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Saturated Fat Restriction for Cardiovascular Disease Prevention: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

The recommendation to limit dietary saturated fat intake is primarily drawn from observational studies rather than randomized controlled trials of cardiovascular disease prevention. Thus, we investigated the efficacy of saturated fat reduction in preventing mortality and cardiovascular diseases. In this systematic review and meta-analysis of randomized controlled trials, Cochrane CENTRAL, PubMed, and Ichu-shi databases were searched up to April 2023. Randomized controlled trials on saturated fat reduction to prevent cardiovascular diseases were selected. Cardiovascular and all-cause mortality and cardiovascular outcomes were evaluated. Changes in electrocardiography or coronary angiography findings were excluded because they could be evaluated arbitrarily. Two or more reviewers independently extracted and assessed the data. A random-effects meta-analysis was performed using the Grading of Recommendations Assessment, Development, and Evaluation method. Nine eligible trials with 13,532 participants were identified (two were primary and seven were secondary prevention studies). No significant differences in cardiovascular mortality (RR = 0.94, 95% CI: 0.75–1.19), all-cause mortality (RR = 1.01, 95% CI: 0.89–1.14), myocardial infarction (RR = 0.85, 95% CI: 0.71–1.02), and coronary events (RR = 0.85, 95% CI: 0.65–1.11) were observed between the intervention and control groups. However, due to limited reported cases, we were unable to evaluate the impact of stroke. At present, a reduction in saturated fats cannot be recommended to prevent cardiovascular diseases and mortality. Clinical trials are needed to evaluate the effects of saturated fat reduction under statin administration.

Introduction

After the 1977 Senate report, the USA Dietary Reference Intakes recommended restricting saturated fatty acid (SFA) intake[1] because a positive correlation between SFA and cardiovascular death was shown in the Seven Countries Study.[2] The UK Public Health Dietary Advice adopted this in 1983.[3] SFA intake is associated with serum cholesterol levels. A recent WHO report by Mensink showed that replacing SFA with monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and carbohydrates reduced serum total cholesterol and low-density lipoprotein cholesterol (LDL-C).[4] Therefore, SFA restriction may prevent cardiovascular diseases (CVDs). However, phase 3 trials of cholesteryl ester transfer protein inhibitors have shown that reducing LDL-C does not necessarily prevent CVD. In contrast, in the ILLUMINATE trial, the administration of torcetrapib, which significantly decreased LDL-C levels by 24.9%, significantly increased CVD and all-cause mortality.[5] Thus, although many previous randomized controlled trials (RCTs) have proved that “lowering LDL cholesterol is good,” it is essential to determine “how and in whom”.[6] According to the lipoprotein subfraction analysis by Bergeron et al., restriction of SFA intake reduced large voyant LDL-C but not small dense LDL-C, which are the most atherogenic lipoproteins.[7] Therefore, we conducted a systematic review and meta-analysis of RCT to clarify whether SFA restriction prevents CVD and all-cause mortality.

Methods

Protocol and registration

This systematic review and meta-analysis used a predefined protocol and was registered with PROSPERO (CRD42023428498) in accordance with the PRISMA guidelines. This study was approved by Kitasato Institute Hospital Research Ethics Committee (No. 22057). Our research question was whether SFA restriction could prevent CVDs. Because the outcomes of previous studies included soft endpoints that were questionable, such as chest pain without electrocardiographic changes,[8] we selected cardiovascular death as the primary outcome. Secondary outcomes included all-cause mortality, primary endpoint episodes of each study, myocardial infarction (MI), stroke, and a composite of nonfatal MI, nonfatal stroke, and cardiovascular death.

Data sources and searches

We searched the Cochrane CENTRAL, PubMed, and Ichu-shi databases from inception to April 2023. We selected these three databases according to guideline for systematic review of Medical Information Network Distribution Service Center, Japan Council for Quality Health Care (Minds Centre) who are an official member of Guidelines International Network.[9]

Study selection

We selected only RCTs in the literature review because of the inherent biases in observational research. We did not set limitations regarding publication date or language. Relevant articles were identified according to the literature search strategies developed by the collaborators (librarians) (Supplementary Data S1, S2, and S3). Furthermore, we searched the reference lists of previous studies. The following inclusion criteria were implemented to identify studies for inclusion in our systematic review and meta-analysis: (1) RCT design, (2) the intervention was SFA restriction, (3) the outcome was CVD, and (4) the target population was adults. Two investigators (SY and TS) independently screened the titles and abstracts of articles according to the inclusion criteria. In the next stage of full-text screening, the authors (SY and TS) reached a consensus on which studies should be included or excluded. Disagreements regarding the results of the screened studies were resolved by discussion with a third author (NF).

We used the Rayyan software (Qatar Computing Research Institute) for the screenings. The following information from the eligible studies was extracted by two authors (SY and NF): authors, publication year, country, sample characteristics, sample size, length of follow-up, cardiovascular outcomes, SFA energy percentage (if available), and lipid profile (if available).

Quality assessment

We used the Cochrane Collaboration's risk of bias tool to assess the risk of bias. This tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and others. We also used the Grading of Recommendations Assessment, Development, and Evaluation tool to assess the quality of the evidence based on study limitations, inconsistency of effect, imprecision, indirectness, and publication bias.

Statistical analysis

For the meta-analysis, each relative risk (RR) was combined with SFA restriction, and the pooled RRs with 95% confidence interval (CI) were calculated using the random-effects model. Heterogeneity among the studies was evaluated using I^2 statistics. Funnel plots were used to estimate publication bias. All statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection

A total of 7419 articles were identified during our search; 52 were assessed for their eligibility for inclusion (Fig. 1). Finally, nine studies were included in the systematic review and meta-analysis.[8,10–17]

Characteristics of included studies

Table 1 presents the characteristics of the included studies. The sample sizes in these studies ranged from 50 to 9,057. Five studies were conducted in European countries,[8,10,13,15] two in the USA,[12,14] one in Australia,[16] and one in India.[17] Only two studies were primary prevention trials from the USA[12,14]; the remaining seven were secondary prevention trials. Thus, we did not perform a sub-analysis of primary prevention. Only three studies reported on stroke,[12,15,17] and the incidence of stroke was almost zero in two of those studies.[15,17] Therefore, we did not perform a meta-analysis of stroke and 3-point major adverse cardiovascular events. There was only one study in which the participants took statins, which showed no difference in CVD events between the intervention and control groups.[17] In the other eight studies, no participants used statins. Thus, we did not perform a sub-analysis of statin users. Only one study included female subjects, showing no differences in cardiovascular outcomes between the intervention and control groups.[14] We did not conduct a sub-analysis of sex differences.

