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

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ABSTRACT

Objective: Previous systematic reviews were not restricted to either primary or secondary prevention trials, this study aimed to investigate the effects of reduced and/or modified fat diets and dietary fatty acids on all-cause mortality, cardiovascular mortality and cardiovascular events in participants with established coronary heart disease.

Design: Systematic review, meta-analysis and univariate/multivariate meta-regression.

Eligibility and criteria for selecting studies: Electronic searches for randomised controlled trials comparing reduced/modified fat diets versus control diets were performed in MEDLINE, EMBASE and the Cochrane Library.

Data extraction: Pooled effects were calculated using an inverse-variance random effect meta-analysis. Random effects univariate and multivariate meta-regressions were performed including changes in all types of dietary fatty acids.

Results: Overall, 12 studies enrolling 7150 participants were included in the present systematic review. No significant risk reduction could be observed considering all-cause mortality (relative risk (RR) 0.92, p=0.60; I^2=59%) and cardiovascular mortality (RR 0.96, p=0.84; I^2=69%), combined cardiovascular events (RR 0.85, p=0.30; I^2=75%) and myocardial infarction (RR 0.76, p=0.13; I^2=55%) comparing modified fat diets versus control diets. This results could be confirmed for the reduced fat versus control diets (RR 0.79, p=0.47; I^2=0%), (RR 0.93, p=0.66; I^2=0%), (RR 0.93, p=0.71; I^2=57%) and (RR 1.18, p=0.26; I^2=18%). The multivariate and univariate model showed no significant associations between the independent variables and the changes from saturated fat, monounsaturated fat, polyunsaturated fat and linoleic acid. Sensitivity analyses did not reveal a significant risk reduction for any outcome parameter when polyunsaturated fat was increased in exchange for saturated fat.

Conclusions: The present systematic review provides no evidence (moderate quality evidence) for the beneficial effects of reduced/modified fat diets in the secondary prevention of coronary heart disease. Recommending higher intakes of polyunsaturated fatty acids in replacement of saturated fatty acids was not associated with risk reduction.

Strengths and limitations of this study

- Twelve studies enrolling 7150 participants were included in the present meta-analysis and meta-regression.
- Replacing saturated fatty acids by polyunsaturated fatty acids showed no significant benefit in the secondary prevention of coronary heart disease.
- Some of the included studies date back to 50 years.
- Substantial heterogeneity was observed for several outcomes.

INTRODUCTION

Studies reporting an association between intake of dietary saturated fatty acids (SFA) and serum cholesterol levels go back to the 1950s and 1960s.[1 2] Supported by the epidemiological data observing a correlation between SFA intake and coronary heart disease (CHD) mortality, these findings established a reduction of SFA consumption as a major focus of dietary recommendations in order to prevent the prevalence of CHD[3] although Siri-Tarino *et al*[4] observed no relationship between saturated fats and CHD, stroke and cardiovascular disease (CVD) following a meta-analysis including 21 prospective studies.

Exchanging SFA for polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), carbohydrates (CHO) or protein exerted different effects on blood lipids and lipoproteins.[5] In a systematic review and meta-analysis of cohort studies and randomised controlled trials (RCTs), Skeaff and Miller[6] concluded that there is convincing evidence that replacement of SFA by PUFA decreases the risk of fatal CHD and CHD events; however they could not confirm the hypothesis of a direct association between SFA intake and CHD death.[6] Furthermore,

