the USA *(35)*.

3.2.2 Study design

All included studies were RCTs. Study duration ranged from 14 days to 8 weeks for each intervention period. All studies were highly controlled dietary trials and all but two *(30, 35)* employed a crossover or Latin square design.

3.2.3 Participants

In total, 680 people participated in the studies of total TFA (industrial and ruminant TFA combined): 585 in the studies of industrial TFA intake and 133 in the studies of ruminant TFA intake (38 people participated in studies assessing both industrial and ruminant TFA intake). The number of participants ranged from 16 *(34)* to 80 *(30)*. The study with the greatest number of participants had a parallel design *(30)*, and the largest study with crossover design had 61 participants *(27)*. Nine studies were performed in men and women *(21–24, 26-30)*, two in women only *(33, 35)* and five in men only *(20, 25, 31, 32, 34)*. Data for men and women have been analysed together for this review. Ages ranged from 18 years to over 70 years.

3.2.4 Interventions

The 16 included studies were dietary controlled intervention studies in which 90% or more of the food was supplied and intake was supervised at least five times a week.

Diets high in industrial TFA were compared with a control diet. Four studies of industrial TFA intake had a control diet that was based mainly on *cis*-MUFA *(24, 25, 28, 32)*, one had a control diet consisting mainly of stearic acid *(30)*, and two had a control diet that was based on SFA *(29)* or butter *(31)*. The other industrial TFA studies used *cis*-MUFA, *cis*-PUFA or a combination of fatty acids as control treatments. Intakes of industrial TFA in the studies ranged from 0% to 10.9% of total energy intake, and measured differences in intakes between control and treatment groups ranged from 0.36% to 10.9% of total energy intake.

The studies of ruminant TFA either compared a diet rich in ruminant TFA with a control diet *(20, 33)*, or compared a diet or foods naturally enriched with conjugated linoleic acid (CLA) *(34, 35)* with a control diet. Ruminant TFA intakes in these studies were generally lower than the amounts of TFA provided in the studies of industrial TFA intake. Intakes in the ruminant TFA studies ranged from 0.1% to 3.6% of total energy intake, and the measured differences in intakes between control and treatment groups ranged from 0.27% to 2.9% of total energy intake.

3.2.5 Outcome measures

All 16 studies reported total cholesterol, LDL cholesterol and triglyceride levels, 15 reported HDL levels, and 13 studies reported ApoB (11 of which also reported ApoA-I). **Table 3** shows relevant outcomes measured in each study.

3.3 Excluded studies

We excluded 18 studies that compared TFA intake with a control diet but did not fulfil our inclusion criteria. **Table 2** summarizes the characteristics of these studies and the reasons for exclusion. The main reasons were that participants were already included in other studies in this review, the diet was not fully controlled, cholesterol was not constant over the diets or the studies used a sequential design.

3.4 Effects of interventions

3.4.1 Effect estimates for replacement of TFA with *cis*-MUFA, *cis*-PUFA, carbohydrates or SFA

As indicated in **Section 2**, all values were originally calculated for replacement of TFA by *cis*-MUFA only. The coefficients of Mensink *(18)* were subsequently used to recalculate the effects of replacing industrial or ruminant TFA with either carbohydrates, a mix of SFA or a mix of *cis*-PUFA.

3.4.1.1 Replacement with *cis*-MUFA

Results of replacement with *cis*-MUFA are summarized in **Table 4**. **Figures 2-9** show the individual study points and regression lines (not weighted for study size).

Industrial TFA

Results from meta-regression of industrial TFA studies demonstrate that for each 1% of dietary energy[1] as industrial TFA replaced with an equivalent amount of *cis*-MUFA there is a:

- significant decrease[2] in total cholesterol of 0.027 mmol/L (95% CI: −0.036, −0.018) (**Figure 2a**), in LDL cholesterol of 0.034 mmol/L (95% CI: −0.042, −0.027) (**Figure 3a**), in triglycerides of 0.013 mmol/L (95% CI: −0.022, −0.003; $P = 0.01$) (**Figure 5a**), in the total cholesterol to HDL cholesterol ratio of 0.049 (95% CI: −0.060, −0.037) (**Figure 6a**) and in the LDL cholesterol to HDL cholesterol ratio of 0.044 (95% CI: −0.054, −0.033) (**Figure 7a**);
- significant increase[2] in HDL cholesterol of 0.010 mmol/L (95% CI: 0.006, 0.015) (**Figure 4a**);
- non-significant increase in ApoA-I of 0.84 mg/dL (95% CI: −0.62, 2.29; $P = 0.24$) (**Figure 8a**); and
- non-significant decrease in ApoB of 1.25 mg/dL (95% CI: −2.66, 0.17; $P = 0.08$) (**Figure 9a**).

Ruminant TFA

Results from meta-regression of ruminant TFA studies demonstrate that for each 1% of dietary energy as ruminant TFA replaced with an equivalent amount of *cis*-MUFA there is a:

- significant decrease[2] in LDL cholesterol of 0.052 mmol/L (95% CI: −0.097, −0.006; $P = 0.035$) (**Figure 3b**);

[1] As a percentage of total energy intake

[2] $P < 0.001$ unless otherwise noted

- non-significant decrease in total cholesterol of 0.041 mmol/L (95% CI: −0.090, 0.009; *P* = 0.09) (**Figure 2b**), in the total cholesterol to HDL cholesterol ratio of 0.051 (95% CI: −0.134, 0.032; *P* = 0.15) (**Figure 6b**), in the LDL cholesterol to HDL cholesterol ratio of 0.053 (95% CI: −0.125, 0.019; *P* = 0.10) (**Figure 7b**) and in ApoB of 0.17 mg/dL (95% CI: −1.38, 1.04; *P* = 0.69) (**Figure 9b**); and
- non-significant increase in HDL cholesterol of 0.008 mmol/L (95% CI: −0.017, 0.033; *P* = 0.42) (**Figure 4b**), in triglycerides of 0.008 mmol/L (95% CI: −0.049, 0.065; *P* = 0.72) (**Figure 5b**) and in ApoA-I of 0.86 mg/dL (95% CI: −17.8, 16.1; *P* = 0.85) (**Figure 8b**).

Total TFA

Results from meta-regression of total TFA studies (13 industrial TFA studies combined with four ruminant TFA studies) demonstrate that for each 1% of dietary energy as total TFA replaced with an equivalent amount of *cis*-MUFA there is a:

- significant decrease[1] in total cholesterol of 0.027 mmol/L (95% CI: −0.035, −0.019) (**Figure 2c**), in LDL cholesterol of 0.035 mmol/L (95% CI: −0.042, −0.028) (**Figure 3c**), in triglycerides of 0.012 mmol/L (95% CI: −0.021, −0.004; *P* = 0.006) (**Figure 5c**), in the total cholesterol to HDL cholesterol ratio of 0.049 (95% CI: −0.059, −0.038) (**Figure 6c**), in the LDL cholesterol to HDL cholesterol ratio of 0.044 (95% CI: −0.053, −0.034) (**Figure 7c**) and in ApoB of 1.23 mg/dL (95% CI: −2.44, −0.14; *P* = 0.048) (**Figure 9c**);
- significant increase[1] in HDL cholesterol of 0.010 mmol/L (0.007, 0.014) (**Figure 4c**); and
- non-significant increase in ApoA-I of 0.84 mg/dL (95% CI: −0.50, 2.17; *P* = 0.20) (**Figure 8c**).

3.4.1.2 Replacement with *cis*-PUFA

Results are summarized in **Table 5**.

Industrial TFA

Results from meta-regression of industrial TFA studies demonstrate that for each 1% of dietary energy as industrial TFA replaced with an equivalent amount of *cis*-PUFA, there is a:

- significant decrease[1] in total cholesterol of 0.045 mmol/L (95% CI: −0.054, −0.036), in LDL cholesterol of 0.047 mmol/L (95% CI: −0.055, −0.040), in triglycerides of 0.017 mmol/L (95% CI: −0.027, −0.008; *P* = 0.001), in the total cholesterol to HDL cholesterol ratio of 0.059 (95% CI: −0.071, −0.047), in the LDL cholesterol to HDL cholesterol ratio of 0.052 mmol/L (95% CI: −0.064, −0.040), in ApoA-I of 1.64 mg/dL (95% CI: −2.82, −0.47) and in ApoB of 3.10 mg/dL (95% CI: −4.44, −1.76; *P* = 0.001); and
- significant increase[1] in HDL cholesterol of 0.008 mmol/L (95% CI: 0.004, 0.013; *P* = 0.001).

Ruminant TFA

Results from meta-regression of ruminant TFA studies demonstrate that for each 1% of dietary energy as ruminant TFA replaced with an equivalent amount of *cis*-PUFA there is a:

- significant decrease[1] in total cholesterol of 0.058 mmol/L (95% CI: −0.109, −0.008; *P* = 0.032), in LDL cholesterol of 0.064 mmol/L (95% CI: −0.110, −0.018; *P* = 0.018) and in ApoB of 2.63 mg/dL (95% CI: −3.76, −1.51; *P* = 0.005);
- non-significant decrease in the total cholesterol to HDL cholesterol ratio of 0.059 (95% CI: −0.142, 0.024; *P* = 0.11), in the LDL cholesterol to HDL cholesterol ratio of 0.059 (95% CI: −0.131, 0.013; *P* = 0.08) and in ApoA-I of 2.29 mg/dL (95% CI: −19.55, 14.97; *P* = 0.63); and
- non-significant increase in HDL cholesterol of 0.006 mmol/L (95% CI: −0.019, 0.031; *P* = 0.54) and in triglycerides of 0.003 mmol/L (95% CI: −0.054, 0.060; *P* = 0.89).

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[1] *P* < 0.001 unless otherwise noted

Total TFA

Results from meta-regression of total TFA studies demonstrate that for each 1% of dietary energy as total TFA replaced with an equivalent amount of *cis*-PUFA there was a:

- significant decrease[1] in total cholesterol of 0.045 mmol/L (95% CI: −0.053, −0.037), in LDL cholesterol of −0.048 mmol/L (95% CI: −0.055, −0.041), in triglycerides of 0.017 mmol/L (95% CI: −0.026, −0.009), in the total cholesterol to HDL cholesterol ratio of 0.059 mmol/L (95% CI: −0.070, −0.048), in the LDL cholesterol to HDL cholesterol ratio of 0.052 (95% CI: −0.063, −0.042), in ApoA-I of 1.65 mg/dL (95% CI: −2.75, −0.55; P = 0.005) and in ApoB of 3.09 mg/dL (95% CI: −4.27, −1.91); and
- significant increase[1] in HDL cholesterol of 0.008 mg/dL (95% CI: 0.005, 0.012).

3.4.1.3 Replacement with carbohydrates

Results are summarized in **Table 6.**

Industrial TFA

Results from meta-regression of industrial TFA studies demonstrate that for each 1% of dietary energy as industrial TFA replaced with an equivalent amount of carbohydrates there is a:

- significant decrease[1] in total cholesterol of 0.023 mmol/L (95% CI: −0.032, −0.014), in LDL cholesterol of 0.025 mmol/L (95% CI: −0.033, −0.018), in the total cholesterol to HDL cholesterol ratio of 0.024 (95% CI: −0.038, −0.010; *P* = 0.002), in the LDL cholesterol to HDL cholesterol ratio of 0.024 (95% CI: −0.038, −0.011; *P* = 0.001) and in ApoA-I of 3.25 mg/dL (95% CI: −4.75, −1.75);
- significant increase[1] in ApoB of 2.36 mg/dL (95% CI: 1.13, 3.59; *P* = 0.001); and
- non-significant increase in HDL cholesterol of 0.003 mmol/L (95% CI: −0.002, 0.007; *P* = 0.25) and in triglycerides of 0.003 mmol/L (95% CI: −0.006, 0.013; *P* = 0.44).

Ruminant TFA

Results from meta-regression of ruminant TFA studies demonstrate that for each 1% of dietary energy as ruminant TFA replaced with an equivalent amount of carbohydrates there is a:

- significant increase[1] in ApoB of 4.17 mg/dL (95% CI: 2.79, 5.55; *P* = 0.002);
- non-significant decrease in total cholesterol of 0.037 mmol/L (95% CI: −0.086, 0.013; *P* = 0.11), in LDL cholesterol of 0.043 mmol/L (95% CI: −0.088, 0.003; *P* = 0.06), in the total cholesterol to HDL cholesterol ratio of 0.024 (95% CI: −0.109, 0.061; *P* = 0.44), in the LDL cholesterol to HDL cholesterol ratio of 0.029 (95% CI: −0.102, 0.043; *P* = 0.29) and in ApoA-I of 4.55 mg/dL (95% CI: −22.04, 12.94; *P* = 0.38); and
- non-significant increase in triglycerides of 0.024 mmol/L (95% CI: −0.033, 0.081; *P* = 0.31).

There was no change observed in HDL cholesterol (0 mmol/L [95% CI: −0.025, 0.025; *P* = 0.99]).

Total TFA

Results from meta-regression of total TFA studies demonstrate that for each 1% of dietary energy as total TFA replaced with an equivalent amount of carbohydrates there is a:

- significant decrease[1] in total cholesterol of 0.023 mmol/L (95% CI: −0.031, −0.015), in LDL cholesterol of 0.026 mmol/L (95% CI: −0.033, −0.019), in the total cholesterol to HDL cholesterol ratio of 0.024 (95% CI: −0.037, −0.012), in the LDL cholesterol to HDL cholesterol ratio of 0.024 (95% CI: −0.036, −0.012) and in ApoA-I of 3.26 mg/dL (95% CI: −4.66, −1.87);
- significant increase[1] in ApoB of 2.38 mg/dL (95% CI: 1.29, 3.48); and

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[1] *P* < 0.001 unless otherwise noted

- non-significant increase in HDL cholesterol of 0.002 mmol/L (95% CI: −0.001, 0.006; *P* = 0.20) and in triglycerides of 0.004 mmol/L (95% CI: −0.005, 0.012; *P* = 0.36).

3.4.1.4 Replacement with SFA

Results are summarized in **Table 7.**

Industrial TFA

Results from meta-regression of industrial TFA studies demonstrate that for each 1% of dietary energy as industrial TFA replaced with an equivalent amount of SFA there is a:

- significant decrease[1] in total cholesterol to HDL cholesterol ratio of 0.023 (95% CI: −0.035, −0.010; *P* = 0.002) and in the LDL cholesterol to HDL cholesterol ratio of 0.018 (95% CI: −0.030, −0.005; *P* = 0.009);
- significant increase[1] in total cholesterol of 0.022 mmol/L (95% CI: 0.013, 0.031), in LDL cholesterol of 0.010 mmol/L (95% CI: 0.002, 0.018; *P* = 0.01), in HDL cholesterol of 0.013 mmol/L (95% CI: 0.009, 0.018), in ApoA-I of 2.61 mg/dL (95% CI: 1.25, 3.97; *P* = 0.001) and in ApoB of 5.21 mg/dL (95% CI: 3.40, 7.03); and
- non-significant decrease in triglycerides of 0.009 mmol/L (95% CI: −0.018, 0.001; *P* = 0.07).

Ruminant TFA

Results from meta-regression of ruminant TFA studies demonstrate that for each 1% of dietary energy as ruminant TFA replaced with an equivalent amount of SFA there is a:

- significant increase[1] in ApoB of 7.81 mg/dL (95% CI: 6.27, 9.36; *P* = 0.001);
- non-significant decrease in LDL cholesterol of 0.007 mmol/L (95% CI: −0.051, 0.037; *P* = 0.67), in the total cholesterol to HDL cholesterol ratio of 0.022 (95% CI: −0.106, 0.062; *P* = 0.47) and in the LDL cholesterol to HDL cholesterol ratio of 0.024 (95% CI: −0.096, 0.048; *P* = 0.37); and
- non-significant increase in total cholesterol of 0.008 mmol/L (95% CI: −0.040, 0.055; *P* = 0.68), in HDL cholesterol of 0.011 mmol/L (95% CI: −0.014, 0.035; *P* = 0.28), in triglycerides of 0.012 (95% CI: −0.045, 0.069; *P* = 0.59) and in ApoA-I of 3.71 mg/dL (95% CI: −12.95, 20.36; *P* = 0.44).