Table 1
Characteristics of included studies.

First Author (Publication Year)	Study Name	Country	Population	Number of Subjects (Intervention/Control)	Sex	Follow-up Year	Primary Outcome
Rose et al. (1965)[10]	St. Mary Hosp	UK	Post-MI or angina	54/26	n.a.	2	Sudden death or MI
Leren (1966)[11]	Oslo Diet Heart	Norway	Post-MI	206/206	Male 100%	5	CHD relapse
Research Committee (1968)[8]	MRC	UK	Post-MI	199/194	Male 100%	5	MI
Dayton et al. (1969)[12]	Los Angeles Veterans Administration	USA	Veterans domicile	424/422	Male 100%	8	Sudden death or definite MI
Burr et al. (1989)[13]	DART	UK	Post-MI	1018/1015	Male 100%	2	MI
Frantz et al. (1989)[14]	Minnesota Coronary Survey	USA	Mental hospital or nursing home	4541/4516	Female 41.5%, Male 48.5%	4.5	MI, sudden death, or death
Watts et al. (1992)[15]	STARS	UK	CAG	26/24	Male 100%	3.25	CAG change
Ramsden et al. (2013)[16]	Sydney Diet Heart Study	Australia	Post-ACS	221/237	Male 100%	5	Death
Vijayakumar et al. (2016)[17]	Amrita Institute	India	Stable CAD	100/100	Female 6.6%, Male 93.4%	2	Anthropometric change, lipid profile

ACS, acute coronary syndrome; CAG, coronary angiography; CHD, coronary heart disease; MI, myocardial infarction; CAD, coronary artery diseases

Results of the meta-analysis

Combining all trials, the pooled risk reduction for cardiovascular mortality was not significant (RR = 0.94, 95% CI: 0.75–1.19) (Fig. 2). There was no reduction in all-cause mortality (RR = 1.01, 95% CI: 0.89–1.14) (Fig. 3). There were no statistically significant reductions in RR regarding MI (RR = 0.85, 95% CI: 0.71–1.02), any coronary events (RR = 0.85, 95% CI: 0.65–1.11), or primary events in each study (RR = 0.93, 95% CI: 0.75–1.16) (Figs. 4, 5, and 6).

Test of bias

Funnel plots of cardiovascular mortality and all-cause mortality showed no publication bias, as well as any other outcomes (Figs. 7 and 8). Given the possibility that some studies had insufficient SFA restriction for statistical significance, we plotted the relationship between the difference in SFA intake between the two groups and the relative risk reduction (RRR) for each trial. There was no association between the difference in SFA intake and RRR for all outcomes (Fig. 9). Furthermore, there was no association between the study duration and RRR or absolute risk reduction for any outcome, considering metabolic memory and legacy effect (data not shown).

Discussion

Recent discussion

Although SFA restriction has long been advocated by ACC/AHA guideline,[18] it is based on observational studies only.[19,20] One showed positive correlation between SFA intake and all-cause mortality[19] but not in another.[20] The Prospective Urban Rural Epidemiology (PURE) study showed negative correlation between SFA intake and all-cause mortality.[20] Thus, it has recently been debated.[21–24] In debate papers in the *American Journal of Clinical Nutrition*, Krauss and Kris-Etherton could not agree on several points.[22–24] The first point is "Does lowering SFA intake reduce the incidence of CVD?".[24]

Previous meta-analysis 1

Several meta-analyses of RCT have been conducted on SFA restriction[25–27] and are referred to as evidence supporting the recommendation of SFA restriction in ESC/EAS.[28] Mozaffarian et al.[25] reported a significant reduction in CVD events with SFA restriction. The discrepancy between our current meta-analysis and previous studies is due to differences in the included studies (Table 2). Because Mozaffarian et al. did not describe their strategy for the literature search, we could not follow their search and study selection strategy. However, the Finnish Mental Hospital Studies,[29,30] which were adopted in Mozaffarian et al.'s study, were excluded from our current study. The reason for this exclusion was that these were non-randomized cross-over trials. Moreover, in these studies, the subject population was admitted patients in two mental hospitals, and they could discharge or admit during study period. In a male study, among a total of 676 hospitalized patients, only 36.4% (n = 246) remained hospitalized during both interventional and control periods.[29] In a female study, only 20.6% (122 out of 591) remained hospitalized during both periods.[30] The majority of these studies were non-randomized and did not follow a cross-over design.[29,30] We believe these studies might have been influenced by differences in patient characteristics and treatment policies other than by diet. Furthermore, there were differences in the interventional and conventional diets between the two mental hospitals.[29,30] We think these studies should be excluded in Mozaffarian et al.'s study.[25] Several studies which were included in our meta-analysis were not adopted by Mozaffarian et al.[25] For example, Rose et al.'s study[10] and the Sydney Diet Heart Study[16] would have been great additions to Mozaffarian et al.'s study.[25]

Table 2
Characteristics of excluded studies which were included in other meta-analyses.