the authors inferred that replacing SFA with CHO had no relation to CHD. The follow-up final report from the FAO stated that SFA intake should not be higher than 10% of the total energy consumption and that SFA should be replaced with PUFA.[7] In their meta-analysis of cohort studies, Jakobsen *et al*[8] observed that replacing SFA with PUFA reduced the risk of coronary events by 13% and the risk of coronary deaths by 26%, respectively. In contrast, replacement of SFA by CHO or MUFA marginally increased the risk of coronary events, whereas no significant effects on coronary death could be observed. Mozaffarian *et al*[9] investigated the effects of increasing PUFA in replacement of SFA, and observed a significant decrease in the risk of CHD or associated mortality rates, while Hooper *et al*[10] reported a reduction in cardiovascular risk subsequent to a long-term reduction or modification in dietary fat intake. In an update of their meta-analysis, the same research team suggested that lowering of SFA intake led to a 14% decrease of the risk of cardiovascular events, however without affecting the cardiovascular or total mortality rates.[11] It should be noted that reduction in cardiovascular risk was not associated with total fat in this study, but rather with a modification in dietary fat without clarifying the ideal type of unsaturated fat to replace SFA. Nevertheless, the US Dietary Guidelines recommend that <10% of total energy content (TEC) should come from SFA and that saturated fat should be replaced with MUFA and PUFA.[12] In 2011, the American Heart Association (AHA) and the American College of Cardiology (ACC) published a joint guideline endorsing less than 7% of TEC in the form of SFA for patients with coronary as well as other atherosclerotic vascular diseases.[13] Since previous systematic reviews were not restricted to either primary or secondary prevention trials, this study aimed to investigate the effects of reduced/modified fat diets versus control diets on all-cause mortality, cardiovascular mortality, cardiovascular events (myocardial infarction, stroke) in participants with established CHD. The aim of the meta-regression was to include clinical outcomes and all dietary fatty acid changes in a univariate and multivariate model.

MATERIALS AND METHODS

Literature search

Queries of literature were performed using the electronic databases MEDLINE, EMBASE and the Cochrane Trial Register (until February 2014, respectively) with restrictions to RCTs, but no restrictions to language and calendar date using the following search terms: *(dietary fat OR fatty acids OR low fat diet OR modified fat diet) in combination with (secondary prevention OR cardiovascular disease OR myocardial infarction OR coronary heart disease).* Moreover, the reference lists from retrieved articles, systematic reviews and meta-analyses were checked to search for further relevant studies. This systematic review was planned, conducted and reported in adherence to the standards of quality for reporting meta-analyses.[14] Literature search was conducted independently by both the authors, with disagreements resolved by consensus.

Eligibility criteria

Studies were included in the meta-analysis if they met all of the following criteria: (1) randomised controlled design; (2) minimum intervention period with a follow-up of 12 months; (3) comparing a reduced fat (<30% of TEC) and/or modified fat diet versus control diet (SFA, MUFA, PUFA, linolenic acid and α-linolenic acid values were either extracted from intervention/dietary protocols or calculated from published data); (4) assessment of the 'outcome of interest' markers: all-cause mortality, cardiovascular mortality, combined cardiovascular events, myocardial infarctions (fatal and non-fatal); (5) report of the number of events and sample size for each group and (6) only participants with established CHD (survivor of myocardial infarction, stable/unstable angina pectoris, acute coronary insufficiency) or coronary artery disease (CAD, verified by coronary angiography).

Types of intervention

The focus of this systematic review was set on examining the effects of reduced/modified fat diets as compared with control diets on 'hard' clinical endpoints.

Risk of bias assessment and quality assessment

Full copies of studies were independently assessed for methodological quality by both the authors using the risk of bias assessment tool by the Cochrane Collaboration. The following sources of bias were detected: selection bias (random sequence generation, allocation concealment), performance/detection bias (blinding of participants and personnel, blinding of outcome assessment), attrition bias (incomplete data outcome), reporting bias (selective reporting) and other bias (figure 1).[15 16]

Data extraction and statistical analysis

The following data were extracted from each study: the first author's last name, publication year, study duration, participant's sex and age, body mass index, sample size, SFA, MUFA, PUFA, linoleic acid, α-linolenic acid, dietary cholesterol content of intervention protocol or dietary protocol, caloric intake, information on supplements, primary outcomes, number of events. For each outcome measure of interest, a random-effects inverse-variance meta-analysis was performed in order to determine the pooled effect of the intervention in terms of relative risks (RRs) and number of events of the reduced fat versus control diets, and modified fat versus control groups. All data were analysed using the REVIEW MANAGER V.5.1 software, provided by the Cochrane Collaboration (http://ims.cochrane.org/revman). Heterogeneity between trial results was tested with a standard χ^2 test. The I^2 parameter was used to quantify