Total TFA

Results from meta-regression of total TFA studies demonstrate that for each 1% of dietary energy as total TFA replaced with an equivalent amount of SFA there is a:

- significant decrease[1] in the total cholesterol to HDL cholesterol ratio of 0.023 (95% CI: −0.034, −0.011; *P* = 0.001) and in the LDL cholesterol to HDL cholesterol ratio of 0.018 (95% CI: −0.029, −0.006; *P* = 0.004);
- significant increase[1] in total cholesterol of 0.022 mmol/L (95% CI: 0.014, 0.030), in LDL cholesterol of 0.010 mmol/L (95% CI: 0.003, 0.017; *P* = 0.007), in HDL cholesterol of 0.013 mmol/L (95% CI: 0.010, 0.017), in ApoA-I of 2.62 mg/dL (95% CI: 1.35, 3.89) and in ApoB of 5.25 mg/dL (95% CI: 3.65, 6.85); and
- non-significant decrease in triglycerides of 0.008 mmol/L (95% CI: −0.017, 0.000; *P* = 0.053).

3.4.2 Effect estimates for replacement of *cis*-MUFA, *cis*-PUFA, carbohydrates or SFA with TFA

Effect estimates for replacement of *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates with TFA are the reverse of what was reported for TFA replacement with *cis*-MUFA, carbohydrates, SFA or *cis*-PUFA in **Section 3.4.1** and are summarized in GRADE evidence profiles 2, 4, 8 and 9 in **Annex 7**.

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[1] *P* < 0.001 unless otherwise noted

3.4.3 TFA intake at less than 1% of total energy intake

The range of TFA intakes reported in the studies included in this analysis was approximately 0–10.9% of total energy intake. All studies included in the analysis had at least one group achieving TFA intake of less than 1% of total energy intake and all but one study had at least one group with TFA intake greater than 1% of total energy intake. The model generated by regression analysis was linear, and demonstrated consistent effects on blood lipids and lipoproteins across all levels of reduction in TFA intake.

3.4.4 Validity of the model

The residuals plot indicates that the relationship between TFA intake and change in LDL cholesterol is fairly consistent across the entire range of TFA intakes (**Annex 5**). In addition, results of the Breusch-Pagan test indicated no significant heteroscedasticity ($P = 0.11$).

3.4.5 Conjugated linoleic acid

Conjugated linoleic acid (CLA) is a minor component of the natural diet. It is always included as part of ruminant TFA in the studies of ruminant TFA intake, and it is impossible to judge its effect apart from the other ruminant TFA in these studies. Studies performed with supplemental, synthetically produced CLA were not included in this analysis, but such studies do not give any indication that CLA behaves significantly differently from other TFA in relation to effects on LDL cholesterol and HDL cholesterol *(3, 26)*.

3.5 Quality of the evidence

The results from the risk of bias assessment indicate that, although there was some uncertainty about the randomization process and blinding (especially of trial personnel) in some studies, this did not pose a serious risk of bias overall (**Annex 6**). Although it is unclear if funnel plot analysis is an appropriate method to assess publication bias in this analysis, given that the results of the studies are highly dependent on the amount of TFA being exchanged for other nutrients, funnel plot analysis was nevertheless conducted. Visual inspection of funnel plots for LDL cholesterol (**Annex 7**) and other outcomes did not reveal any significant asymmetry which suggests publication bias is not present.

The assessment of the quality of evidence for priority outcomes is found in the GRADE evidence profiles (**Annex 8**). With few exceptions, the evidence for an effect of replacing industrial or total TFA with *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates on all outcomes was judged to be high. Depending on replacement nutrient, triglycerides, ApoA-I, ApoB and HDL cholesterol were judged to be of moderate quality due to serious imprecision (**Annex 8,** GRADE evidence profiles 1, 2 and 5–7). The judgements for all outcomes when replacing *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates with industrial or total TFA (**Annex 8,** GRADE evidence profiles 8 and 9) were identical to those for replacing industrial or total TFA with *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates.

The evidence for an effect of replacing ruminant TFA with *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates on most outcomes was judged to be low, due to serious inconsistency and serious imprecision (**Annex 8,** GRADE evidence profile 3). Exceptions to this were the effect on LDL cholesterol when replacing ruminant TFA with *cis*-MUFA or *cis*-PUFA, the effect on total cholesterol when replacing ruminant TFA with *cis*-PUFA, and the effect on ApoB when replacing ruminant TFA with *cis*-PUFA, SFA or carbohydrates, all of which were judged to be of moderate quality for serious inconsistency only. The judgements for all outcomes when replacing *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates with ruminant TFA (**Annex 8,** GRADE evidence profile 4) were identical to those for replacing ruminant TFA with *cis*-MUFA, *cis*-PUFA, SFA or carbohydrates.

4. Discussion

4.1 Industrial, ruminant and total TFA

The results of this meta-regression analysis show clearly and consistently that reducing intake of total or industrial TFA by replacing either with *cis*-MUFA or *cis*-PUFA, and to a lesser extent, carbohydrates, improves the lipid and lipoprotein profiles towards reduced risk of CVD. The results on ruminant TFA studies were less conclusive, because of the limited number of high-quality ruminant TFA studies meeting the inclusion criteria. Although there is some inconsistency across the individual ruminant TFA studies (primarily in studies with small contrasts), and the meta-regression analysis did not provide clear answers for some outcomes, analysis of effects on LDL cholesterol did show that replacement of ruminant TFA by either *cis*-MUFA or *cis*-PUFA led to significantly lower levels of LDL cholesterol. Furthermore, with the exception of the effect on triglycerides, replacement of ruminant TFA by either *cis*-MUFA or *cis*-PUFA led to results in the same direction as replacement of industrial TFA.

Industrial and ruminant TFA have historically been considered separately, based on the perception that the difference in chemical composition represents a possible difference in function, despite the fact that both industrial and ruminant TFA contain the same TFA isomers, albeit in different proportions *(11, 12)*. Although the number of high-quality ruminant TFA studies meeting the inclusion criteria for this study was limited, the results of this and a previous analysis *(3)* suggest that the effect on blood lipids resulting from changes in ruminant or industrial TFA are similar, and therefore that assessing them together is a sound approach. Furthermore, results of a study that was published after this analysis was completed, show that a diet enriched with the predominant TFA isomer in ruminant TFA, vaccenic acid, not only raises LDL cholesterol significantly compared to a control diet, but also in comparison to a diet high in industrial TFA *(39)*, further lending support to the conclusion that the effect of industrial and ruminant TFA on blood lipids is similar.

The results of this meta-regression analysis suggest that the effects observed for ruminant studies may actually have been a result of differences in dose rather than type of TFA. As noted, the difference in intake between the treatment and the control diets, as well as the absolute intakes, were generally smaller than in the industrial TFA studies. For example, in the study of Brown et al. *(35)* the difference in intake between the treatment and the control was only 0.27% of total energy intake. Small contrasts and low absolute intakes make it more difficult to pick up any effects if present. This is not unique to ruminant TFA. If the only studies available for industrial TFA also had small contrasts and absolute intakes, it would again have been difficult to pick up an effect. In fact, only one study included in the industrial TFA analysis contributed a data point with a contrast of less than 1% of total energy intake and absolute intakes of less than 1% of total energy intake *(23)*, and the corresponding impact on blood lipids was negligible. In contrast, other data points within the same study, with larger contrasts and absolute intakes of industrial TFA, did show significant effects on blood lipid profiles. The main reason that the intake in the ruminant TFA studies was smaller is because it is difficult to design diets comprising natural, unmodified foods with high intakes of ruminant TFA. This suggests that in current real-world settings, intakes of ruminant TFA are generally low, which would correspond to a small resulting risk of negative health effects. However, with declining intake of industrial TFA in many European countries, intake of ruminant TFA is now exceeding intake of industrial TFA in many populations *(36)*.

4.2 Selecting the method of analysis

Studies included in this overview were selected on the basis of strict inclusion criteria. Those most likely to give the most precise estimate of a true effect of the studied fat are studies in which the diet is fully controlled, in which participants are weight stable and in which cholesterol intakes are kept constant. Earlier studies reporting specifically on ruminant TFA used more relaxed inclusion criteria *(3, 37, 38)*. However, including less controlled studies gives a higher chance of introducing less precise and more biased estimates of the effect of TFA, and thereby a lower chance of measuring a true effect.

The main reasons for choosing a linear regression model, as explained in an earlier publication *(3)*, are that it fits the data and it is biologically plausible. A zero exposure will always result in a zero response and, therefore, the regression lines were forced through zero. Furthermore, the sizes of the included studies are taken into account by weighting for N. A critical assumption for linear modelling is that the residuals are randomly dispersed around the x-axis. To assess appropriateness of the model developed for the present analysis, we conducted a residuals analysis for the main outcome parameter, LDL cholesterol, when TFA were replaced with *cis*-MUFA. The residuals plot indicated that the residuals and the fitted values were uncorrelated, which suggests normally distributed errors and homoscedasticity, indicating that the model is appropriate for these data (**Annex 5**).

4.3 TFA intake at less than 1% of total energy intake

The population nutrient intake goal for TFA recommended by the joint WHO/FAO expert consultation *(39)* is less than 1% of total energy intake. Studies included in the regression analysis reported a wide range of TFA intakes, from 0–10.9% of total energy intake and the model generated by regression analysis was linear, demonstrating a consistent effect on blood lipids and lipoproteins across all levels of reduction (or increase) in TFA intake. Additionally, at least one intervention group in every study included in the analysis achieved a TFA intake below 1% of total energy intake. The results of this analysis therefore suggest that reducing TFA intake to less than 1% of total energy intake by replacing TFA with *cis*-PUFA, *cis*-MUFA or carbohydrates may have additional benefit in terms of improving the overall blood lipid profile. Similarly, the results suggest a negative effect on the overall blood lipid profile when increasing TFA intake from a starting point of less than 1% of total energy intake.

4.4 CLA

As indicated in **Section 3.4.5**, CLA is a very small part of the average diet and thus separate analysis of naturally-occurring CLA was not possible. Studies performed with supplemental, synthetically produced CLA were not included in this analysis, but such studies do not give any indication that CLA behaves significantly differently from other TFA in relation to effects on LDL cholesterol and HDL cholesterol *(3, 25)*. The CLA study of Wanders et al. *(27)* was also not included in the meta-regression analysis, as though the diets were fully controlled and met all other inclusion criteria, the ruminant TFA used in the study was in fact synthesized and not from a naturally-occurring source. The outcome of the Wanders et al. study was nevertheless, consistent with the other TFA studies included in the present meta-regression analysis in that total cholesterol, LDL cholesterol and the total cholesterol to HDL cholesterol ratio increased and HDL cholesterol decreased with higher intakes of CLA (i.e. when *cis*-MUFA was replaced with CLA). Results of a study that was published after the present analysis was completed found that, in comparison to a control diet of SFA, CLA intake did not have a significant negative impact on blood lipids and lipoproteins *(40)*. CLA intake in the intervention group was less than 1% of total energy intake, however, and as discussed earlier in **Section 4.1**, intake of any TFA at this level would not be expected to have a significant effect on blood lipids and lipoproteins. Thus the results are consistent with those of other TFA studies presented in this report.

4.5 Choice of replacement

The positive effect of replacement of TFA by *cis*-PUFA and *cis*-MUFA on the blood lipid and lipoprotein profile was quite clear, except for the effect on ApoA-I when TFA were replaced with *cis*-PUFA, which was in the opposite direction.

Replacement with carbohydrates led to some mixed results, which may have been a result of the different types of carbohydrates used as replacement in the studies included in the meta-regression analysis. Detailed analysis of the types of carbohydrates used in each study was not performed and it is possible that replacement with more complex carbohydrates could have had different effects on blood lipids than replacement with refined carbohydrates, as has been shown for replacement of dietary SFA with carbohydrates and cardiovascular outcomes *(41, 42)*.

Replacement by SFA led to lower HDL cholesterol levels and improved ratios of total to HDL cholesterol and of LDL to HDL cholesterol, but increased levels of total cholesterol, LDL cholesterol and ApoB. Studies comparing the effect of substituting SFA for TFA on LDL cholesterol are limited and results of previous meta-analyses are inconclusive as to whether replacing TFA with SFA significantly raises or lowers LDL cholesterol *(2, 43)*. Evidence for an effect on HDL cholesterol and the total cholesterol to HDL cholesterol ratio is more conclusive, with most studies reporting an increase in HDL cholesterol and decreases in the total cholesterol to HDL cholesterol ratio when TFA are replaced with SFA *(2, 43)*.

Taken together, the results suggest that TFA replacement by unsaturated fatty acids leads to the greatest improvement in the lipid and lipoprotein profile, with *cis*-PUFA providing slightly greater benefit than *cis*-MUFA.

5. Conclusion

Replacement of industrial TFA by *cis*-MUFA, *cis*-PUFA or carbohydrates led to increased levels of HDL cholesterol, decreased levels of total cholesterol and LDL cholesterol, and decreases in the total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol ratios, with replacement by *cis*-PUFA showing the strongest effects. Only replacement with *cis*-PUFA showed a significant effect on reducing triglycerides. Replacement of industrial TFA by SFA led to increased levels of total, LDL and HDL cholesterol, and reductions in the ratios of total to HDL cholesterol, and of LDL to HDL cholesterol. Effects on triglycerides, ApoA-I and ApoB were inconsistent.

Although the number of studies of ruminant TFA intake was limited, significant reductions were observed in total and LDL cholesterol when ruminant TFA were replaced with *cis*-PUFA, and in LDL cholesterol when they were replaced with *cis*-MUFA. With the exception of effects on triglycerides and HDL cholesterol when ruminant TFA were replaced with SFA, outcomes for ruminant TFA were in the same direction as for industrial TFA.

The results of all TFA studies indicate that replacement of total TFA (sum of industrial and ruminant TFA) by *cis*-MUFA, *cis*-PUFA or carbohydrates leads to increased levels of HDL cholesterol and decreased levels of total and LDL cholesterol, as well as decreased ratios of total to HDL cholesterol and of LDL to HDL cholesterol, with replacement by *cis*-PUFA showing the strongest effects. Only replacement with *cis*-MUFA and *cis*-PUFA showed a significant effect in reducing triglycerides. Effects on ApoA-I and ApoB were inconsistent. Replacement of TFA by SFA leads to increased levels of ApoA-I, ApoB and total, LDL and HDL cholesterol, and reductions in the ratios of total cholesterol to HDL cholesterol, and LDL cholesterol to HDL cholesterol.

Overall, this meta-regression analysis showed that replacement of TFA from any source by *cis*-PUFA consistently lowers total cholesterol, LDL cholesterol and ApoB for all TFA. It also suggests that replacement of TFA by *cis*-PUFA improves HDL cholesterol, and ratios of total cholesterol to HDL cholesterol, and of LDL cholesterol to HDL cholesterol, in a direction associated with reduced risk of CVD.