First Author (Publication Year)	Study Name	Population	Reason of Exclusion
Turpeinen et al. (1979)[29]	Finnish Mental Hospital Study (Men)	Mental Hospital Patient	Non-randomized study Cross-over design without evaluation of carry-over effect
Miettinen et al. (1983)[30]	Finnish Mental Hospital Study (Women)	Mental Hospital Patient	Non-randomized study Cross-over design without evaluation of carry-over effect
Black et al. (1994)[31]	n.a.	Previous skin cancer	Total fat reduction intervention but not SFA No data for CVD or death
Houtsmuller et al. (1980)[32–34]	n.a.	Diabetes	Unknown definition of cardiac ischemia Glucose improvement only in female
Ley et al. (2004)[35]	n.a.	Prediabetes	Total fat reduction intervention but not SFA No data for CVD or death
Moy et al. (2001)[36]	n.a.	Healthy siblings with a family history of CHD	No data for CVD or death
Howard et al. (2006)[37]	Women's Health Initiative	Postmenopausal women	Total fat reduction intervention but not SFA

SFA, saturated fatty acids; CVD, cardiovascular diseases; n.a, not applicable

Previous meta-analysis 2

In the presidential advisory of the AHA by Sacks et al.,[26] the literature search strategy was not described, similar to Mozaffarian et al.'s study.[25] They also adopted the Finnish Mental Hospital Studies,[29,30] which are non-randomized cross-over trials. We believe a cross-over design trial is not appropriate for the cardiovascular outcome trial because there may be a carry-over effect, which is called metabolic memory or legacy effect (Table 2).

Previous meta-analysis 3

Regarding the Cochrane Systematic Review by Hooper et al.,[27] the results of cardiovascular (RR = 0.96; 95% CI: 0.90–1.03) and all-cause mortalities (RR = 0.94; 95% CI 0.78–1.13) were similar to those of our current study (RR = 0.94; 95% CI: 0.75–1.19 for cardiovascular mortality and RR = 1.01; 95% CI: 0.89–1.14 for all-cause mortality). However, Hooper et al. reported a statistically significant reduction (p = 0.03) in combined cardiovascular events with SFA reduction (RR = 0.83, 95% CI: 0.70–0.98),[27] different from that of our study. As they did not describe the literature search strategy, as with the two previous meta-analyses,[25,26] we could not follow their search and study selection strategy. However, they included several studies we could not include in the current study (Table 2).[31–37] First, Black et al. reported the outcomes of patients with skin cancer and actinic keratosis.[31] Furthermore, dietary intervention involves the reduction of total fat but not SFA. Second, the primary outcome of Houtsmuller et al.'s study was diabetic microangiopathy or retinopathy, but not CVD.[32] Other reports of Houtsmuller et al.'s studies have reported cardiovascular outcomes; however, the definition or criteria for cardiac ischemia have not been described.[33,34] Furthermore, there was a statistically significant difference in the glucose levels between the two groups in females only.[33] However, this phenomenon could not be explained in terms of causality. We judged this study to be too unique

for inclusion in the current study. Third, we could not determine the incidence of cardiovascular events in Ley et al.'s study.[35] The outcome of this study was CVD risk factors but not CVD events. Furthermore, the dietary intervention in this study was solely a reduction in total fat but not in SFA.[35] Fourth, in Moy et al.'s study, we could not determine the incidence of any cardiovascular events.[36] The outcome of this study was adherence to dietary counseling, but not CVD events.[36] Finally, the intervention of the Women's Health Initiative was solely a reduction in total fat but not in SFA.[37] In this largest RCT on total fat reduction, there was no difference in CV outcomes among the study participants. However, deterioration of CV outcomes and all-cause mortality were reported in secondary prevention subpopulations despite an approximately 4 mg/dl reduction in LDL-C.[37,38] Again, we must recognize that "lowering LDL cholesterol is good," but determining "how and in whom" is crucial.[6]

The narrow evidence of SFA restriction

Owing to the limitations of previous meta-analyses on SFA reduction, we attempted to renew the meta-analysis in a methodologically understandable manner. We found no statistically significant CVD prevention owing to SFA reduction. Furthermore, in several studies that reported positive results for SFA reduction in our meta-analysis,[8,11,12,15] no participants were prescribed statins. Moreover, no study has supported SFA reduction in women. According to the WHO report by Mensink, the replacement of 1% energy from SFA with PUFA reduced LDL-C by 0.055 mmol/L (2.1 mg/dl); MUFA and carbohydrates reduced LDL-C by 0.042 mmol/L (1.6 mg/dl) and 0.033 mmol/L (1.3 mg/dl), respectively.[4] Such small changes in LDL-C do not appear to affect cardiovascular outcomes and serum lipid profiles under the administration of statins, which can reduce LDL-C by approximately 50 mg/dl.[39] Furthermore, if the LDL-C level remains higher than the target level under statin administration, ezetimibe and PCSK9 inhibitors can be administered.[40]

Limitations

Our study has some limitations. RCTs on diet cannot be completely blinded, and there is a proportional risk of bias. However, this is a common limitation in studies on dietary interventions. Second, most studies were conducted in Western countries and failed to examine racial or ethnic differences. Third, many studies have been conducted on interventions that change animal fats to vegetable fats and have not analyzed individual saturated fatty acids with different chain lengths. For example, the difference between milk and meat fats remains unclear.

Conclusions

The evidence available from RCTs does not support SFA restriction for the prevention of CVDs. Clinical trials are needed to evaluate the effect of SFA reduction under statin administration and to recommend SFA reduction for CVD prevention and LDL-C reduction. In such trials, researchers should address the sex-related differences.

Abbreviations

CI - confidence interval

CVD - cardiovascular diseases

LDL-C - low-density lipoprotein cholesterol

MUFA - monounsaturated fatty acids

PUFA - polyunsaturated fatty acids

RCT - randomized controlled trials

RR - relative risk

RRR - relative risk reduction

SFA - saturated fatty acid

Declarations

Ethics approval and consent to participate

The protocol for this study has been approved by the Kitasato Institute Hospital Research Ethics Committee (Approval No.22057). The ethics committee waived the need for informed consent as this is a systematic review.

Consent for publication

Not Applicable

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/. Satoru Yamada received honoraria for lectures from Elly Lilly and Eat Fun Health Association and has stock in LOCABO® Inc. Tomomi Shirai, Sakiko Inaba, Gaku Inoue, Minami Torigoe, and Naoto Fukuyama declare no competing of interest.