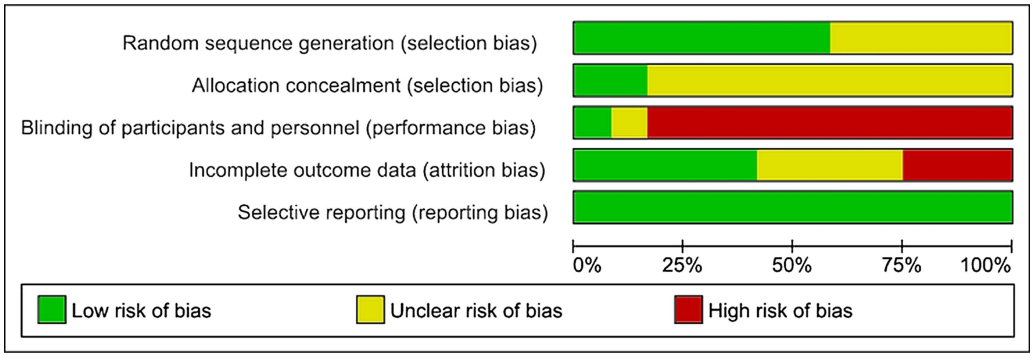

Figure 1 Risk of bias assessment tool. Across trials, information is either from trials at a low risk of bias (green), or from trials at unclear risk of bias (yellow), or from trials at high risk of bias (red). For each study, every bias domain will be checked, the given summary represents an assessment of bias risk across studies. For each bias domain, low risk of bias means that information is from studies at low risk of bias, high risk of bias indicates the proportion of information from studies at high risk of bias which might be sufficient to affect the interpretation of the results, and unclear risk of bias refers to information from studies at low or unclear risk of bias.

any inconsistency: $I^2=[(Q-df)]/Q\times100\%$, where Q is the χ^2 statistic and df is its degrees of freedom. A value for $I^2>50\%$ was considered to represent substantial heterogeneity.[17] To consider heterogeneity, the random-effects model was used to estimate RRs and MDs with 95% CIs. Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI.

A random-effects univariate meta-regression was performed to examine the association between the change in percentage energy from SFA, PUFA (mixed n-6 and n-3), MUFA, as well as linoleic acid in the interventions versus control groups, and the dependent variables (log change RRs for all-cause mortality, CVD mortality, cardiovascular events and myocardial infarction). Furthermore, multivariate analyses were performed including all dietary fatty acid changes in a meta-regression model. As reported previously by Mensink *et al*,[5] effects of protein (available only for five studies) and alcohol could not be estimated. The p values for differences in effects between the covariates were obtained using the *metareg* function of STATA V.12.0 (Stata-Corp, College Station, Texas, USA). Two sided p values <0.05 were considered to be statistically significant. To determine the presence of publication bias, the symmetry of the funnel plots was assessed in which mean differences were plotted against their corresponding SEs. Sensitivity analyses were carried out to evaluate the influence of single trials on each meta-regression result. In addition, sensitivity analyses for PUFA versus SFA trials focusing on secondary prevention and sensitivity analysis for trials adopting 'fish advice' versus 'no fish advice' and combining reduced and modified fat diets were performed.

The quality of evidence was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.[18 19]

Missing data

Exposure data (SFA, PUFA, MUFA) for three study control groups[20–22] were imputed based on average background dietary intakes in similar populations at that time period, the corresponding data were derived from the National Diet Heart Study control group.[23] For evaluating linoleic acid, all of the trials that reported on total PUFA were included. Except for the Lyon Diet Heart Study, none of these studies had a major focus on n−3 fatty acids. Therefore, total PUFA in each of these other trials would be nearly all (90%+) linoleic acid. For studies giving information on the type of vegetable oil used, the proportion of linoleic acid and α-linolenic acid in total PUFA could be directly calculated.