6. Tables

Table 1. Characteristics of included TFA studies

Study ID	Citation(s)	Participant characteristics			Study characteristics					
		Average age in years	Average BMI in kg/m^2	Number of participants (male/female)	TFA source	Design	Difference in total TFA intake (absolute intakes)[1]	Duration	Control treatment	Notes
Almendingen 1995	*(31)*	26 (range 21–34)	19–34 (26)	31 (31/0)	Industrial	Crossover	7.6 (0.9, 8.5; PHSO) and 7.1 (0.9, 8.1; PHFO)[2]	19–21 days	Butter	Control treatment butter
Aro 1997	*(30)*	29 (range 20–52)	15.2–32.8 (22.9)	80 (31/49)	Industrial	Parallel	8.3 (0.4, 8.7)	35 days	Stearic acid	Control treatment stearic acid
Brown 2011	*(35)*	20–40 (range)	19–30	18 (0/18)	Ruminant	Parallel	0.27 (0.11, 0.38)	56 days	Mainly palmitic and oleic acids	Cholesterol intakes were not significantly different, but fat intake was
de Roos 2001	*(29)*	30 (SD 16)	22.5 (SD 2.4)	32 (11/21)	Industrial	Crossover	9 (0.3, 9.3)	21–32 days (average 27 days)	SFA	Control treatment is SFA
Desroches 2005	*(34)*	36.6 (SD 12.4)	31.2 (SD 4.4)	16 (16/0)	Ruminant	Crossover	2.2 (0.32, 2.48)	28 days	Mainly SFA	
Judd 1994	*(24)*	42.6 (SD 10.7)	26.4 (SD 3.6)	58 (29/29)	Industrial	Latin square	5.7 (0.7, 6.6) and 3.0 (0.7, 3.8)	42 days	Oleic acid	
Judd 2002	*(25)*	42	26.2	50 (50/0)	Industrial	Crossover	8.2 (0.1, 8.3)	35 days	Corn oil	
Lacroix 2012	*(33)*	38.3 (SD 17.1)	23.6 (SD 2.9)	61 (0/61)	Ruminant	Crossover	1.2 (0.6, 1.8)	28 days	Mainly *cis*-MUFA	
Lichtenstein 1999	*(23)*	63 (SD 6)	27.4 (SD 3)	36 (18/18)	Industrial	Crossover	0.36 (0.91), 2.75 (3.30), 3.60 (4.15), and 6.17 (6.72) – (low intake 0.55 for all)	35 days	Soy bean	
Lichtenstein 2006	*(22)*	63 (SD 8)	26.2 (SD 4.2)	30 (14/16)	Industrial	Crossover	1.9 (0.61, 2.52)	35 days	Soy bean	
Lovejoy 2002	*(21)*	28 (SD 2)	23.5 (SD 0.5)	25 (12/13)	Industrial	Crossover	7.3 (0, 7.3)	28 days	*cis*-MUFA / SFA	
Mensink 1990	*(28)*	Men 25 / women 26	22	59 (25/34)	Industrial	Crossover	10.9 (0, 11)	21 days	Oleic acid	
Motard-Belanger 2008	*(20)*	32.8 (SD 15)	23.6 (SD 3.3)	38 (38/0)	Industrial	Latin square	2.9 (0.8, 3.6)2	28 days	Butter / peanut oil / canola	Difference between TFA and control is in *cis*-MUFA/*cis*-PUFA

Study ID	Citation(s)	Participant characteristics			Study characteristics					
		Average age in years	Average BMI in kg/m^2	Number of participants (male/female)	TFA source	Design	Difference in TFA intake[1]	Duration	Control treatment	Notes
Motard-Belanger 2008	*(20)*	32.8 (SD 15)	23.6 (SD 3.3)	38 (38/0)	Ruminant	Latin square	0.7 (0.8, 1.5) and 2.9 (0.8, 3.6)	28 days	*cis*-MUFA + *cis*-PUFA	
Sanders 2003	*(32)*	24.2 (SD 5.9)	24.2 (SD 2.2)	29 (29/0)	Industrial	Latin square	9.5 (0.1, 9.6)	14 days	Oleic acid	
Wanders 2010	*(27)*	30.9 (SD 13.7)	22.8 (SD 3.2)	61 (25/36)	Industrial	Crossover	7.3 (0.2, 7.5)	21 days	Oleic acid	
Zock 1992	*(26)*	Men 25 / women 24	21.5	56 (26/30)	Industrial	Crossover	7.6 (0.1, 7.7)	21 days	Linoleic acid	

BMI, body mass index; *cis*-MUFA, monounsaturated fatty acids; *cis*-PUFA, polyunsaturated fatty acids; PHFO, partially hydrogenated fish oil; PHSO, partially hydrogenated soybean oil; SD, standard deviation; SFA, saturated fatty acids; TFA, *trans*-fatty acids

[1] Difference between treatment groups expressed as percentage of total energy intake, with absolute intakes of treatment groups in parentheses; slight differences between absolute intakes and reported contrast are the result of rounding up of reported absolute intakes

[2] The higher TFA diets contained less butter fat and, therefore, slightly less ruminant TFA

Table 2. Characteristics of excluded TFA studies

Study ID	Citation(s)	Participant characteristics			Study characteristics					
		Average age in years	Average BMI in kg/m^2	Number of participants (male/female)	TFA source	Design	Difference in TFA intake[1]	Duration	Control treatment	Reasons for exclusion/ Notes
Chardigny 2008	*(44)*	27.6	22.0	40 (19/21)	Industrial and ruminant	Crossover	5.8	21 days	Ruminant TFA / industrial TFA	Treatment is industrial versus ruminant TFA
Dyerberg 2004	*(45)*	20–60 (range)	24.6	79 (79/0)	Industrial	Parallel	5.9	56 days	SFA	Unclear whether cholesterol is kept constant over the groups / Control treatment is SFA
French 2002	*(46)*	Not provided	23.9 (SD 0.8)	10 (0/10)	Industrial	Crossover	5.6	30 days	Palmitic acid	Unclear whether cholesterol is kept constant, or whether weight is stable / Control treatment is palmitic acid
Han 2007	*(47)*	64.7	28.8	19 (8/11)	Industrial	Crossover	6.1	32 days	Soy bean	Population is part of Lichtenstein 1999 study
Lichtenstein 1993	*(48)*	63 (SD 12)	27.4 (SD 4.4)	14 (6/8)	Industrial	Sequential	3.8	28 days	Corn oil	Sequential design
Louheranta 1999	*(49)*	23 (SD 3)	20.8 (SD 2.1)	14 (0/14)	Industrial	Crossover	5.1	28 days	*cis*-MUFA	Diet not fully controlled
Malpuech-Brugère 2010	*(50)*	26 (SD 7)	21.9 (SD 2.5)	107 (54/53)	Ruminant	Parallel	0.32 and 2.41	21 days	SFA + *cis*-MUFA + *cis*-PUFA	Diet not fully controlled
Muller 1998 – BJN	*(51)*	22 (SD 2.7)	23 (SD 2.3)	16 (0/16)	Industrial	Crossover	6.6	14 days	Vegetable oil (*cis*-MUFA + SFA)	Cholesterol not constant
Muller 1998 – Lipids	*(52)*	27 (SD 5.8)	26.5 (SD 4.1)	27 (0/27)	Industrial	Crossover	6.8	17 days	*cis*-PUFA	Cholesterol not constant
Nestel 1992	*(53)*	46.8 (SD 9.6)	Not provided	27 (27/0)	Industrial	Sequential	4.3	21 days	Oleic acid	Sequential design
Sundram 1997	*(54)*	29.4 (SD 4.6)	22.7 (SD 2.6)	29 (20/9)	Industrial	Crossover	5.5	28 days	MUFA	Diet not fully controlled
Sundram 2007	*(55)*	30 (SD 8)	22 (SD 4)	32 (11/21)	Industrial	Crossover	3.2	28 days	Palm oil	Diet not fully controlled
Tholstrup 2006	*(56)*	25.2 (SD 3.9)/ 26.1 (SD 3.6)[2]	23 (SD 2.4)/ 22.5 (SD 2.1)[2]	42 (42/0)	Ruminant	Parallel	1.7	35 days	Mainly SFA and butter group received less fat	Diet not fully controlled
Tricon 2006	*(57)*	45.5 (SD 8.7)	25.0 (SD 3.4)	32 (32/0)	Ruminant	Crossover	2.3	42 days	*cis*-MUFA + *cis*-PUFA + SFA (dairy fat)	Diet not fully controlled

Study ID	Citation(s)	Participant characteristics			Study characteristics					
		Average age in years	Average BMI in kg/m^2	Number of participants (male/female)	TFA source	Design	Difference in TFA intake[1]	Duration	Control treatment	Reasons for exclusion/ Notes
Vega-Lopez 2006	*(58)*	63.9 (SD 5.7)	26 (2.4)	15 (5/10)	Industrial	Crossover	3.6	35 days	Soy bean oil	Industrial TFA treatment is the same as the 3.6 en% group in Lichtenstein 1999
Venkatraman 2010	*(59)*	46.6 (SD 2.0)	25–30 (range)	15 (10/5)	Ruminant	Crossover	1.66	56 days	Untreated milk	Diet not fully controlled
Werner 2013	*(60)*	61.9 (SD 4.9)/ 60.7 (SD 5.9)[2]	25.4 (SD 2.7)/ 26.5 (SD 3.6)[2]	38 (15/23)	Ruminant	Parallel	0.13	84 days	Conventional butter	Diet not fully controlled
Wood 1993	*(61)*	42 (SD 8)	Not provided	38 (38/0)	Ruminant	Latin square	1.01	42 days	Soft margarine with no TFA	Diet not fully controlled

BMI, body mass index; *cis*-MUFA, *cis*-monounsaturated fatty acids; *cis*-PUFA, polyunsaturated fatty acids; en%, percentage of total energy intake; SD, standard deviation; SFA, saturated fatty acids; TFA, *trans*-fatty acids

[1] Difference between treatment groups expressed as percentage of total energy intake
[2] Intervention group / control group

Table 3. Outcomes reported by study

Study ID	Citation(s)	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides	ApoA-I	ApoB
Almendingen 1995	*(31)*	•	•	•	•	•	•
Aro 1997	*(30)*	•	•	•	•	•	•
Brown 2011	*(35)*	•	•		•		
de Roos 2001	*(29)*	•	•	•	•		
Desroches 2005	*(34)*	•	•	•	•		•
Judd 1994	*(24)*	•	•	•	•	•	•
Judd 2002	*(25)*	•	•	•	•	•	•
Lacroix 2012	*(33)*	•	•	•	•	•	•
Lichtenstein 1999	*(23)*	•	•	•	•	•	•
Lichtenstein 2006	*(22)*	•	•	•	•	•	•
Lovejoy 2002	*(21)*	•	•	•	•		
Mensink & Katan 1990	*(28)*	•	•	•	•	•	•
Motard-Belanger 2008	*(20)*	•	•	•	•	•	•
Sanders 2003	*(32)*	•	•	•	•	•	•
Wanders 2010	*(27)*	•	•	•	•		•
Zock 1992	*(26)*	•	•	•	•		

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein;

Table 4. Effect estimates on lipids when TFA are replaced with *cis*-MUFA

Outcome	Studies	Data points	Effect estimate (95% CI)[1]
1.1 Total cholesterol (mmol/L)			
1.1.1 Industrial TFA	13	18	−0.027 (−0.036, −0.018)
1.1.2 Ruminant TFA	4	5	−0.041 (−0.090, 0.009)
1.1.3 Total TFA	16	23	−0.027 (−0.035, −0.019)
1.2 LDL cholesterol (mmol/L)			
1.2.1 Industrial TFA	13	18	−0.034 (−0.042, −0.027)
1.2.2 Ruminant TFA	4	5	−0.052 (−0.097, −0.006)
1.2.3 Total TFA	16	23	−0.035 (−0.042, −0.028)
1.3 HDL cholesterol (mmol/L)			
1.3.1 Industrial TFA	13	18	0.010 (0.006, 0.015)
1.3.2 Ruminant TFA	3	4	0.008 (−0.017, 0.033)
1.3.3 Total TFA	15	22	0.010 (0.007, 0.014)
1.4 Triglycerides (mmol/L)			
1.4.1 Industrial TFA	13	18	−0.013 (−0.022, −0.003)
1.4.2 Ruminant TFA	4	5	0.008 (−0.049, 0.065)
1.4.3 Total TFA	16	23	−0.012 (−0.021, −0.004)
1.5 Total to HDL cholesterol ratio			
1.5.1 Industrial TFA	13	18	−0.049 (−0.060, −0.037)
1.5.2 Ruminant TFA	3	4	−0.051 (−0.134, 0.032)
1.5.3 Total TFA	15	22	−0.049 (−0.059, −0.038)
1.6 LDL to HDL cholesterol ratio			
1.6.1 Industrial TFA	13	18	−0.044 (−0.054, −0.033)
1.6.2 Ruminant TFA	3	4	−0.053 (−0.125, 0.019)
1.6.3 Total TFA	15	22	−0.044 (−0.053, −0.034)
1.7 ApoA-I (mg/dL)			
1.7.1 Industrial TFA	9	14	0.84 (−0.62, 2.29)
1.7.2 Ruminant TFA	2	3	0.86 (−17.8, 16.1)
1.7.3 Total TFA	10	17	0.84 (−0.50, 2.17)
1.8 ApoB (mg/dL)			
1.8.1 Industrial TFA	10	15	−1.25 (−2.66, 0.17)
1.8.2 Ruminant TFA	3	4	−0.17 (−1.38, 1.04)
1.8.3 Total TFA	12	19	−1.23 (−2.44, −0.14)

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; *cis*-MUFA, *cis*-monounsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TFA, *trans*-fatty acids

[1] Regression coefficients: estimates of the predicted change in the mean serum lipid or apolipoprotein concentration or ratio when intake of TFA decreases by 1% of total energy intake and that of *cis*-MUFA increases by the same amount (i.e. isocaloric exchange or replacement). Studies are weighted by study size, by taking the number of subjects (N) into account with weighted least square regression.

Table 5. Effect estimates on lipids when TFA are replaced with *cis*-PUFA

Outcome	Studies	Data points	Effect estimate (95% CI)[1]
1.1 Total cholesterol (mmol/L)			
1.1.1 Industrial TFA	13	18	−0.045 (−0.054, −0.036)
1.1.2 Ruminant TFA	4	5	−0.058 (−0.109, −0.008)
1.1.3 Total TFA	16	23	−0.045 (−0.053, −0.037)
1.2 LDL cholesterol (mmol/L)			
1.2.1 Industrial TFA	13	18	−0.047 (−0.055, −0.040)
1.2.2 Ruminant TFA	4	5	−0.064 (−0.110, −0.018)
1.2.3 Total TFA	16	23	−0.048 (−0.055, −0.041)
1.3 HDL cholesterol (mmol/L)			
1.3.1 Industrial TFA	13	18	0.008 (0.004, 0.013)
1.3.2 Ruminant TFA	3	4	0.006 (−0.019, 0.031)
1.3.3 Total TFA	15	22	0.008 (0.005, 0.012)
1.4 Triglycerides (mmol/L)			
1.4.1 Industrial TFA	13	18	−0.017 (−0.027, −0.008)
1.4.2 Ruminant TFA	4	5	0.003 (−0.054, 0.060)
1.4.3 Total TFA	16	23	−0.017 (−0.026, −0.009)
1.5 Total to HDL cholesterol ratio			
1.5.1 Industrial TFA	13	18	−0.059 (−0.071, −0.047)
1.5.2 Ruminant TFA	3	4	−0.059 (−0.142, 0.024)
1.5.3 Total TFA	15	22	−0.059 (−0.070, −0.048)
1.6 LDL to HDL cholesterol ratio			
1.6.1 Industrial TFA	13	18	−0.052 (−0.064, −0.040)
1.6.2 Ruminant TFA	3	4	−0.059 (−0.131, 0.013)
1.6.3 Total TFA	15	22	−0.052 (−0.063, −0.042)
1.7 ApoA-I (mg/dL)			
1.7.1 Industrial TFA	9	14	−1.64 (−2.82, −0.47)
1.7.2 Ruminant TFA	2	3	−2.29 (−19.55, 14.97)
1.7.3 Total TFA	10	17	−1.65 (−2.75, −0.55)
1.8 ApoB (mg/dL)			
1.8.1 Industrial TFA	10	15	−3.10 (−4.44, −1.76)
1.8.2 Ruminant TFA	3	4	−2.63 (−3.76, −1.51)
1.8.3 Total TFA	12	19	−3.09 (−4.27, −1.91)

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; *cis*-PUFA, *cis*-polyunsaturated fatty acids; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TFA, *trans*-fatty acids

[1] Regression coefficients: estimates of the predicted change in the mean serum lipid or apolipoprotein concentration or ratio when intake of TFA decreases by 1% of total energy intake and that of *cis*-PUFA increases by the same amount (i.e. isocaloric exchange or replacement). Studies are weighted by study size by taking the number of subjects (N) into account with weighted least square regression.