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Author contributions

Conceptualization, SY, TS, SI, MT, and NF. Methodology, SY and TS. Literature Search, SY, TS, SI, and MT. Data Screening, SY, TS, and NF. Formal Analysis, SY, TS, and GI. Writing-Original Draft Preparation, SY. Supervision, NF. Guarantor: SY. The guarantor accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figures

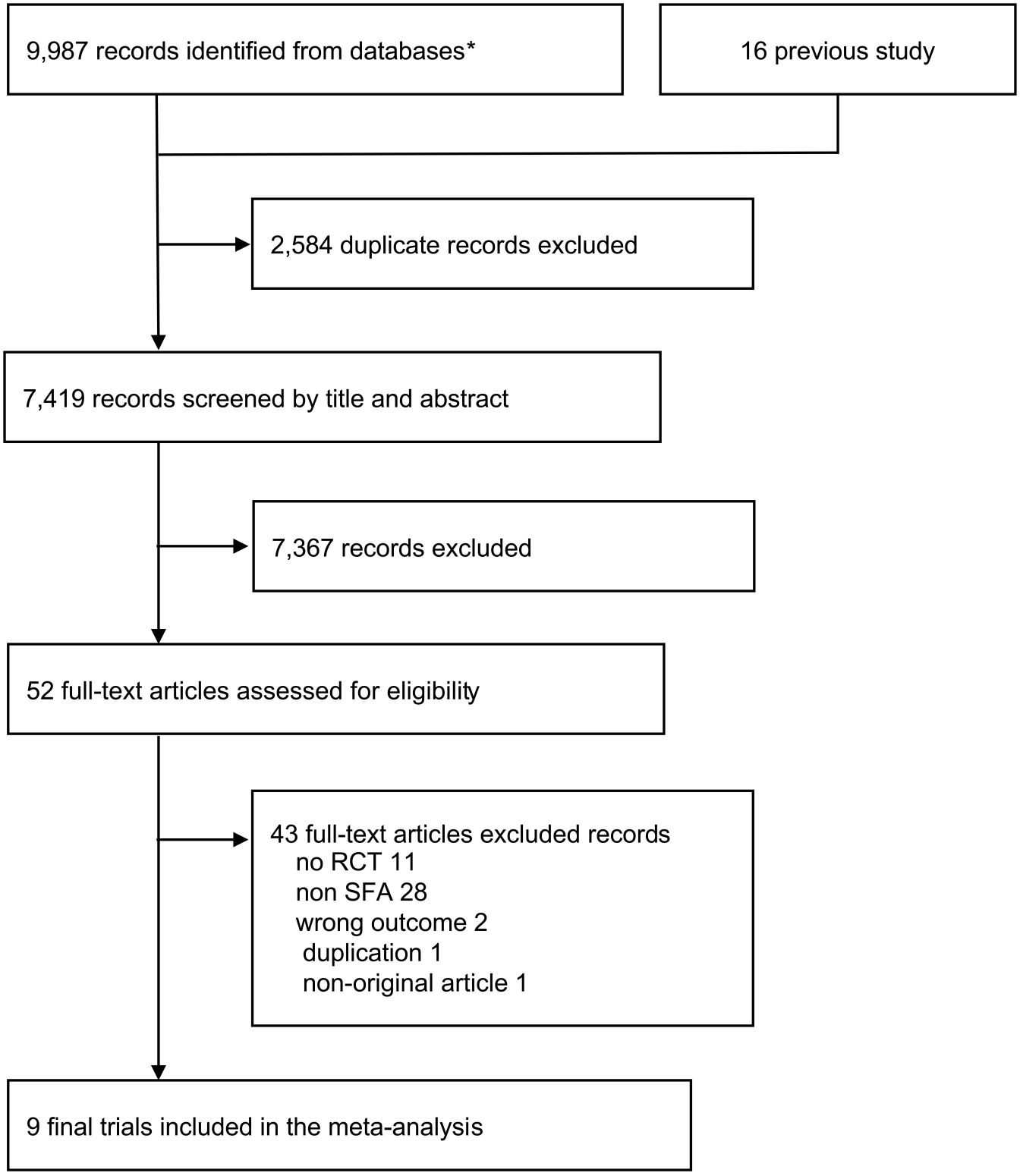

Figure 1

Results of the systematic search and study selection process.

* indicates The PubMed, Cochrane CENTRAL, and Ichusi databases.

A total of 9987 studies were included: 3969 from PubMed, 5919 from Cochrane CENTRAL, and 99 from Ichusi.