RESULTS

Study characteristics

Altogether, 12 studies extracted from 2059 articles met the inclusion criteria and were included in the quantitative analysis.[20–22 24–33] The study by Singh *et al*[31] was included only in the sensitivity analysis, since this publication has been questioned for veracity.[34 35] The detailed steps of the meta-analysis/meta-regression article selection process are described as a flow diagram in the online supplementary figure S1.

All studies included were RCTs with a duration ranging between 12 months and 6 years, published between 1965 and 2013 and enrolling a total of 6744 participants (7150 including the Singh trial). General and specific study characteristics are summarised in table 1 and online supplementary table S1, respectively.

All studies included participants with established CHD. Some trials had to be excluded due to various reasons: one study enrolled participants at high risk of CHD with only 50% of its participants suffering from CAD[36]; another trial was not randomised[37]; a recently performed secondary prevention RCT comparing a Mediterranean versus a low fat diet did not fulfil the inclusion criteria, since the intervention groups were not distinguished with respect to SFA intake[38]; all secondary prevention studies with multifactorial

intervention protocols (eg, smoking cessation, better drug control, stress management or exercise) were excluded as well.[39–44]

In the reduced/modified diet groups, the range for SFA varied between 7.2% and 14%, while the respective values in the control group varied between 11.7% and 26.4%. PUFA intakes were in the range 5–20.9%, MUFA ranged between 8% and 26%, and linoleic acid intake was at in the range 3.6–19.7% in the reduced/modified fat diet groups, respectively. Results of the univariate and multivariate meta-regression are summarised in table 2.

Reduced versus control diets; modified fat versus control diets

With respect to clinical endpoints, no significant risk reduction could be observed considering all-cause mortality (RR 0.79 (95% CI 0.42 to 1.48), p=0.47; I^2=0%) and cardiovascular mortality (RR 0.93 (95% CI 0.66 to 1.31), p=0.66; I^2=0%), combined cardiovascular events (RR 0.93 (95% CI 0.65 to 1.34), p=0.71; I^2=57%) and myocardial infarction (RR 1.18 (95% CI 0.88 to 1.59), p=0.26; I^2=19%) comparing reduced fat versus control diets (see online supplementary figures S2–S5). Furthermore comparing modified fat versus control diets showed no significant effects on all-cause mortality (RR 0.92 (95% CI 0.68 to 1.25), p=0.60; I^2=59%) and cardiovascular mortality (RR 0.96 (95% CI 0.65 to 1.42), p=0.84; I^2=69%), combined cardiovascular events (RR 0.85 (95% CI 0.63 to 1.15), p=0.30; I^2=75%) and myocardial infarction (RR 0.76 (95% CI 0.54 to 1.09), p=0.13; I^2=55%) could be observed (see online supplementary figures S6–S9). Pooling reduced and modified fat diets all together resulted in no significant changes (see online supplementary figures S10–S13).

Univariate meta-regression

Taken together, the univariate meta-regression showed no significant association between changes in SFA, PUFA, MUFA, linoleic acid and risk of all-cause mortality, cardiovascular mortality, total cardiovascular events and myocardial infarction (see online supplementary figures S14–S29).

Multivariate meta-regression

Similar to the univariate model, the multivariate meta-regression did not reveal any significant association between changes in SFA, PUFA and MUFA and risk of all-cause mortality, cardiovascular mortality, cardiovascular events and myocardial infarction.

Sensitivity analyses

Sensitivity analyses were performed to evaluate the influence of single trials on each meta-regression. None of the trials had a significant impact on the results of the univariate and multivariate meta-regression.

An additional sensitivity analysis was carried out according to the main analysis of Mozaffarian *et al*[9] as well as Skeaff and Miller,[6] evaluating the replacement of SFA by PUFA (including the new data of the Sydney Diet Heart Study[33]). The results showed that replacing SFA by PUFA was not associated with a significant risk reduction for all-cause mortality, cardiovascular mortality, combined cardiovascular events and myocardial infarction (see online supplementary figures S30–S33) in participants with established CHD/CAD.