Table 6. Effect estimates on lipids when TFA are replaced with carbohydrates

Outcome	Studies	Data points	Effect estimate (95% CI)[1]
1.1 Total cholesterol (mmol/L)			
1.1.1 Industrial TFA	13	18	−0.023 (−0.032, −0.014)
1.1.2 Ruminant TFA	4	5	−0.037 (−0.086, 0.013)
1.1.2 Total TFA	16	23	−0.023 (−0.031, −0.015)
1.2 LDL cholesterol (mmol/L)			
1.2.1 Industrial TFA	13	18	−0.025 (−0.033, −0.018)
1.2.2 Ruminant TFA	4	5	−0.043 (−0.088, 0.003)
1.2.3 Total TFA	16	23	−0.026 (−0.033, −0.019)
1.3 HDL cholesterol (mmol/L)			
1.3.1 Industrial TFA	13	18	0.003 (−0.002, 0.007)
1.3.2 Ruminant TFA	3	4	0.000 (−0.025, 0.025)
1.3.3 Total TFA	15	22	0.002 (−0.001, 0.006)
1.4 Triglycerides (mmol/L)			
1.4.1 Industrial TFA	13	18	0.003 (−0.006, 0.013)
1.4.2 Ruminant TFA	4	5	0.024 (−0.033, 0.081)
1.4.3 Total TFA	16	23	0.004 (−0.005, 0.012)
1.5 Total to HDL cholesterol ratio			
1.5.1 Industrial TFA	13	18	−0.024 (−0.038, −0.010)
1.5.2 Ruminant TFA	3	4	−0.024 (−0.109, 0.061)
1.5.3 Total TFA	15	22	−0.024 (−0.037, −0.012)
1.6 LDL to HDL cholesterol ratio			
1.6.1 Industrial TFA	13	18	−0.024 (−0.038, −0.011)
1.6.2 Ruminant TFA	3	4	−0.029 (−0.102, 0.043)
1.6.3 Total TFA	15	22	−0.024 (−0.036, −0.012)
1.7 ApoA-I (mg/dL)			
1.7.1 Industrial TFA	9	14	−3.25 (−4.75, −1.75)
1.7.2 Ruminant TFA	2	3	−4.55 (−22.04, 12.94)
1.7.3 Total TFA	10	17	−3.26 (−4.66, −1.87)
1.8 ApoB (mg/dL)			
1.8.1 Industrial TFA	10	15	2.36 (1.13, 3.59)
1.8.2 Ruminant TFA	3	4	4.17 (2.79, 5.55)
1.8.3 Total TFA	12	19	2.38 (1.29, 3.48)

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TFA, *trans*-fatty acids

[1] Regression coefficients: estimates of the predicted change in the mean serum lipid or apolipoprotein concentration or ratio when intake of TFA decreases by 1% of total energy intake and that of carbohydrates increases by the same amount (i.e. isocaloric exchange or replacement). Studies are weighted by study size by taking the number of subjects (N) into account with weighted least square regression.

Table 7. Effect estimates on lipids when TFA are replaced with SFA

Outcome	Studies	Data points	Effect estimate (95% CI)[1]
1.1 Total cholesterol (mmol/L)			
1.1.1 Industrial TFA	13	18	0.022 (0.013, 0.031)
1.1.2 Ruminant TFA	4	5	0.008 (–0.040, 0.055)
1.1.3 Total TFA	16	23	0.022 (0.014, 0.030)
1.2 LDL cholesterol (mmol/L)			
1.2.1 Industrial TFA	13	18	0.010 (0.002, 0.018)
1.2.2 Ruminant	4	5	–0.007 (–0.051, 0.037)
1.2.3 Total TFA	16	23	0.010 (0.003, 0.017)
1.3 HDL cholesterol (mmol/L)			
1.3.1 Industrial TFA	13	18	0.013 (0.009, 0.018)
1.3.2 Ruminant TFA	3	4	0.011 (–0.014, 0.035)
1.3.3 Total TFA	15	22	0.013 (0.010, 0.017)
1.4 Triglycerides (mmol/L)			
1.4.1 Industrial TFA	13	18	–0.009 (–0.018, 0.001)
1.4.2 Ruminant TFA	4	5	0.012 (–0.045, 0.069)
1.4.3 Total TFA	16	23	–0.008 (–0.017, 0.000)
1.5 Total to HDL cholesterol ratio			
1.5.1 Industrial TFA	13	18	–0.023 (–0.035, –0.010)
1.5.2 Ruminant TFA	3	4	–0.022 (–0.106, 0.062)
1.5.3 Total TFA	15	22	–0.023 (–0.034, –0.011)
1.6 LDL to HDL cholesterol ratio			
1.6.1 Industrial TFA	13	18	–0.018 (–0.030, –0.005)
1.6.2 Ruminant TFA	3	4	–0.024 (–0.096, 0.048)
1.6.3 Total TFA	15	22	–0.018 (–0.029, –0.006)
1.7 ApoA-I (mg/dL)			
1.7.1 Industrial TFA	9	14	2.61 (1.25, 3.97)
1.7.2 Ruminant TFA	2	3	3.71 (–12.95, 20.36)
1.7.3 Total TFA	10	17	2.62 (1.35, 3.89)
1.8 ApoB (mg/dL)			
1.8.1 Industrial TFA	10	15	5.21 (3.40, 7.03)
1.8.2 Ruminant TFA	3	4	7.81 (6.27, 9.36)
1.8.3 Total TFA	12	19	5.25 (3.65, 6.85)

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids; TFA, *trans*-fatty acids

[1] Regression coefficients: estimates of the predicted change in the mean serum lipid or apolipoprotein concentration or ratio when intake of TFA decreases by 1% of total energy intake and that of saturated fatty acids increases by the same amount (i.e. isocaloric exchange or replacement). Studies are weighted by study size by taking the number of subjects (N) into account with weighted least square regression.

7. Figures

Figure 1. Flow diagram of study selection

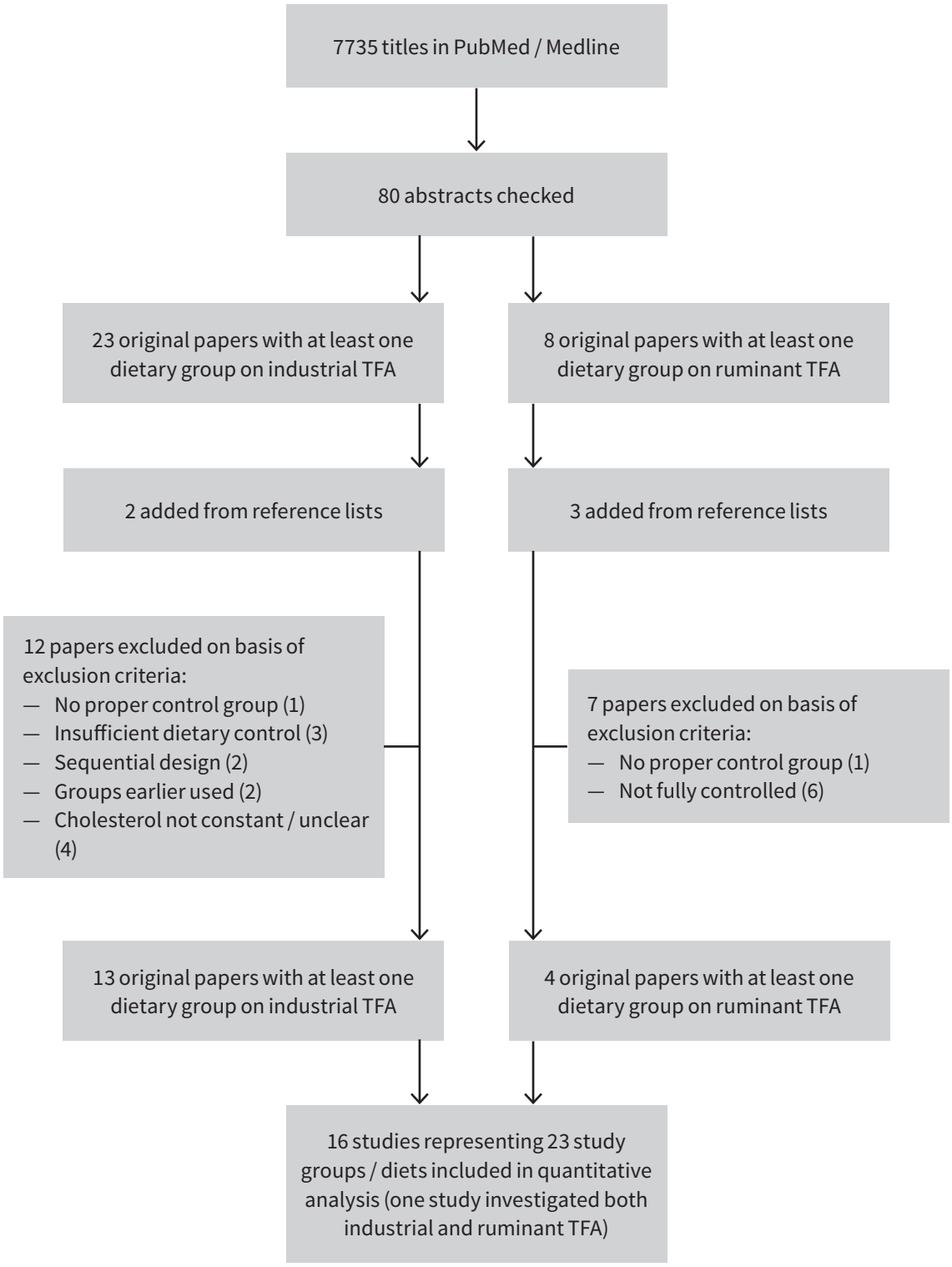
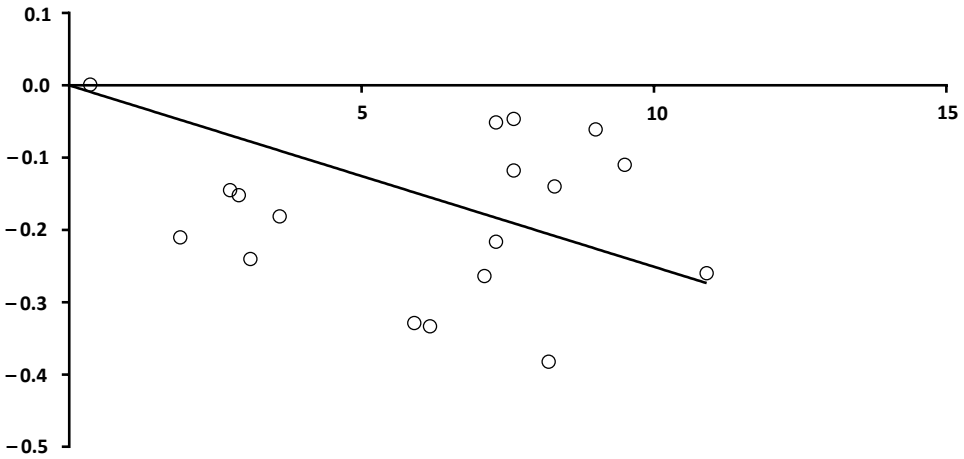


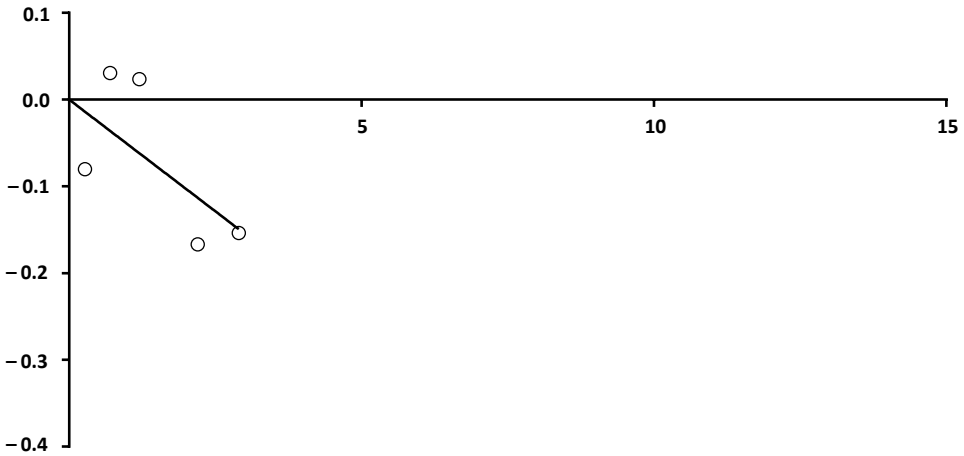
Figure 2. Effect on total cholesterol of replacing TFA with *cis*-MUFA

Effects on total cholesterol when *cis*-MUFA isocalorically replaces industrial TFA (2A), ruminant TFA (2B) or total TFA (2C). Y axis = change in total cholesterol (mmol/L); X axis = amount of TFA replaced with *cis*-MUFA as a a percentage of energy intake. Regression lines are not weighted for study size.

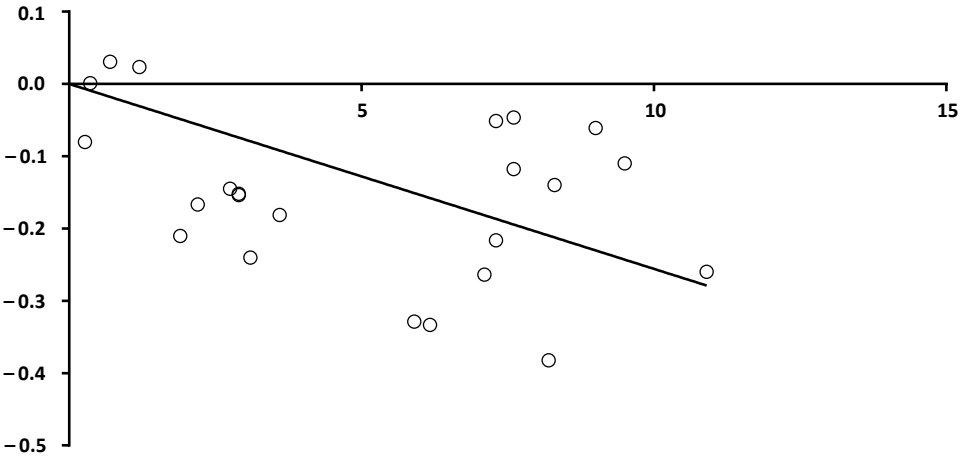
2A



2B



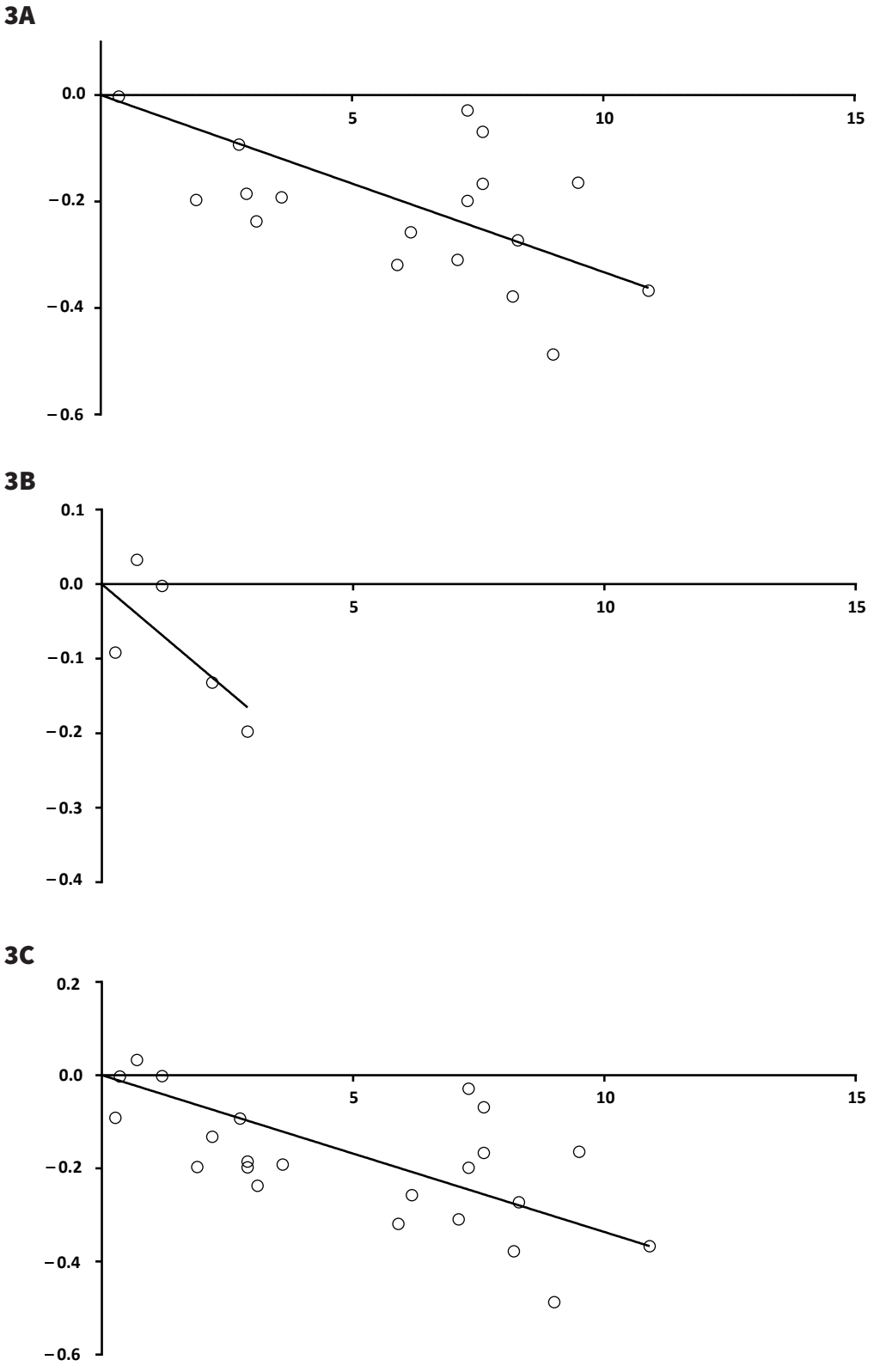
2C



cis-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; TFA, *trans*-fatty acids