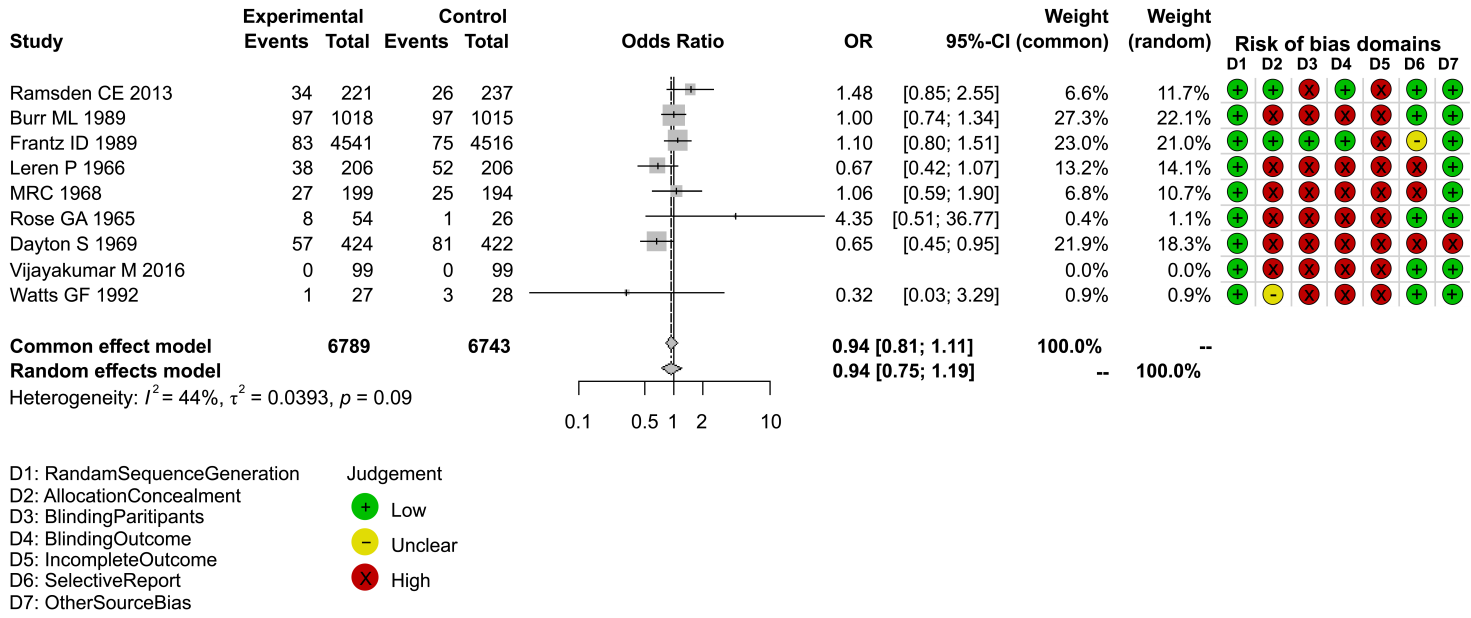

Figure 2

Forest plots of saturated fatty acid reduction trials on cardiovascular mortality.

There was no statistically significant reduction.

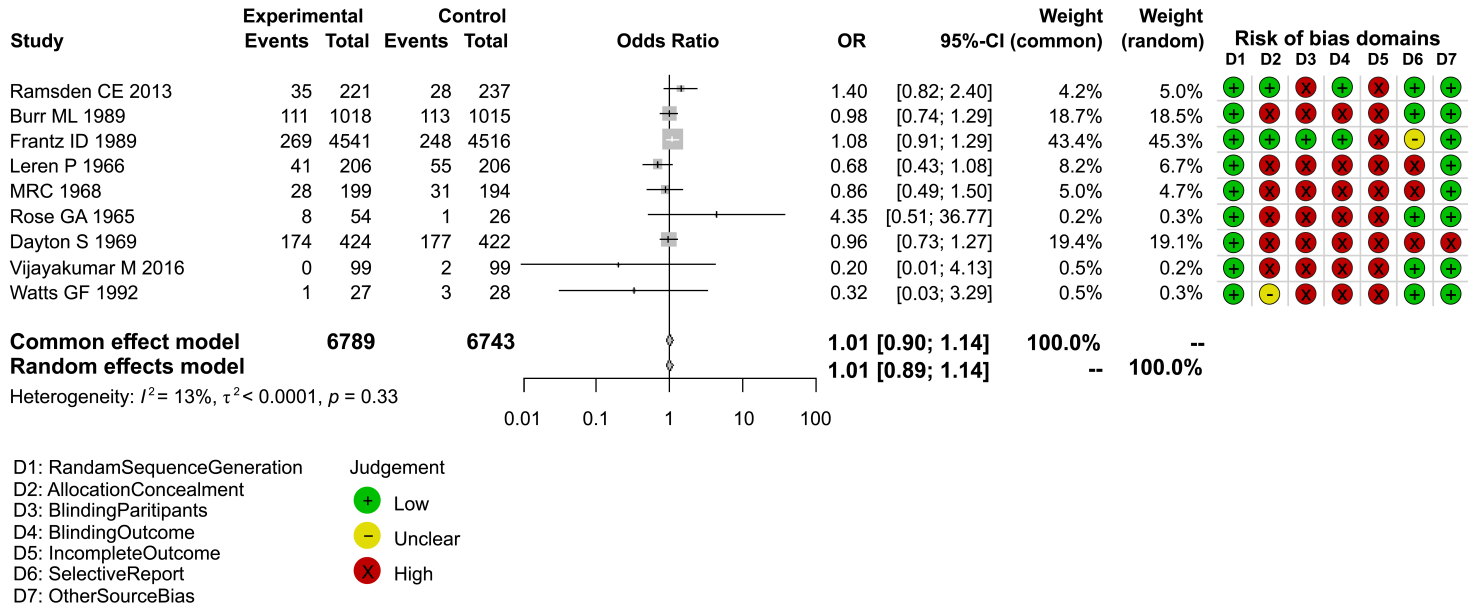

Figure 3

Forest plots of saturated fatty acid reduction trials on all-cause mortality.

There was no statistically significant reduction.

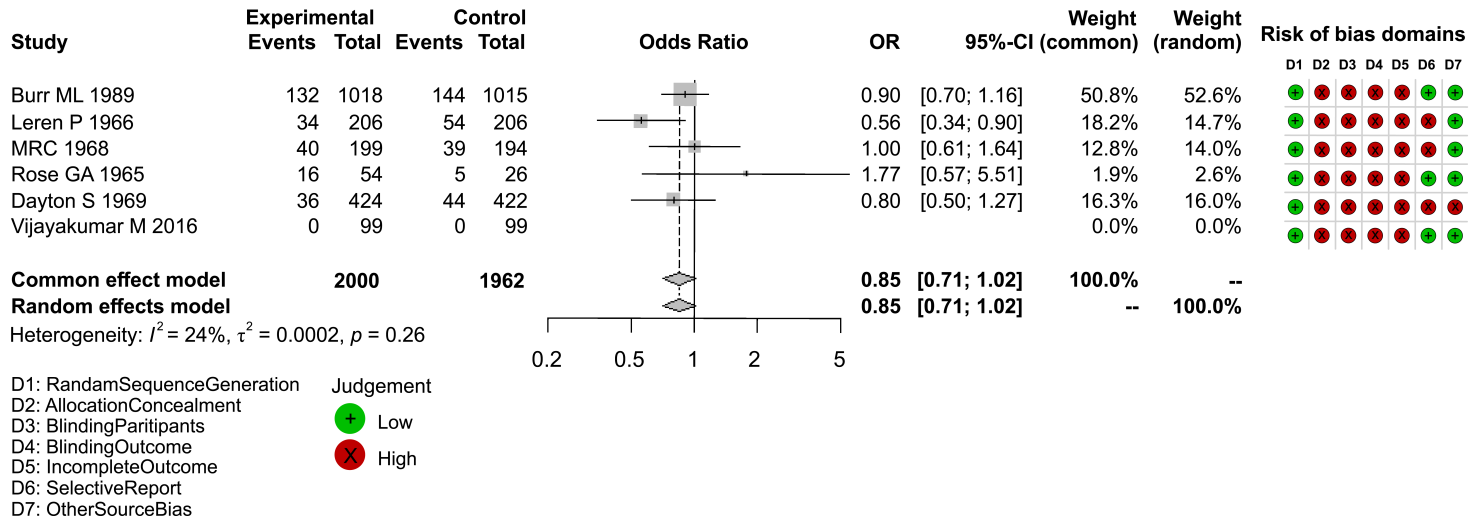

Figure 4

Forest plots of saturated fatty acid reduction trials on myocardial infarction.