Another sensitivity analysis was performed including only those trials recommending a higher consumption of fatty fish. This resulted in a significant reduction of cardiovascular events, cardiovascular mortality and all-cause mortality (see online supplementary figures S34–S36).

Since in the Sydney Diet Heart Study a commercial margarine probably high in transfatty acids was used to deliver PUFA to the intervention group, a sensitivity analysis was performed excluding this trial. However, all results of the primary analysis could be confirmed.

Publication bias

The funnel plots indicate moderate asymmetry, suggesting that publication bias cannot be completely excluded as a factor of influence on the present meta-analysis (see online supplementary figures S37–S40).

Overall quality of evidence

The overall quality of evidence rated according to the GRADE guidelines for all outcomes was moderate.

DISCUSSION

In this systematic review of 7150 participants with established CHD or CAD comparing reduced and/or modified fat diets versus control diets, no significant risk reduction (moderate quality of evidence) for all-cause mortality, cardiovascular mortality, cardiovascular events and myocardial infarction could be observed. Since no previous meta-analysis compared the effects of reduced and/or modified fat diets as a means for secondary prevention, the present data will be discussed together with results of combined primary/secondary prevention trials.

Small but nevertheless significant reductions in cardiovascular events could be observed by Hooper *et al*[45] as well as Truswell[46] following their respective meta-analyses of intervention studies investigating the effects of a modification of fatty acid intake as a secondary preventive measure in patients with CVD. Systematic reviews analysing trials targeted both at primary and secondary prevention found that replacing SFA with unsaturated fatty acids reduced cardiovascular events.[11] The question whether these benefits are due to CHO, MUFA or due to PUFA is discussed controversially. The systematic review by Skeaff and Miller observed a significant increase in risk (by 25%) of CHD death in the highest category of dietary PUFA. In contrast, pooling RCTs indicated that a 5% increase in PUFA intake was associated with a significant reduction in CHD events.[6] Mente *et al*[47] observed a

Table 1 General study characteristics

Reference	Sample size, baseline BMI (kg/m²)	Age (years), female (%) male (%)	Duration (years)	SFA/PUFA/MUFA/trans FA (as indicated by the investigators)	LA, ALA	Fish consumption advice	TF, cholesterol	Inclusion criteria	Supplement	Energy amount (end of the study)	Outcomes
Ball *et al* (1965)[20]*	264 nd	<65 100%	4	I: 9%, 5%, 8% C: 16–18%, 7%, 15%	I: 4.5% C: 6.3%		I: 22%, 330 mg C: 47%, 650–750 mg	Post-MI	–	2030 2360	ACM, CVM, CVE, MI
Burr *et al* (1989)[27]	2033	56.6 100%	2	I: 11.3%, 8.9%, 12.1% C: 15%, 6.4%, 13.6%	I: 8.01% C: 5.76%		I: 32.3% C: 35%, 650–750 mg	Post-MI	–	nd	ACM, CVM, CVE
de Lorgeril *et al* (1994)[24]	605 nd	53.5 9.25% 90.75%	4	I: 8.3%, 8.2%, 12.9% C: 11.7%, 11.4%, 10.3%	I: 3.6%, 0.81% C: 5.3%, 0.27%	yes	I: 30.5%, 217 C: 32.7%, 318 mg	Post-MI	I: Canola oil based margarine	1928 2140	ACM, CVM, CVE
Howard *et al* (2006)[32]	2277 29.1	62.3 100%	6	I: 9.5%, 6.1%, 10.8%, 1.8% C: 12.4%, 7.5%, 14.2%, 2.4%	I: 5.49% C: 6.75%		I: 28.8%, 193.6 mg C: 37%, 243.5 mg	Post-MI, stroke, CABG or PCI	–	1431 1546	CVM, CVE, MI, stroke
Leren *et al* (1970)[21]*	412 nd	56.25 100%	5	I: 8.5%, 20.7%, 10.1% C: 16–18%, 7%, 15%	I: 14.8%, 2.7% C: 3.3%, nd	yes	I: 39%; 264 mg C: 40%, 650–750 mg	Post-MI	I: 75 g Soya-bean oil	2380	ACM, CVM, CVE, MI
MRC (1968)[26]	393 nd	53.5 100%	5	I: 11.3%, 20.4%, 14.3% C: 26.4%, 4.4%, 12.2%	I: 16.3%, 2.3% C: 3.96		I: 46% C: 43%, 650–750 mg	Post-MI	I: 85 g soya-bean oil	nd nd	ACM, CVM, CVE, MI
Michalsen *et al* (2006)[29]	101 26.55	59.4 23% 77%	1	I: 10.1%, 6.1%, 10.6% C: 13%, 7.4%, 12.2%	I: 4.8%, 0.72% C: 6.2%, 0.7%	yes	I: 32.2%, 251 C: 35.2%, 265 mg	CAD verified by coronary angiography	–	2241 2237	–
Rose *et al* (1965)*[22]	80 nd	<70 100%	2	I: instructed to avoid fried foods, fatty meats, sausages, pastry,	I-olive: 8.2%, 0.28% I-corn: 19.7%, 0.07% C: 6.3%		I-olive: 46.2% I-corn: 50.5% C: 32.5%	Post-MI, angina pectoris	I: 80 g olive oil; 80 g corn oil	2045 2070 1933	ACM, CVM, CVE, MI