Figure 3. Effect on LDL cholesterol of replacing TFA with *cis*-MUFA

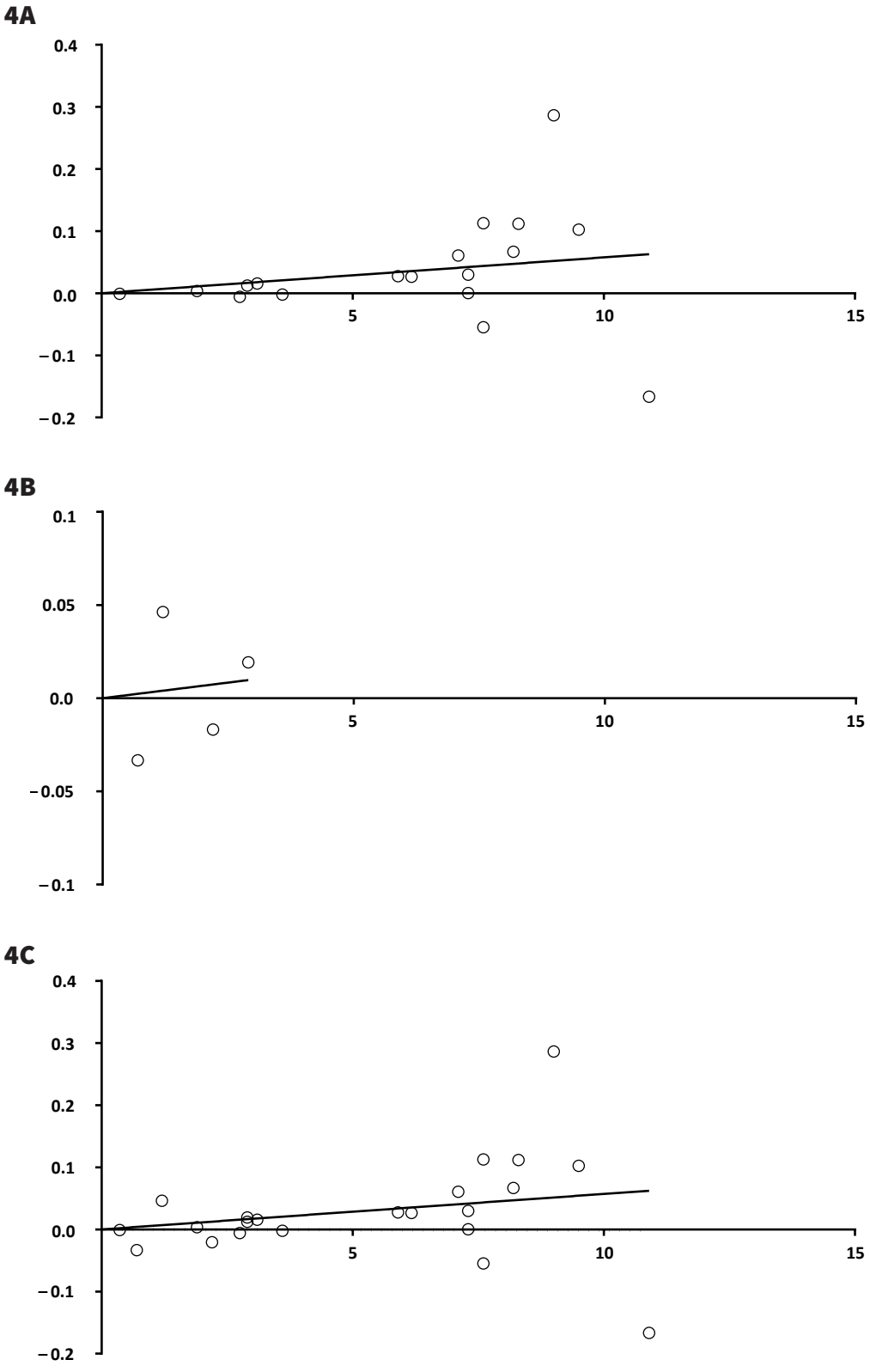
Effects on LDL cholesterol when *cis*-MUFA isocalorically replaces industrial TFA (3A), ruminant TFA (3B) or total TFA (3C). Y axis = change in LDL cholesterol (mmol/L); X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.



cis-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; LDL, low-density lipoprotein; TFA, *trans*-fatty acids

Figure 4. Effect on HDL cholesterol of replacing TFA with *cis*-MUFA

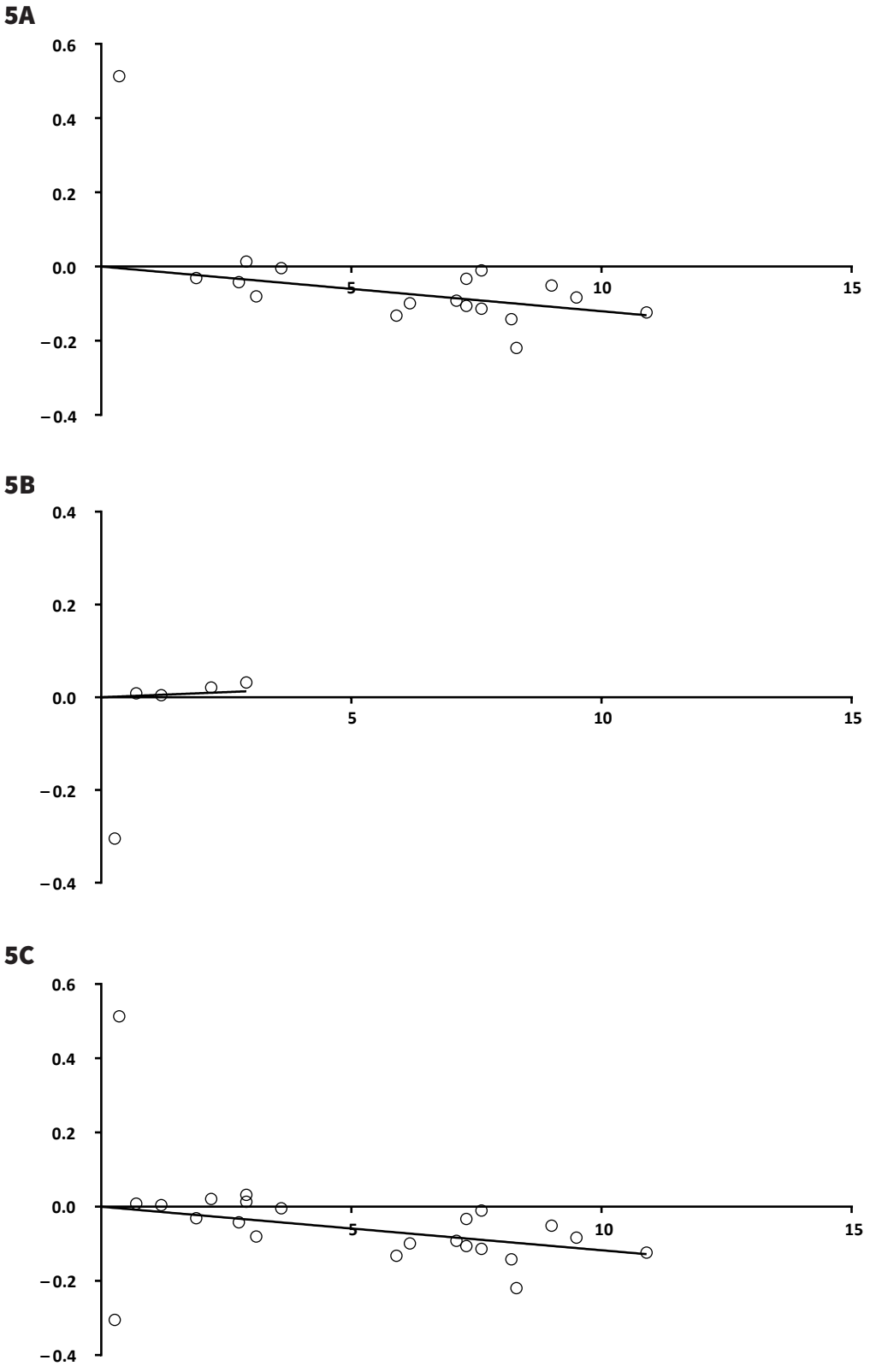
Effects on HDL cholesterol when *cis*-MUFA isocalorically replaces industrial TFA (4A), ruminant TFA (4B) or total TFA (4C). Y axis = change in HDL cholesterol (mmol/L); X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.



cis-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; HDL, high-density lipoprotein; TFA, *trans*-fatty acids

Figure 5. Effect on triglycerides of replacing TFA with *cis*-MUFA

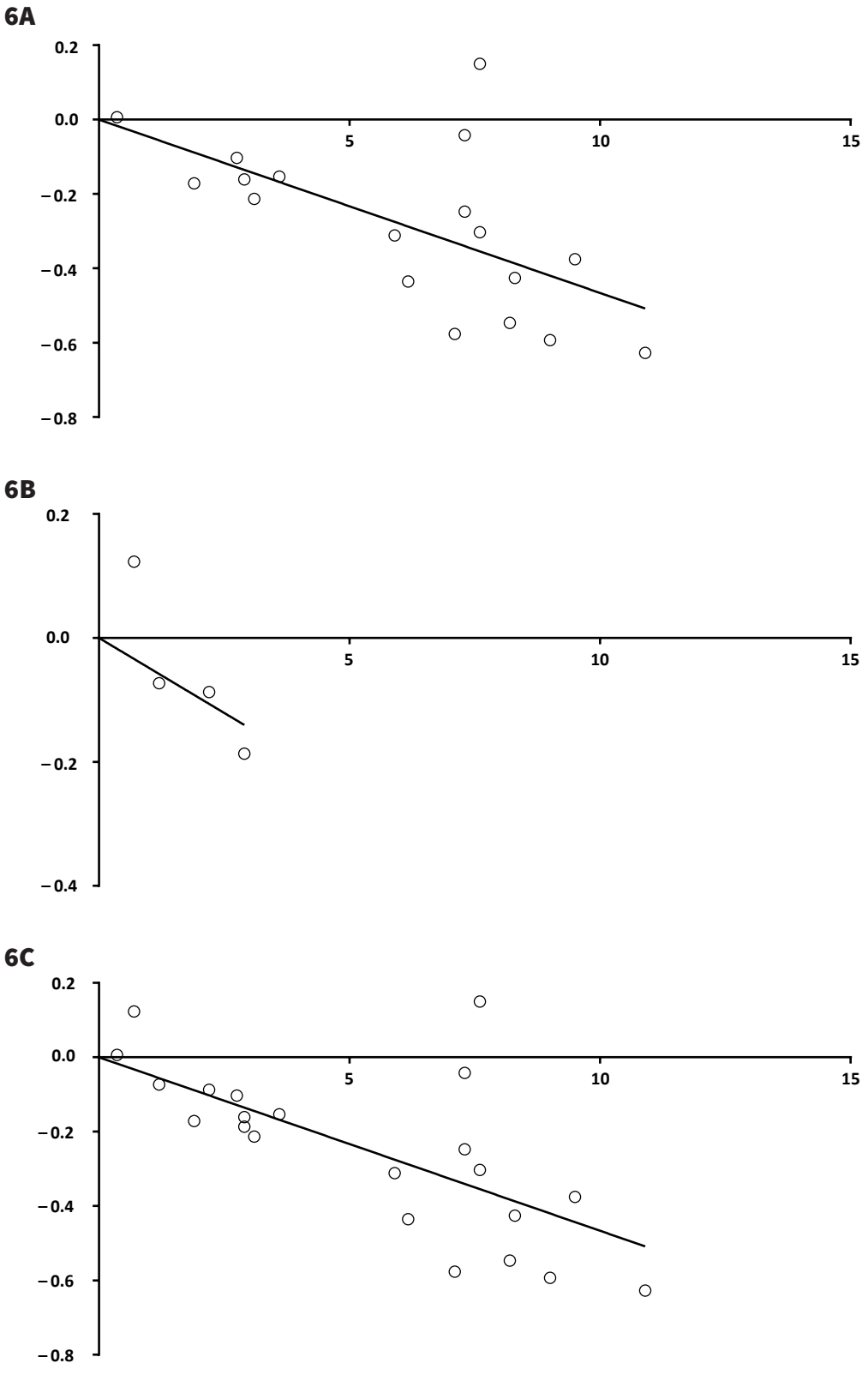
Effects on triglycerides when *cis*-MUFA isocalorically replaces industrial TFA (5A), ruminant TFA (5B) or total TFA (5C). Y axis = change in triglycerides (mmol/L); X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.



cis-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; TFA, *trans*-fatty acids

Figure 6. Effect on the total to HDL cholesterol ratio of replacing TFA with *cis*-MUFA