There was no statistically significant reduction.

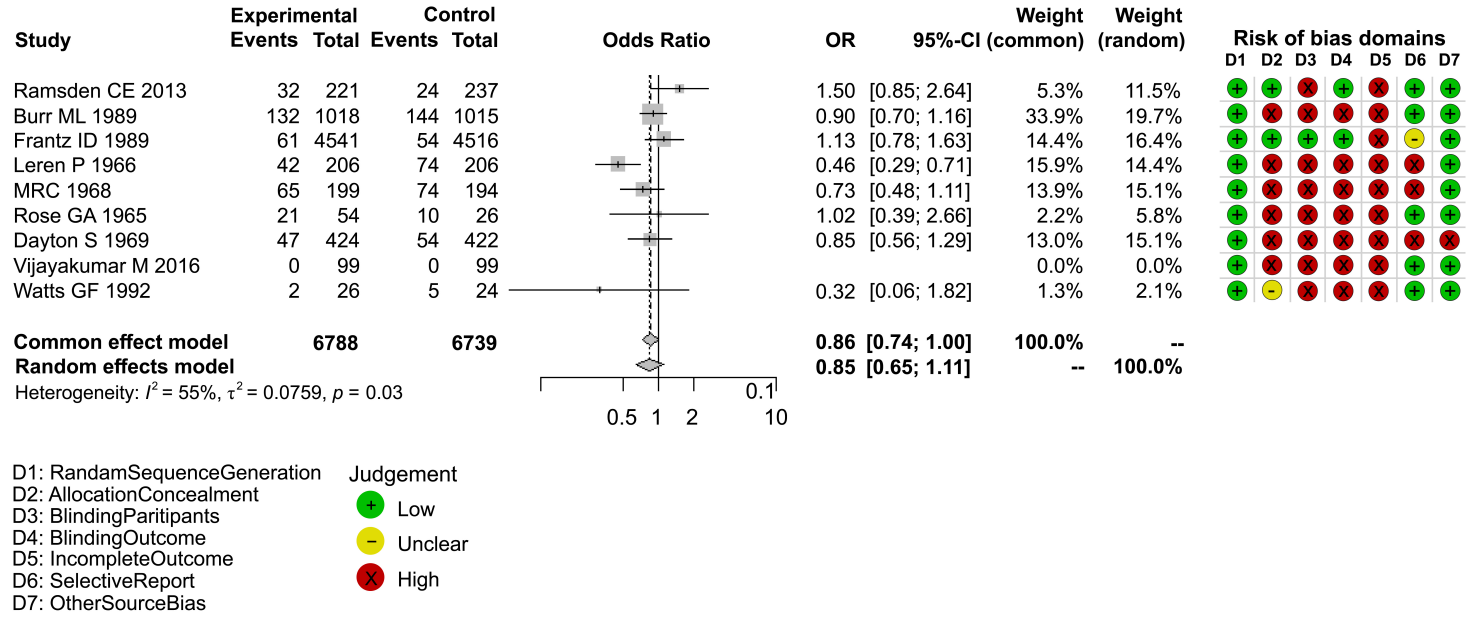

Figure 5

Forest plots of saturated fatty acid reduction trials on any coronary event.

There was no statistically significant reduction.

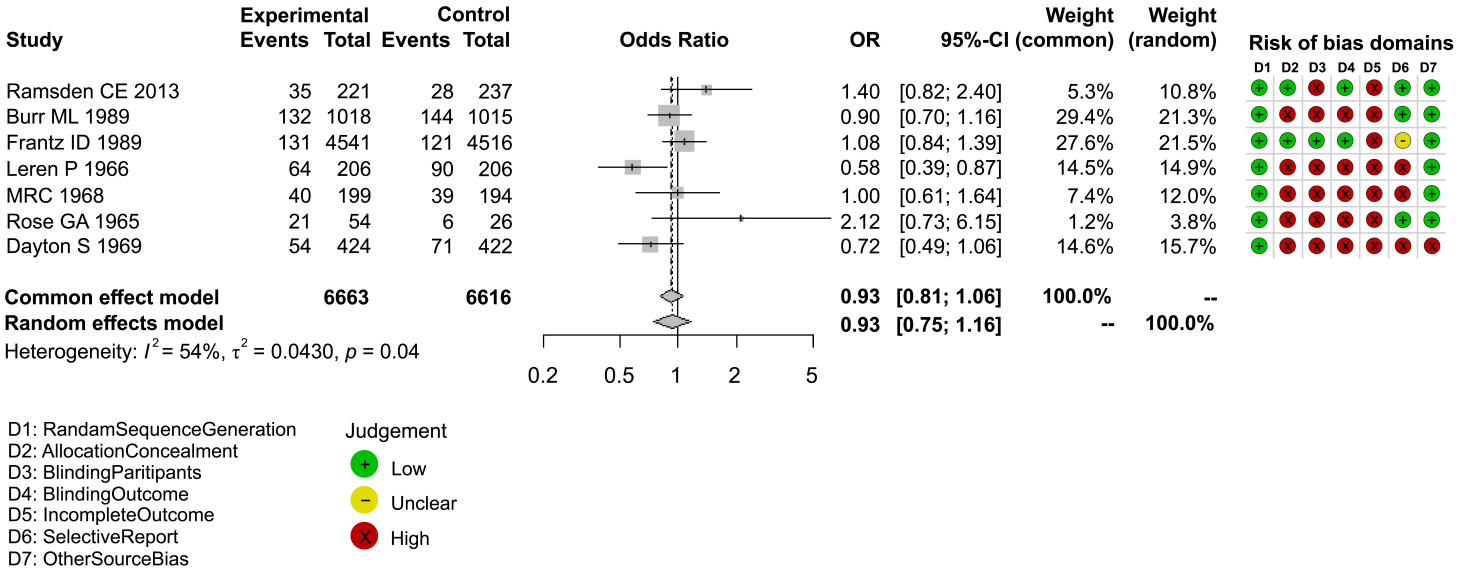

Figure 6

Forest plots of saturated fatty acid reduction trials on the primary outcomes in each study.