Continued

Table 1 Continued

Reference	Sample size, baseline BMI (kg/m²)	Age (years), female (%) male (%)	Duration (years)	SFA/PUFA/MUFA/trans FA (as indicated by the investigators)	LA, ALA	Fish consumption advice	TF, cholesterol	Inclusion criteria	Supplement	Energy amount (end of the study)	Outcomes
				ice-cream, cheese, cakes, butter, milk, eggs restricted I-olive: 11.7%, 8.7%, 26% I-corn: 14%, 21.85%, 14.9% C: no advice on dietary fat C: 16–18%, 7%, 7%							
Singh *et al* (1992)[31]	406 23.8	51.25 12% 88%	1	I: 7.2%, 8.6%, 8% C: 10.8%, 7%, 10.2%	I: 7.74% C: 6.3%	yes	I: 23.8% C: 28%	Post-MI, unstable angina pectoris	–	1810 1940	ACM, CVM, CVE, MI
Sondergaard *et al* (2003)[30]	131 nd	62.5 30% 70%	1	I: 10.3%, 7.5%, 8.4% C: 12%, 6.8%, 10.1%	I: 6.75% C: 6.3%	yes	I: 26.2% C: 28.9%	Post-MI, stable/unstable angina pectoris	–	1520 1550	–
Watts *et al* (1992)[28]	90 26.25	51.4 100%	3	I: 8–10%, 8%, 10%, 1.08% C: 17%, 5.2%,14.8%,, 1.8%	I: 5%, 0.32% C: 3.9%, 0.41%		I: 27% C: 37%	Angina pectoris	–	nd	ACM, CVM, CVE, MI
Woodhill *et al* (1978)[25] Ramsden *et al* (2013)[33]	458 nd	49 100%	5	I: 9.8%, 15.2%, 11.5% C: 13.5%, 8.9%, 13.8%	I: 15%, nd C: 8%, nd		I: 38.3%, 248 C: 38.1%, 342	Post-MI, angina pectoris, coronary insufficiency	–	2289 2191	ACM, CVM, CVE

*SFA, MUFA and PUFA for study control groups were imputed based on average background dietary intakes in similar populations of the Diet Heart Study control group of 1968.[26]
ACM, all-cause mortality; ALA, α-linolenic acid; BMI, body mass index; C, control; CABG, coronary artery bypass graft ,CAD, coronary artery disease; CVE, cardiovascular events; CVM, cardiovascular mortality; FA, fatty acids; HDL-C, high-density lipoprotein cholesterol; I, intervention; LA, linoleic acid; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MUFA, monounsaturated fat; nd, no data; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fat; SFA, saturated fat; TC, total cholesterol; TF, total fat; TG, triacylglycerols.