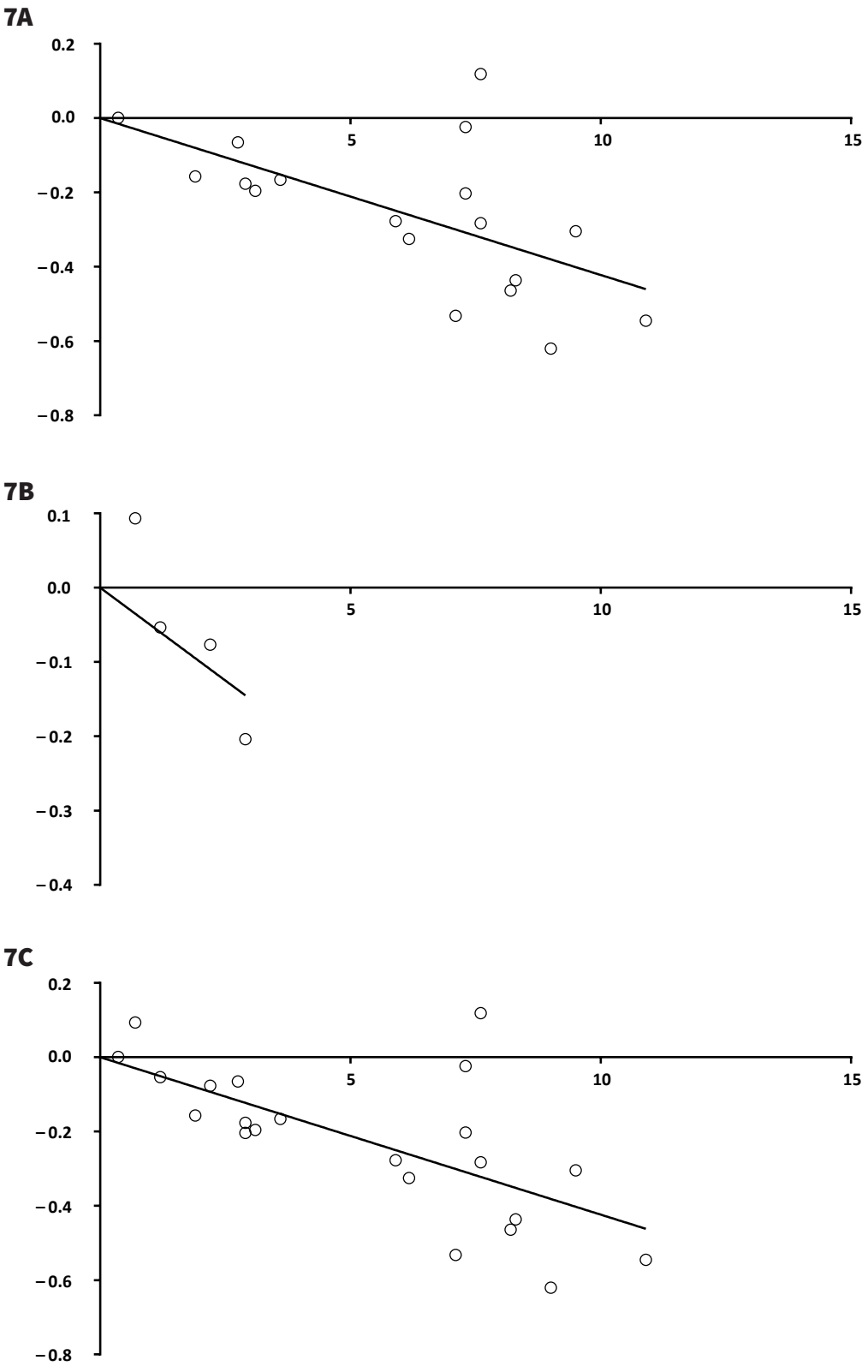
Effects on the total to HDL cholesterol ratio when *cis*-MUFA isocalorically replaces industrial TFA (6A), ruminant TFA (6B) or total TFA (6C). Y axis = change in the total to HDL cholesterol ratio; X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.



cis-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; HDL, high-density lipoprotein; TFA, *trans*-fatty acids

Figure 7. Effect on the LDL to HDL cholesterol ratio of replacing TFA with *cis*-MUFA

Effects on the LDL to HDL cholesterol ratio when *cis*-MUFA isocalorically replaces industrial TFA (7A), ruminant TFA (7B) or total TFA (7C). Y axis = change in the LDL to HDL cholesterol ratio; X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.

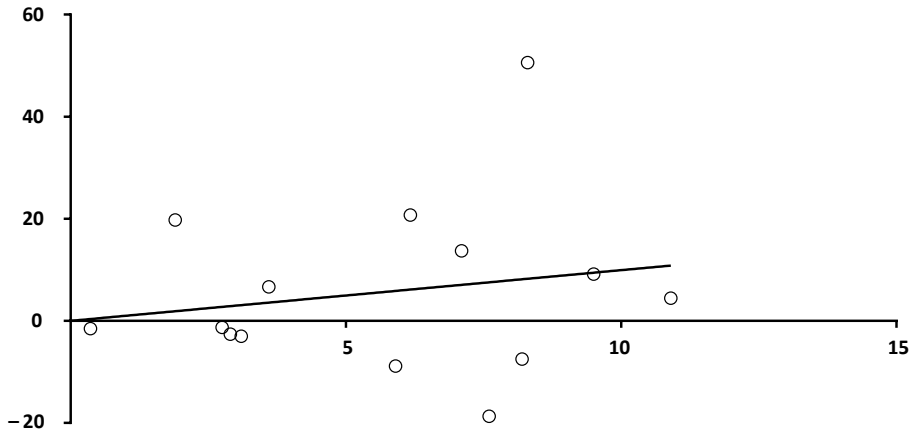


cis-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TFA, *trans*-fatty acids

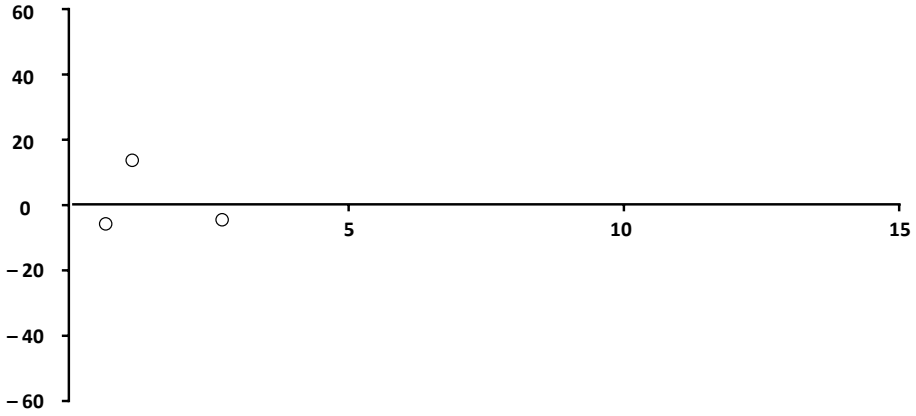
Figure 8. Effect on ApoA-I of replacing TFA with *cis*-MUFA

Effects on ApoA-I when *cis*-MUFA isocalorically replaces industrial TFA (8A), ruminant TFA (8B) or total TFA (8C). Y axis = change in ApoA-I (mg/dL); X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.

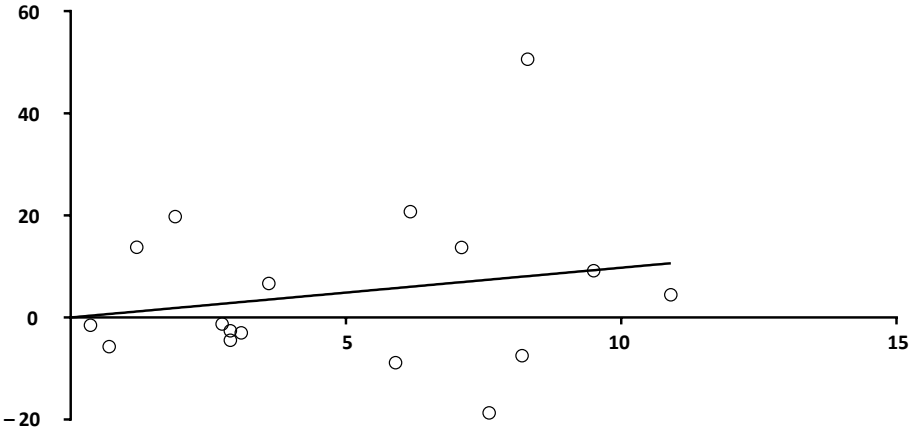
8A



8B



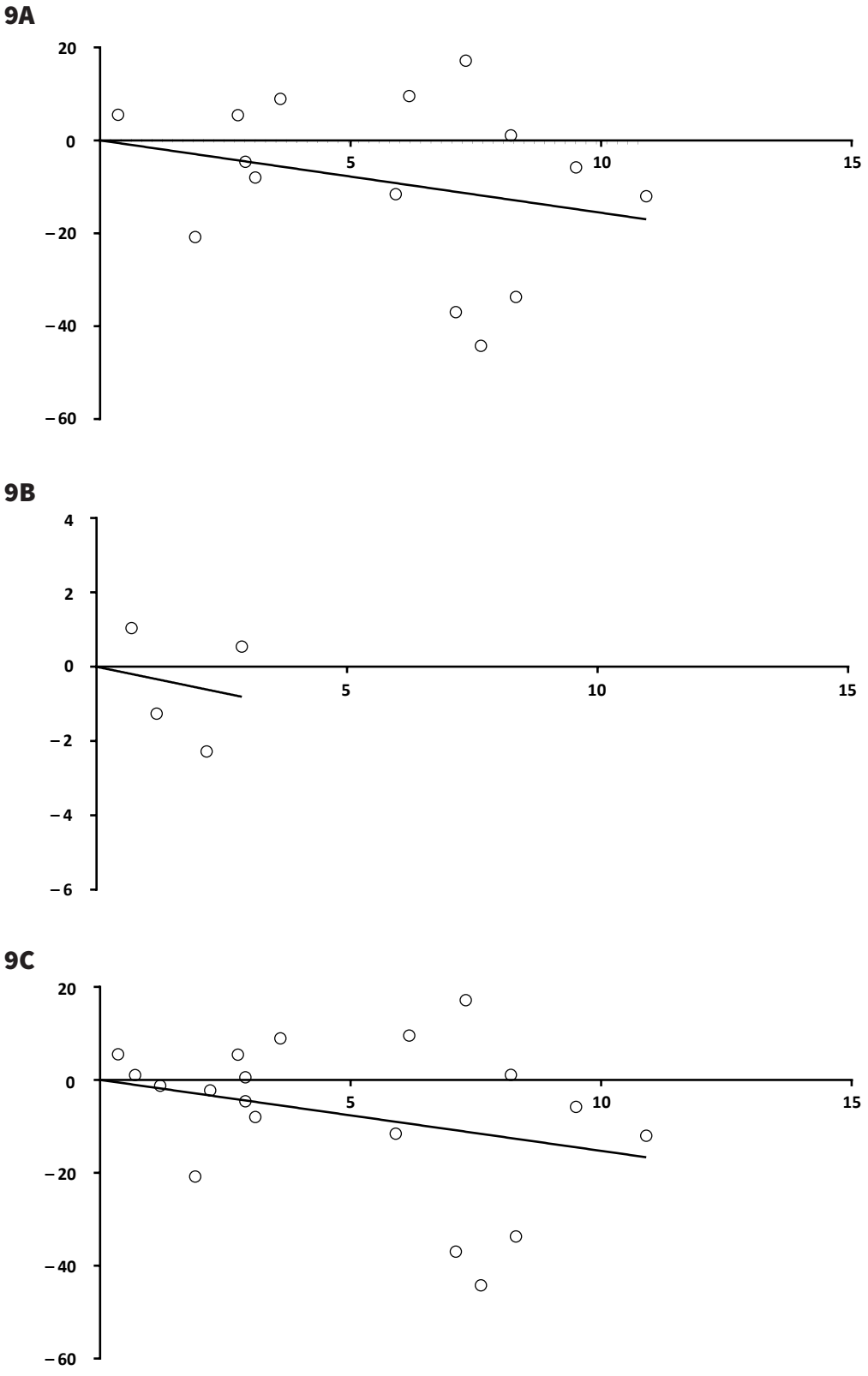
8C



ApoA-I, apolipoprotein A-I; *cis*-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; TFA, *trans*-fatty acids

Figure 9. Effect on ApoB of replacing TFA with *cis*-MUFA

Effects on ApoB when *cis*-MUFA isocalorically replaces industrial TFA (9A), ruminant TFA (9B) or total TFA (9C). Y axis = change in ApoB (mg/dL); X axis = amount of TFA replaced with *cis*-MUFA as a percentage of energy intake. Regression lines are not weighted for study size.



ApoB, apolipoprotein B; *cis*-MUFA, *cis*-monounsaturated fatty acids; en%, percentage of total energy intake; TFA, *trans*-fatty acids

ANNEX 1.

PICO questions

1. What is the effect in the population of reduced percentage of total energy intake from trans-fatty acids (TFA) relative to higher intake for reduction in risk of noncommunicable diseases (NCDs)?
2. What is the effect in the population of a reduction in percentage of total energy intake from TFA from 1% in gradual increments relative to higher intake for reduction in risk of NCDs?
3. What is the effect in the population of reduced percentage of total energy intake from industrial/ruminant TFA relative to higher intake for reduction in risk of NCDs?
4. What is the effect in the population of consuming 0% of total energy intake as industrial/ruminant TFA relative to >0% of total energy intake as industrial/ruminant TFA intake for reduction in risk of NCDs?
5. What is the effect in the population of reduced percentage of total energy intake from 18:2n-6/18:3n–3 isomers of TFA relative to higher intake for the reduction in risk of NCDs?
6. What is the effect in the population of replacing percentage of total energy intake from TFA with conjugated linoleic acid (CLA) isomers (9-*cis*, 11-*trans* and 10-*trans*, 12-*cis*)?
7. What is the effect in the population of replacing TFA with monounsaturated fatty acids, polyunsaturated fatty acids, carbohydrates (refined vs. unrefined) or saturated fatty acids, relative to no replacement on 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 and lipoproteins including total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, LDL cholesterol to HDL cholesterol ratio, total cholesterol to HDL cholesterol ratio, triglycerides to HDL cholesterol ratio and lipoprotein (a)
6. Type 2 diabetes incidence and insulin sensitivity including glucose tolerance (HOMA-IR, IV-GTT, clamp, HbA-IC)
7. 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”[MeSH Terms] AND “humans”[MeSH Terms] AND “dietary fats”[MeSH Terms] OR “trans fatty acids”[MeSH Terms]

ANNEX 4.

Sample data extraction form

Extractor:		
Authors:		
Title:		
Journal:		
Year:	Volume (issue):	Pages:
Sponsor/funding source:		
STUDY		
Study duration:		
Study type:		
Study location:	Setting:	
Eligible population (describe):		
PARTICIPANT POPULATION		
Number approached:	Intervention:	Control:
Number enrolled:	Intervention:	Control:
Number followed up:	Intervention:	Control:
Reasons for drop out:	Intervention:	Control:
Mean age:	Intervention:	Control:
Age range:	Intervention:	Control:
% male (n):	Intervention:	Control:
Ethnicity:	Intervention:	Control:
Weight:	Intervention:	Control:
Height:	Intervention:	Control:
Health status: ☐ Healthy ☐ Hyperlipidaemic ☐ Obese/overweight ☐ Hypertensive ☐ Other (describe):		
Inclusion criteria:		
Exclusion criteria:		
Method of recruitment (describe):		
INTERVENTION		
Type of intervention: ☐ Dietary advice ☐ Provision of food ☐ Other		
Intervention designed to reduce : ☐ TFA ☐ Total fat ☐ Cholesterol ☐ Other		
Multifactorial intervention?		
Description of intervention:		
Duration of intervention	Intervention:	Control:
Duration of follow-up	Intervention:	Control:
Outcomes measured at	Intervention:	Control:
Ad libitum or iso-energetic?		
Intention to directly reduce/replace TFA?		
How many comparison/control groups?		
Treatment of comparison group(s):		
Difference between intervention and comparison group:		
Dietary assessment (describe):		