There was no statistically significant reduction.

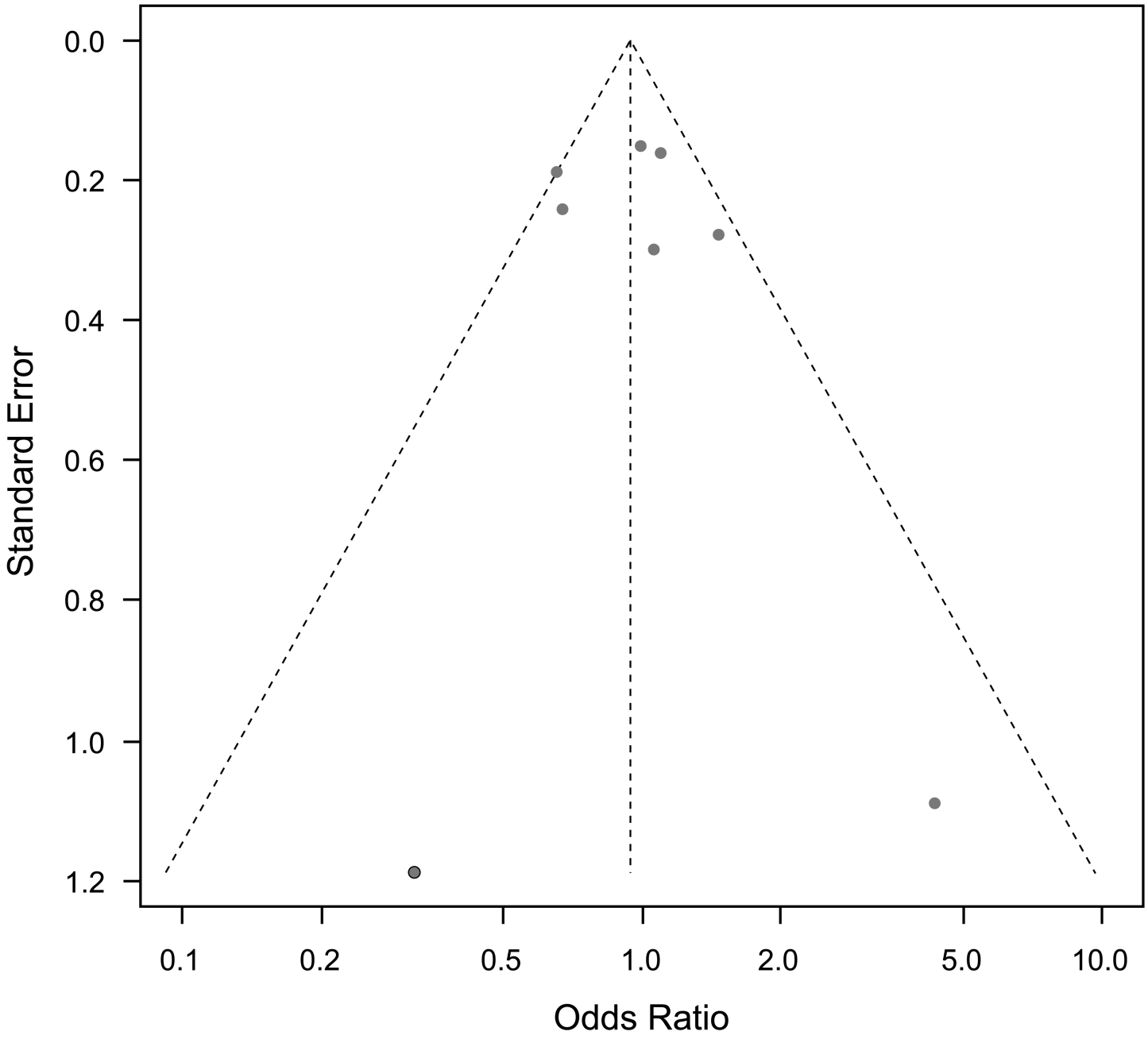

Figure 7

Funnel plots of saturated fatty acid reduction trials on cardiovascular mortality.

There was no publication bias.