Table 2 Univariate and multivariate meta-regression for change in dietary fatty acid (covariate=percentage energy change in SFA, PUFA, MUFA and LA between intervention vs control groups)

Covariate	Number of studies or subsets	β-Coefficient	95% CI	p Value	Heterogeneity (I^2) (%)
	All-cause mortality (univariate)				
SFA	8	0.0029	−0.1156 to 0.1216	0.953	75.24
PUFA	8	0.0253	−0.0351 to 0.0858	0.345	72.97
MUFA	8	−0.0024	−0.1475 to 0.1426	0.968	72.04
LA	8	0.0355	−0.0387 to 0.1099	0.286	73.04
	Cardiovascular mortality (univariate)				
SFA	9	0.0089	−0.0900 to 0.1079	0.836	56.89
PUFA	9	0.0182	−0.0449 to 0.0813	0.517	58.23
MUFA	9	0.0186	−0.1428 to 0.1801	0.793	56.58
LA	9	0.0245	−0.0517 to 0.1008	0.472	58.10
	Total cardiovascular events (univariate)				
SFA	9	0.0181	−0.0884 to 0.1247	0.699	70.88
PUFA	9	0.0157	−0.0444 to 0.0759	0.556	73.70
MUFA	9	−0.0069	−0.1172 to 0.1033	0.885	75.80
LA	9	0.0224	−0.0492 to 0.0940	0.484	74.05
	Myocardial infarction (univariate)				
SFA	9	0.0114	−0.0813 to 0.1041	0.780	66.23
PUFA	9	0.0011	−0.0529 to 0.0551	0.962	66.60
MUFA	9	−0.0224	−0.1267 to 0.0818	0.627	69.19
LA	9	0.0028	−0.0627 to 0.06840	0.922	66.87
	All-cause mortality (multivariate)				
SFA	8	0.0800	−0.1390 to 0.2991	0.368	77.39
PUFA	8	0.0568	−0.0534 to 0.1671	0.226	
MUFA	8	−0.0230	−0.2254 to 0.1793	0.768	
	Cardiovascular mortality (multivariate)				
SFA	9	0.0768	−0.1422 to 0.2959	0.409	67.14
PUFA	9	0.0584	−0.0660 to 0.1830	0.281	
MUFA	9	−0.0381	−0.2691 to 0.1927	0.689	
	Total cardiovascular events (multivariate)				
SFA	9	0.1103	−0.0691 to 0.2898	0.175	77.96
PUFA	9	0.0638	−0.0347 to 0.1623	0.157	
MUFA	9	−0.0825	−0.2417 to 0.0765	0.240	
	Myocardial infarction (multivariate)				
SFA	9	0.0665	−0.1237 to 0.2568	0.410	75.28
PUFA	9	0.0355	−0.0703 to 0.1414	0.428	
MUFA	9	−0.0675	−0.2424 to 0.1072	0.366	

LA, linoleic acid; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

significant inverse correlation between MUFA (but not PUFA) intake and CHD events, thus favouring MUFA as a mediator for the beneficial effects of reduced SFA intake. Furthermore, a review of 16 meta-analyses indicated that a diet rich in MUFA has several beneficial effects on a broad range of CVD risk factors, in the primary prevention of CVD.[48]

In contrast to the data presented in this systematic review, a recent meta-analysis of observational studies suggests that replacing SFAs with PUFAs may have a greater benefit than replacing SFAs with CHO or MUFA.[8] Moreover, the meta-analysis of RTCs by Mozaffarian *et al*[9] reported a significant reduction in CHD events (by 19%) following the replacement of SFA by PUFA. However, adapting (for secondary prevention) and updating (including new data from the Sydney Diet Heart Study) the meta-analysis by Mozaffarian *et al*,[9] as was carried out in a sensitivity analysis investigating the replacement of SFA by PUFA in the present study, resulted in neither beneficial nor detrimental effects on all outcome parameters. Compared with meta-analyses of observational studies, those of RCTs are considered to have a higher grade of quality.[18] RCTs of lifestyle behaviours such as diet are often limited by lack of double blinding, non-compliance, cross-over and dropout—as evidenced by the trials in the current meta-analysis—so that well-designed analyses in prospective cohort studies provide important evidence with complementary strengths and limitations.