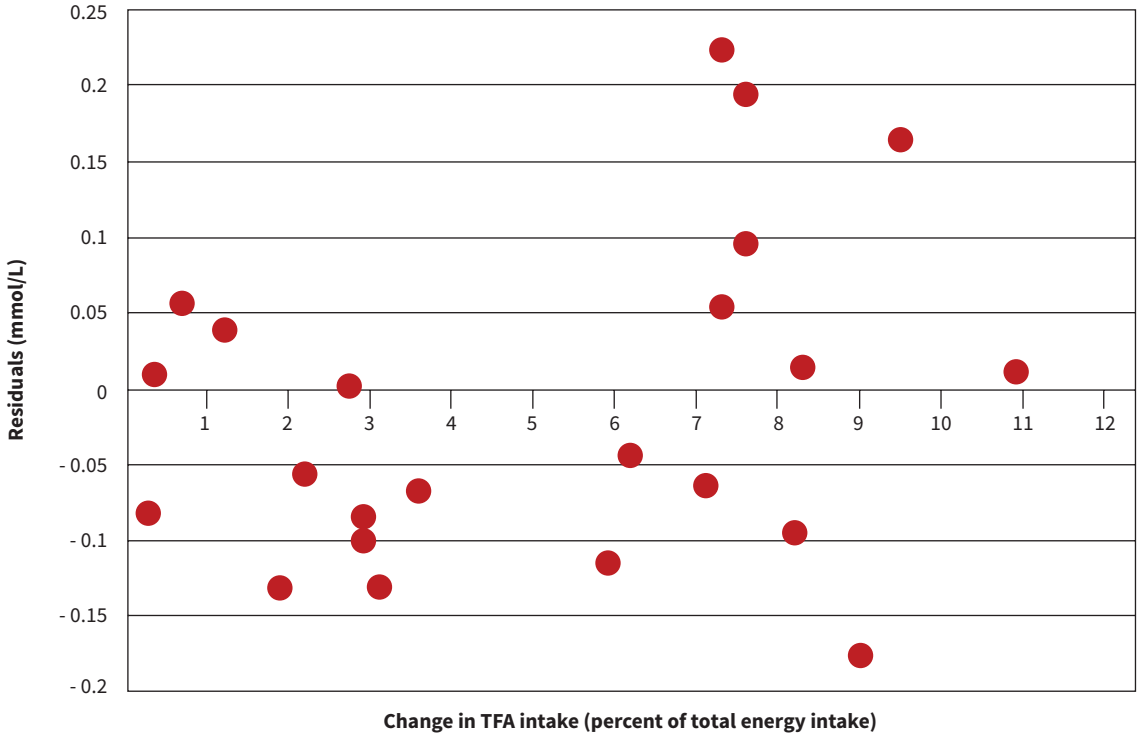
Dietary assessment validated? If yes describe:				
Delivery of intervention:				
If run-in period to trial, describe:				
Requires imputation?				
OUTCOMES				
Primary/Secondary outcomes of study:				
Priority outcomes:				
Changes observed in intakes: ☐ Total energy ☐ Cholesterol	☐ Total fat ☐ Protein	☐ SFA ☐ Carbohydrates	☐ *cis*-MUFA ☐ Other	☐ *cis*-PUFA ☐ None
Change in weight/BMI between groups?				
Statistical models used:				

Outcome	How/who/ when measured	Mean Intervention baseline	SD	N	Mean Control baseline	SD	N	Mean intervention follow-up	SD	N	Mean control follow-up	SD	N	Mean difference Follow-up	SE	Effect size (95% CI)	Significance (P-value)	Adjusted for Confounders? (mean differences only)
Total cholesterol (mmol/L)																		
LDL (mmol/L)																		
HDL (mmol/L)																		
TG (mmol/L)																		
BMI (kg/m^2)																		
BMI z score																		
Weight (kg)																		
Waist circumference																		
Height (cm)																		
DIETARY INTAKES																		
Energy (kJ)																		
Total fat (g)																		
Saturated fat (g)																		
Total fat (% energy)																		
Saturated fat (% energy)																		
Pentadecanoic acid (%)																		
CHO (% energy)																		
MUFA (% energy)																		
Comments																		

ANNEX 5.

Residuals analysis

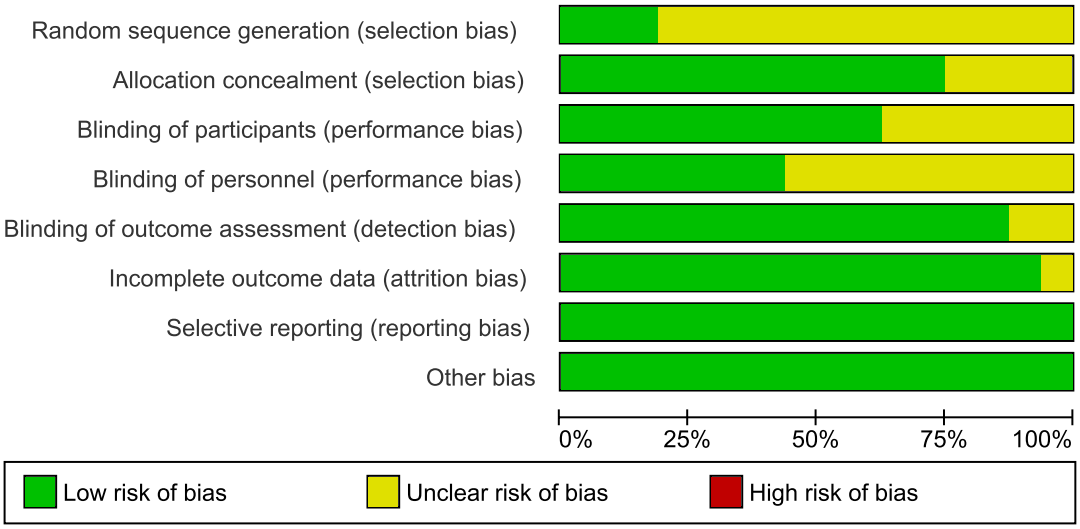
Residuals analysis for LDL cholesterol when TFA are replaced with *cis*-MUFA

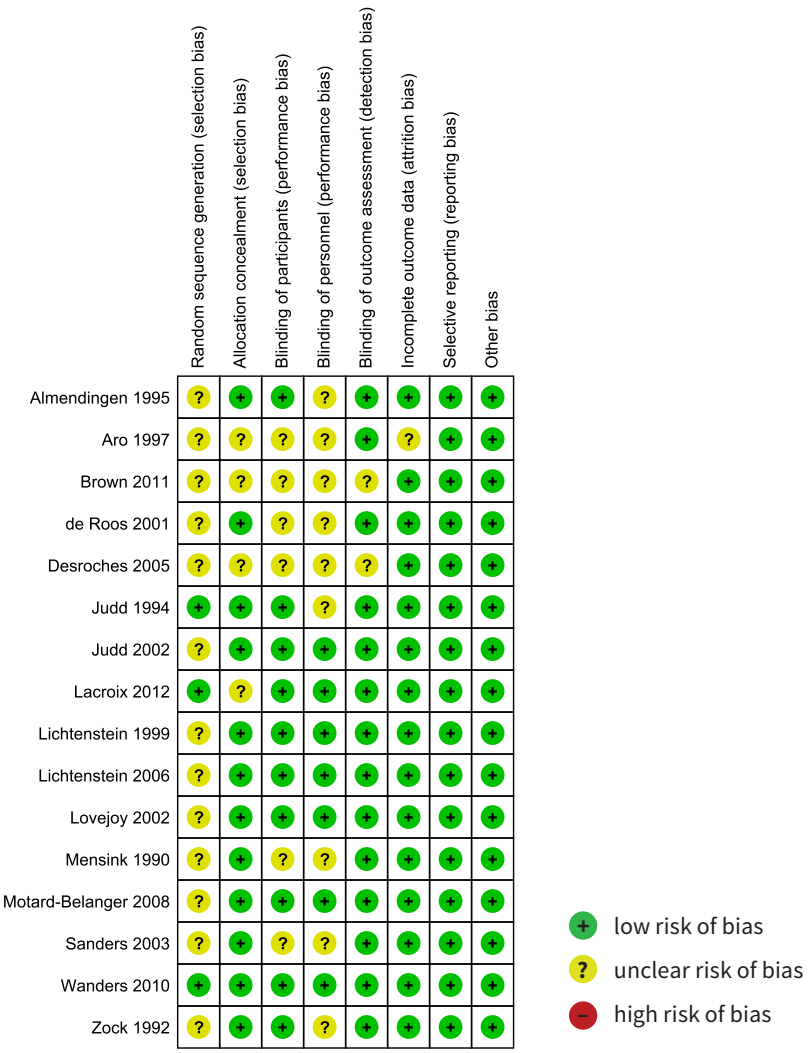


cis-MUFA, *cis*-monounsaturated fatty acids; LDL, low-density lipoprotein; TFA, *trans*-fatty acids

ANNEX 6.

Risk of bias assessment

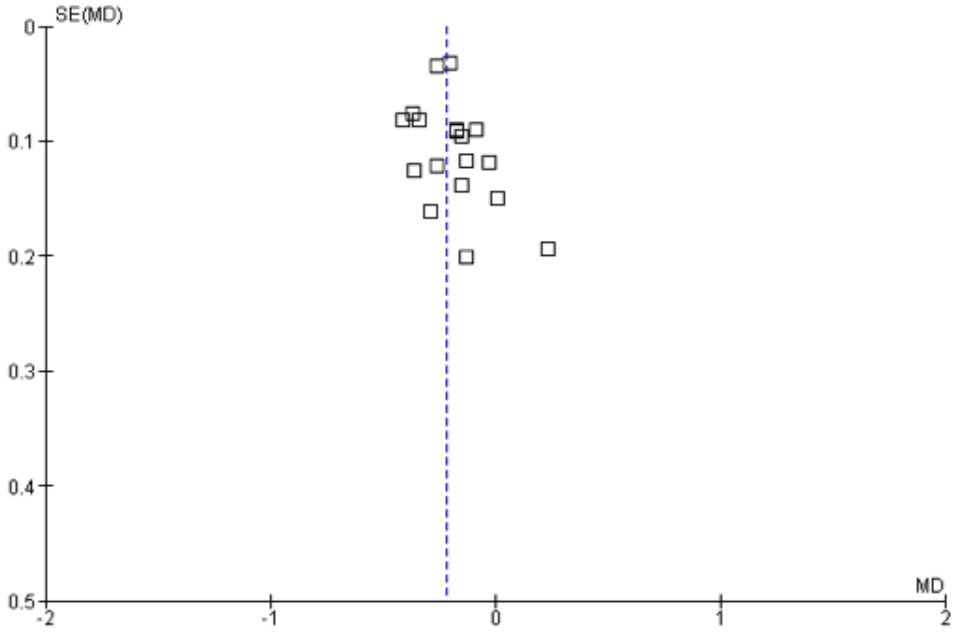




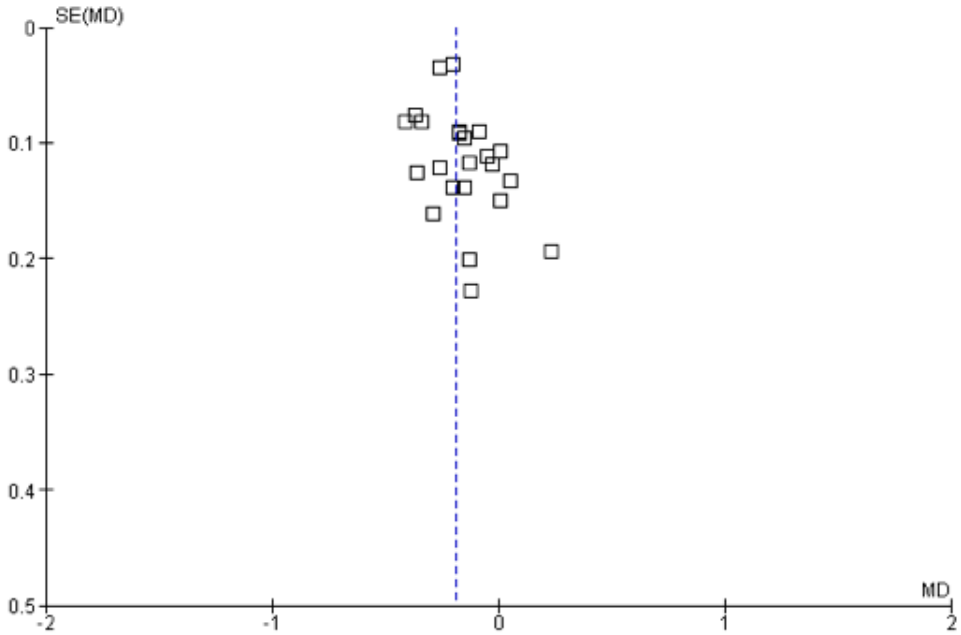
ANNEX 7.

Funnel plot analysis

Higher vs lower industrial TFA intake: LDL cholesterol



Higher vs lower total TFA intake: LDL cholesterol



ANNEX 8.

GRADE evidence profiles

GRADE evidence profile 1

Question: What is the effect of a reduction in industrial *trans*-fatty acid intake in adults?
Population: General adult population

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other8	TFA	Control			
By replacing industrial TFA specifically with *cis*-MUFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.027 (−0.036, −0.018)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/ per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.034 (−0.042, −0.027)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.010 (0.006, 0.015)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.013 (−0.022, −0.003)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.049 (−0.060, −0.037)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.044 (−0.054, −0.033)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	313	313	0.84 (−0.62, 2.29)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	374	374	−1.25 (−2.66, 0.17)	⊕⊕⊕O MODERATE	IMPORTANT

By replacing industrial TFA specifically with *cis*-PUFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.045 (−0.054,−0.036)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.047 (−0.055, −0.040)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.008 (0.004, 0.013)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.017 (−0.027, −0.008)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.059 (−0.071, −0.047)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.052 (−0.064, −0.040)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	313	313	−1.64 (−2.82, −0.47)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	374	374	−3.10 (−4.44, −1.76)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing industrial TFA specifically with carbohydrates?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.023 (−0.032, −0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.025 (−0.033, −0.018)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	545	545	0.003 (−0.002, 0.007)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	545	545	0.003 (−0.006, 0.013)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.024 (−0.038, −0.010)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other8	TFA	Control			
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.024 (−0.038, −0.011)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	313	313	−3.25 (−4.75, −1.75)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	374	374	2.36 (1.13, 3.59)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing industrial TFA specifically with SFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.022 (0.013, 0.031)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.010 (0.002, 0.018)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.013 (0.009, 0.018)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	545	545	−0.009 (−0.018, 0.001)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.023 (−0.035, −0.010)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.018 (−0.030, −0.005)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	313	313	2.61 (1.25, 3.97)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	374	374	5.21 (3.40, 7.03)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] All but one of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[3] Number of comparisons are provided in parentheses.

[4] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 6 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The single study with parallel design was assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[5] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.

[6] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.

[7] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.

[8] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.

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

GRADE evidence profile 2

Question: What is the effect of an increase in industrial *trans*-fatty acid intake in adults?
Population: General adult population

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other[8]	TFA	Control			
By replacing *cis*-MUFA with industrial TFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.027 (0.018, 0.036)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.034 (0.027, 0.042)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.010 (−0.015, −0.006)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.013 (0.003, 0.022)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.049 (0.037, 0.060)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.044 (0.033, 0.054)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	313	313	−0.84 (−2.29, 0.62)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	374	374	1.25 (−0.17, 2.66)	⊕⊕⊕O MODERATE	IMPORTANT
By replacing *cis*-PUFA with industrial TFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.045 (0.036, 0.054)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.047 (0.040, 0.055)	⊕⊕⊕⊕ HIGH	CRITICAL

HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	−0.008 (−0.013, −0.004)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.017 (0.008, 0.027)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.059 (0.047, 0.071)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.052 (0.040, 0.064)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	313	313	1.64 (0.47, 2.82)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	374	374	3.10 (1.76, 4.44)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing carbohydrates with industrial TFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.023 (0.014, 0.032)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.025 (0.018, 0.033)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	545	545	−0.003 (−0.007, 0.002)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	545	545	−0.003 (−0.013, 0.006)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.024 (0.010, 0.038)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.024 (0.011, 0.038)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	313	313	3.25 (1.75, 4.75)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other[8]	TFA	Control			
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	374	374	–2.36 (–3.59, –1.13)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing SFA with industrial TFA?											
Total cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	–0.022 (–0.031, –0.013)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	–0.010 (–0.018, –0.002)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	–0.013 (–0.018, –0.009)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[9]	None	545	545	0.009 (–0.001, 0.018)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.023 (0.010 to 0.035)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–6 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	545	545	0.018 (0.005, 0.030)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	313	313	–2.61 (–3.97, –1.25)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–6 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	374	374	–5.21 (–7.03, –3.40)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] All but one of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[3] Number of comparisons are provided in parentheses.

4 All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 6 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The single study with parallel design was assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[5] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.

[6] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.

[7] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.

[8] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.