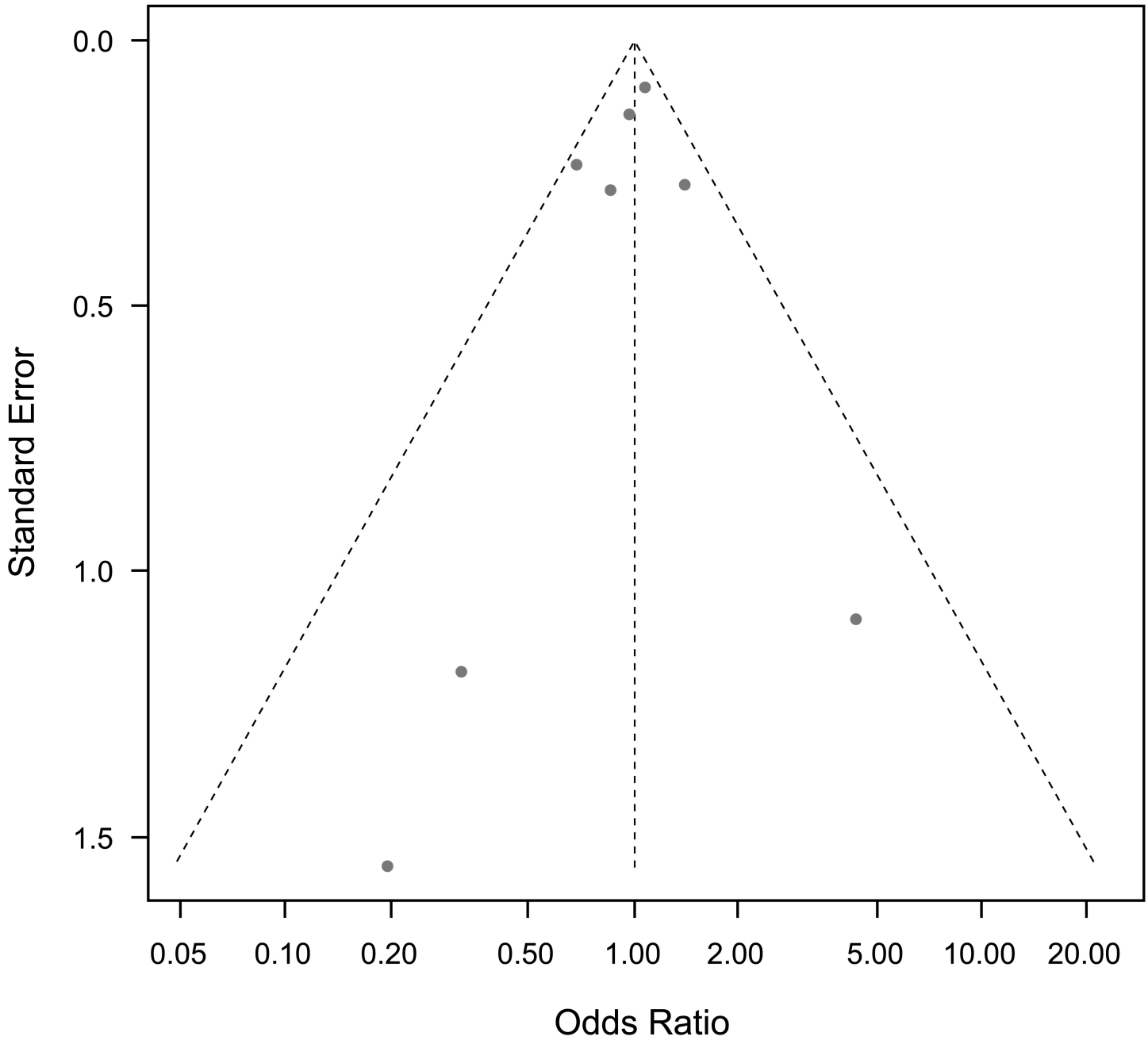

Figure 8

Funnel plots of saturated fatty acid reduction trials on all-cause mortality.

There was no publication bias.

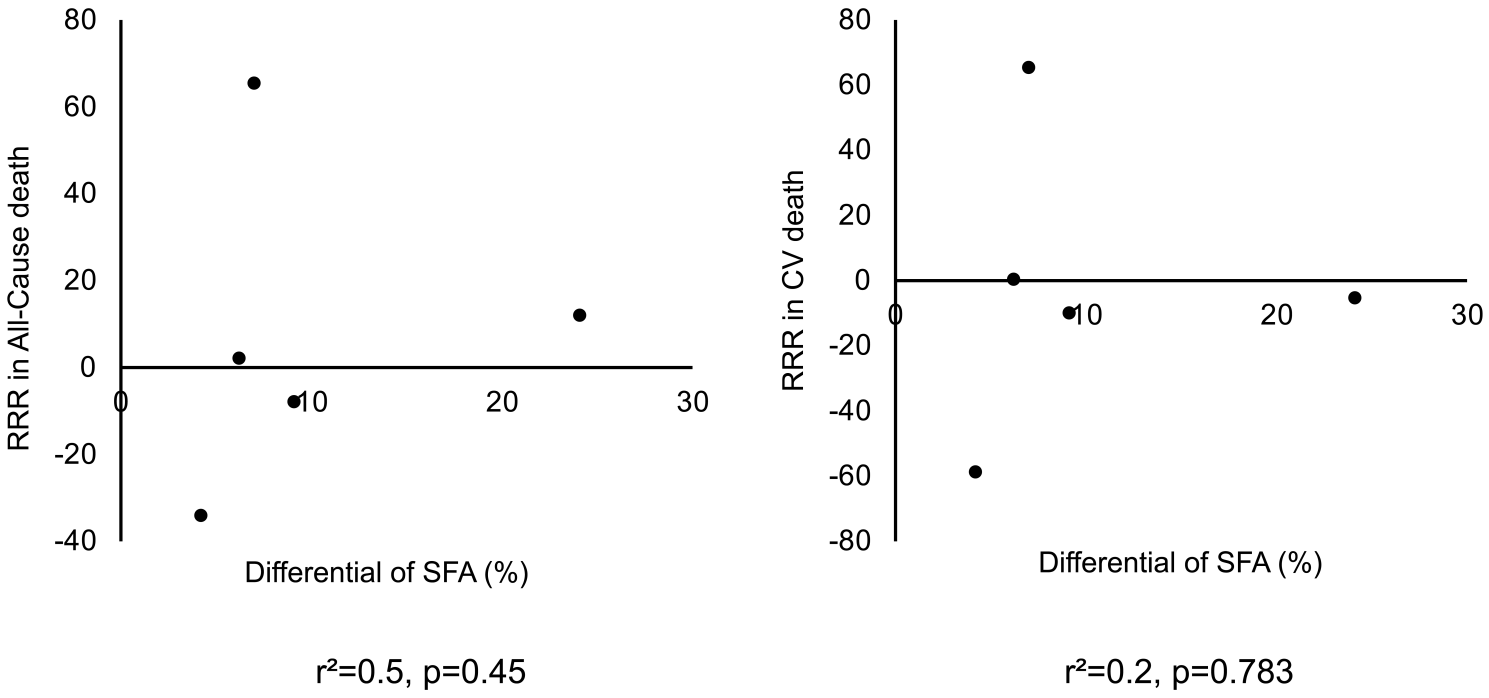

Figure 9

The relationship between the reduction in saturated fatty acid intake and relative risk reduction of cardiovascular mortality (right) and all-cause mortality (left).

There was no association.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020Checklist.docx
- SupplementaryMaterials.docx