[9] 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 a reduction in ruminant *trans*-fatty acid intake in adults?
Population: General adult population

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other[8]	TFA	Control			
By replacing ruminant TFA specifically with *cis*-MUFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	−0.041 (−0.090, 0.009)	⊕⊕⊕O LOW	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	124	124	−0.052 (−0.097, −0.006)	⊕⊕⊕O MODERATE	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.008 (−0.017, 0.033)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.008 (−0.049, 0.065)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	−0.051 (−0.134, 0.032)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	−0.053 (−0.125, 0.019)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
2 (3)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	0.86 (−17.8, 16.1)	⊕⊕OO LOW	IMPORTANT
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	−0.17 (−1.38, 1.04)	⊕⊕OO LOW	IMPORTANT
By replacing ruminant TFA specifically with *cis*-PUFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	124	124	−0.058 (−0.109, −0.008)	⊕⊕⊕O MODERATE	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	124	124	−0.064 (−0.110, −0.018)	⊕⊕⊕O MODERATE	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious Imprecision	None	115	115	0.006 (−0.019, 0.031)	⊕⊕OO LOW	IMPORTANT

Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.003 (–0.054, 0.060)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	–0.059 (–0.142, 0.024)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	–0.059 (–0.131, 0.013)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
2 (3)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	–2.29 (–19.55, 14.97)	⊕⊕OO LOW	IMPORTANT
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	115	115	–2.63 (–3.76, –1.51)	⊕⊕⊕O MODERATE	IMPORTANT
By replacing ruminant TFA specifically with carbohydrates?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious Imprecision	None	124	124	–0.037 (–0.086, 0.013)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	–0.043 (–0.088, 0.003)	⊕⊕OO LOW	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.000 (–0.025, 0.025)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.024 (–0.033, 0.081)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	–0.024 (–0.109, 0.061)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	–0.029 (–0.102, 0.043)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	–4.55 (–22.04, 12.94)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other[8]	TFA	Control			
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	Serious Inconsistency	No serious indirectness	No serious imprecision[9]	None	115	115	4.17 (2.79, 5.55)	⊕⊕⊕O MODERATE	IMPORTANT
By replacing ruminant TFA specifically with SFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.008 (–0.040, 0.055)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	–0.007 (–0.051, 0.037)	⊕⊕OO LOW	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.011 (–0.014, 0.035)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.012 (–0.045, 0.069)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	–0.022 (–0.106, 0.062)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	–0.024 (–0.096, 0.048)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	3.71 (–12.95, 20.36)	⊕⊕OO LOW	IMPORTANT
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	115	115	7.81 (6.27, 9.36)	⊕⊕⊕O MODERATE	IMPORTANT

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

[1] All but one of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[3] Number of comparisons are provided in parentheses.

[4] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 27 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The single study with parallel design was assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and–although 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; hence, 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.

[5] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.

[6] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.

[7] 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 exchanging TFA with the specified replacement nutrients on a particular blood lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.

[8] Too few studies to formally assess publication bias

[9] The 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has therefore not been downgraded for serious imprecision.

GRADE evidence profile 4

Question: What is the effect of an increase in ruminant *trans*-fatty acid intake in adults?
Population: General adult population

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other[8]	TFA	Control			
By replacing *cis*-MUFA with ruminant TFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.041 (−0.009, 0.090)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious Inconsistency	No serious indirectness	No serious imprecision9	None	124	124	0.052 (0.006, 0.097)	⊕⊕⊕O MODERATE	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	−0.008 (−0.033, 0.017)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	−0.008 (−0.065, 0.049)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.051 (−0.032, 0.134)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.053 (−0.019, 0.125)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
2 (3)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	−0.86 (−16.1, 17.8)	⊕⊕OO LOW	IMPORTANT
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.17 (−1.04, 1.38)	⊕⊕OO LOW	IMPORTANT
By replacing *cis*-PUFA with ruminant TFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	124	124	0.058 (0.008, 0.109)	⊕⊕⊕O MODERATE	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	124	124	0.064 (0.018, 0.110)	⊕⊕⊕O MODERATE	CRITICAL

HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	−0.006 (−0.031, 0.019)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
4 (5)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	−0.003 (−0.060, 0.054)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.059 (−0.024, 0.142)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.059 (−0.013, 0.131)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
2 (3)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	2.29 (−14.97, 19.55)	⊕⊕OO LOW	IMPORTANT
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
3 (4)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	115	115	2.63 (1.51, 3.76)	⊕⊕⊕O MODERATE	IMPORTANT
By replacing carbohydrates with ruminant TFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.037 (−0.013, 0.086)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.043 (−0.003, 0.088)	⊕⊕OO LOW	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.000 (−0.025, 0.025)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious Inconsistency	No serious indirectness	Serious imprecision	None	124	124	−0.024 (−0.081, 0.033)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.024 (−0.061, 0.109)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.029 (−0.043, 0.102)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	4.55 (−12.94, 22.04)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No. of participants[1]		Effect[2] (95% CI)	Quality	Importance
No. of studies[3]	Design	Risk of bias[4]	Inconsistency[5]	Indirectness[6]	Imprecision[7]	Other[8]	TFA	Control			
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	115	115	−4.17 (−5.55, −2.79)	⊕⊕⊕O MODERATE	IMPORTANT
By replacing SFA with ruminant TFA?											
Total cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious Imprecision	None	124	124	−0.008 (−0.055, 0.040)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	0.007 (−0.037, 0.051)	⊕⊕OO LOW	CRITICAL
HDL cholesterol (27 days – 4 week intervention period; units mmol/L per 1% energy exchange; better indicated by higher values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	−0.011 (−0.035, 0.014)	⊕⊕OO LOW	IMPORTANT
Triglycerides (4–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	124	124	−0.012 (−0.069, 0.045)	⊕⊕OO LOW	IMPORTANT
Total cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.022 (−0.062, 0.106)	⊕⊕OO LOW	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (4–8 week intervention periods; unitless; better indicated by lower values)											
13 (18)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	115	115	0.024 (−0.048, 0.096)	⊕⊕OO LOW	IMPORTANT
ApoA-I (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by higher values)											
9 (14)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	None	99	99	−3.71 (−20.36, 12.95)	⊕⊕OO LOW	IMPORTANT
ApoB (4 week intervention period; units mg/dL per 1% energy exchange; better indicated by lower values)											
10 (15)	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision[9]	None	115	115	-7.81 (-9.36, -6.27)	⊕⊕⊕O MODERATE	IMPORTANT

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

[1] All but one of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[3] Number of comparisons are provided in parentheses.

[4] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 27 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The single study with parallel design was assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[5] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[6] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.
[7] 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 exchanging TFA with the specified replacement nutrients on a particular blood lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI crosses a threshold of important benefit or harm and the outcome has therefore been downgraded for serious imprecision.
[8] Too few studies to formally assess publication bias
[9] The 95% CI does not cross a threshold of irrelevant benefit or important harm and the outcome has therefore not been downgraded for serious imprecision.

GRADE evidence profile 5

Question: What is the effect of a reduction in *trans*-fatty acid intake in adults?[1]
Population: General adult population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
By replacing TFA specifically with *cis*-MUFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness[7]	No serious imprecision	None	669	669	−0.027 (−0.035, −0.019)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.035 (−0.042, −0.028)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.010 (0.007, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.012 (−0.021, −0.004)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.049 (−0.059, −0.038)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.044 (−0.053, −0.034)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	412	412	0.84 (−0.50, 2.17)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−1.23 (−2.44, −0.14)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with *cis*-PUFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.045 (−0.053,−0.037)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.048 (−0.055, −0.041)	⊕⊕⊕⊕ HIGH	CRITICAL

HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.008 (0.005, 0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.017 (−0.026, −0.009)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.059 (−0.070, −0.048)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.052 (−0.063, −0.042)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−1.65 (−2.75, −0.55)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−3.09 (−4.27, −1.91)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with carbohydrates?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.023 (−0.031, −0.015)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.026 (−0.033, −0.019)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	660	660	0.002 (−0.001, 0.006)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	669	669	0.004 (−0.005, 0.012)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.024 (−0.037, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.024 (−0.036, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−3.26 (−4.66, −1.87)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	2.38 (1.29, 3.48)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with SFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.022 (0.014, 0.030)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.010 (0.003, 0.017)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.013 (0.010, 0.017)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.008 (−0.017, 0.000)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.023 (−0.034, −0.011)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.018 (−0.029, −0.006)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	2.62 (1.35, 3.89)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	5.25 (3.65, 6.85)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration.

[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[4] Number of comparisons are provided in parentheses.

[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.
[8] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.
[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 6

Question: What is the effect of a reduction in *trans*-fatty acids intake in adults with intakes greater than 1%?[1]
Population: General adult population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
By replacing TFA specifically with *cis*-MUFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness[7]	No serious imprecision	None	669	669	−0.027 (−0.035, −0.019)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.035 (−0.042, −0.028)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.010 (0.007, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.012 (−0.021, −0.004)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.049 (−0.059, −0.038)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.044 (−0.053, −0.034)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision10	None	412	412	0.84 (−0.50, 2.17)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−1.23 (−2.44, −0.14)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with *cis*-PUFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.045 (−0.053,−0.037)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.048 (−0.055, −0.041)	⊕⊕⊕⊕ HIGH	CRITICAL

HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.008 (0.005, 0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.017 (−0.026, −0.009)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.059 (−0.070, −0.048)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.052 (−0.063, −0.042)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−1.65 (−2.75, −0.55)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−3.09 (−4.27, −1.91)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with carbohydrates?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.023 (−0.031, −0.015)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.026 (−0.033, −0.019)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	660	660	0.002 (−0.001, 0.006)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	669	669	0.004 (−0.005, 0.012)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.024 (−0.037, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.024 (−0.036, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−3.26 (−4.66, −1.87)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	2.38 (1.29, 3.48)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with SFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.022 (0.014, 0.030)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.010 (0.003, 0.017)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.013 (0.010, 0.017)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.008 (−0.017, 0.000)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.023 (−0.034, −0.011)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.018 (−0.029, −0.006)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	2.62 (1.35, 3.89)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	5.25 (3.65, 6.85)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration. All studies included in this analysis contained at least one group with a TFA intake of more than 1% of total energy intake. The model developed by meta-regression is linear across all TFA intakes from all studies.

[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[4] Number of comparisons are provided in parentheses.

[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.
[8] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.
[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 7

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

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
By replacing TFA specifically with *cis*-MUFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness[7]	No serious imprecision	None	669	669	−0.027 (−0.035, −0.019)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.035 (−0.042, −0.028)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.010 (0.007, 0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.012 (−0.021, −0.004)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.049 (−0.059, −0.038)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.044 (−0.053, −0.034)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	412	412	0.84 (−0.50, 2.17)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−1.23 (−2.44, −0.14)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with *cis*-PUFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.045 (−0.053,−0.037)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.048 (−0.055, −0.041)	⊕⊕⊕⊕ HIGH	CRITICAL

HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.008 (0.005, 0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.017 (−0.026, −0.009)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.059 (−0.070, −0.048)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.052 (−0.063, −0.042)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−1.65 (−2.75, −0.55)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−3.09 (−4.27, −1.91)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with carbohydrates?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.023 (−0.031, −0.015)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.026 (−0.033, −0.019)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	660	660	0.002 (−0.001, 0.006)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	669	669	0.004 (−0.005, 0.012)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.024 (−0.037, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.024 (−0.036, −0.012)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−3.26 (−4.66, −1.87)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	2.38 (1.29, 3.48)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing TFA specifically with SFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.022 (0.014, 0.030)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.010 (0.003, 0.017)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.013 (0.010, 0.017)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.008 (−0.017, 0.000)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.023 (−0.034, −0.011)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.018 (−0.029, −0.006)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	2.62 (1.35, 3.89)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	5.25 (3.65, 6.85)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration. All studies included in this analysis contained at least one group with a TFA intake of less than 1% of total energy intake. The model developed by meta-regression is linear across all TFA intakes from all studies.

[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[4] Number of comparisons are provided in parentheses.

[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.
[8] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.
[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 8

Question: What is the effect of an increase in *trans*-fatty acid intake in adults?[1]
Population: General adult population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
By replacing *cis*-MUFA with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.027 (0.019, 0.035)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.035 (0.028, 0.042)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.010 (−0.014, −0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.012 (0.004, 0.021)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.049 (0.038, 0.059)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.044 (0.034, 0.053)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	412	412	−0.84 (−2.17, 0.50)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	1.23 (0.14, 2.44)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing *cis*-PUFA with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.045 (0.037, 0.053)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.048 (0.041, 0.055)	⊕⊕⊕⊕ HIGH	CRITICAL

HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.008 (−0.012, −0.005)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.017 (0.009, 0.026)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.059 (0.048, 0.070)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.052 (0.042, 0.063)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	1.65 (0.55, 2.75)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	3.09 (1.91, 4.27)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing carbohydrates with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.023 (0.015, 0.031)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.026 (0.019, 0.033)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	660	660	−0.002 (−0.006, 0.001)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	669	669	−0.004 (−0.012, 0.005)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.024 (0.012, 0.037)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.024 (0.012, 0.036)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	3.26 (1.87, 4.66)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−2.38 (−3.48, −1.29)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing SFA with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.022 (−0.030, −0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.010 (−0.017, −0.003)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.013 (−0.017, −0.010)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.008 (0.000, 0.017)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.023 (0.011, 0.034)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.018 (0.006, 0.029)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−2.62 (−3.89, −1.35)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−5.25 (−6.85, −3.65)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration.

[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[4] Number of comparisons are provided in parentheses.

[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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; hence, 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.

[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.
[8] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.
[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 9

Question: What is the effect of an increase in *trans*-fatty acids intake in adults with intakes of less than 1% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
By replacing *cis*-MUFA with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.027 (0.019, 0.035)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.035 (0.028, 0.042)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.010 (−0.014, −0.007)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.012 (0.004, 0.021)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.049 (0.038, 0.059)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.044 (0.034, 0.053)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	412	412	−0.84 (−2.17, 0.50)	⊕⊕⊕O MODERATE	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	1.23 (0.14, 2.44)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing *cis*-PUFA with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.045 (0.037, 0.053)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.048 (0.041, 0.055)	⊕⊕⊕⊕ HIGH	CRITICAL

HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.008 (−0.012, −0.005)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.017 (0.009, 0.026)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.059 (0.048, 0.070)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.052 (0.042, 0.063)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	1.65 (0.55, 2.75)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	3.09 (1.91, 4.27)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing carbohydrates with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.023 (0.015, 0.031)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.026 (0.019, 0.033)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	660	660	−0.002 (−0.006, 0.001)	⊕⊕⊕O MODERATE	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[10]	None	669	669	−0.004 (−0.012, 0.005)	⊕⊕⊕O MODERATE	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.024 (0.012, 0.037)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.024 (0.012, 0.036)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	3.26 (1.87, 4.66)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality	Importance
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control			
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−2.38 (−3.48, −1.29)	⊕⊕⊕⊕ HIGH	IMPORTANT
By replacing SFA with TFA?											
Total cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.022 (−0.030, −0.014)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	−0.010 (−0.017, −0.003)	⊕⊕⊕⊕ HIGH	CRITICAL
HDL cholesterol (2–6 week intervention periods; units mmol/L per 1% energy exchange; better indicated by higher values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	−0.013 (−0.017, −0.010)	⊕⊕⊕⊕ HIGH	IMPORTANT
Triglycerides (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)											
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	0.008 (0.000, 0.017)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.023 (0.011, 0.034)	⊕⊕⊕⊕ HIGH	IMPORTANT
LDL cholesterol to HDL cholesterol ratio (2–8 week intervention periods; unitless; better indicated by lower values)											
15 (22)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660	660	0.018 (0.006, 0.029)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoA-I (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by higher values)											
11 (17)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	412	412	−2.62 (−3.89, −1.35)	⊕⊕⊕⊕ HIGH	IMPORTANT
ApoB (2–8 week intervention periods; units mg/dL per 1% energy exchange; better indicated by lower values)											
13 (19)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	499	499	−5.25 (−6.85, −3.65)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration. All studies included in this analysis contained at least one group with a TFA intake of less than 1% of total energy intake. The model developed by meta-regression is linear across all TFA intakes from all studies.

[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.

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

[4] Number of comparisons are provided in parentheses.

[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. 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 that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although 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;

hence, 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.

[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.

[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the population of interest (adults without disturbances in lipid metabolism or diabetes), and all comparisons within studies were made directly to an appropriate control group or diet.

[8] 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 exchanging TFA with the specified replacement nutrients on a particular blood 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 therefore the outcome has not been downgraded for serious imprecision.

[9] Results of funnel plot analysis did not suggest any publication bias for LDL cholesterol. For other outcomes, publication bias was not formally assessed.

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

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