No detrimental effects of increased amounts of linoleic acid could be observed in meta-regression. The results of the present meta-regression are in discrepancy with the observations of a recent meta-analysis of Ramsden *et al*,[33] providing evidence that replacement of

SFA with linoleic acid was associated with increased rates of death from all causes, CHD and CVD, respectively. In order to rationalise their results, Ramsden *et al* proposed a mechanistic model linking dietary linoleic acid to CVD pathogenesis. It is proposed that diets high in n-6 linoleic acid facilitate production of oxidised linoleic acid metabolites mediating progression of atherosclerosis and thus leading to higher rates of cardiovascular mortality.[33] Owing to the low number of studies available and the inherent biases of the method, the findings of the present meta-regressions must be interpreted in a very conservative manner. However, when using these results to generate a hypothesis, it still seems reasonable to replace SFA by PUFA in the secondary prevention of CHD, although SFA should not be completely substituted by n–6 fatty acids as recommended by the FAO.[7] Instead, dietary advice should rather focus on increasing the uptake of n-3 fatty acids, predominantly in the form of fatty fish.

The present systematic review does not consider unpublished data, and it cannot be excluded that these results may have had at least a moderate impact on the effect size estimates. Examination of funnel plots showed little to moderate asymmetry suggesting that publication bias cannot be completely excluded as a confounder of the present meta-analysis (eg, it remains possible that small studies yielding inconclusive data have not been published). Another limitation of nutritional intervention trials is the heterogeneity of various aspects and characteristics of the study protocols. RCTs in the present analysis varied with respect to the type(s) of diets used (eg, advised to supplement various oils, fatty fish), and size of study population. Some of the included studies date back to 50 years, and not all of the studies provided information on the quality of their respective setup (eg, method of randomisation, follow-up protocol with reasons for withdrawal, see figure 1 for risk of bias assessment according to the Cochrane Collaboration), again demanding a conservative interpretation of results. Another potential limitation of the present meta-analysis is rather specifically related to the research question. Total fat intake in the reduced and/or modified diet groups ranged between 20% and 50% of TEC. In some trials, dietary fat intake was established by adding corn, olive or soybean oil,[21 26] while others implemented canola oil-based margarine.[24] In several trials, the participants in the reduced and/or modified fat groups were provided with additional dietary advice such as to increase the consumption of fatty fish,[21 24 29–31] vegetables and fruits,[24 29–31] or nuts[31] as well as to pay attention to their cholesterol intake. In contrast to these heterogeneous aspects of the study designs, length of trials included in this systematic review was rather homogenous with all RCTs having a running time of at least 1 year. However, this might be interconnected with another major limitation of dietary intervention trials, that is, the issue of compliance. Participants in the different intervention groups may not exactly adhere to the advised or prescribed dietary protocol. In the end, this may not only lead to deviations from the target values but may result in only minimal differences between the study arms.

CONCLUSION

The present meta-analyses and meta-regressions provide no evidence for a beneficial secondary preventive effect of either reduced and/or modified fat diets or replacement of SFA by PUFA in participants with established CVD. Although pharmaceutical treatment via lipid-lowering medications is considered to be an effective therapeutic measure for patients with established CVD, many international authorities recommend modifications of fat intake with a special emphasis on SFA as well.[13 49 50] The current AHA/ACC guidelines promote to reduce the total fat intake to less than 35% of TEC and SFA intake to less than 7% of TEC, respectively. However, recommending higher intakes of PUFA in general instead of SFA might not be appropriate. Sensitivity analysis indicates that it seems reasonable to modify this general recommendation by promoting higher dietary n−3 PUFA as a substitute for SFA.

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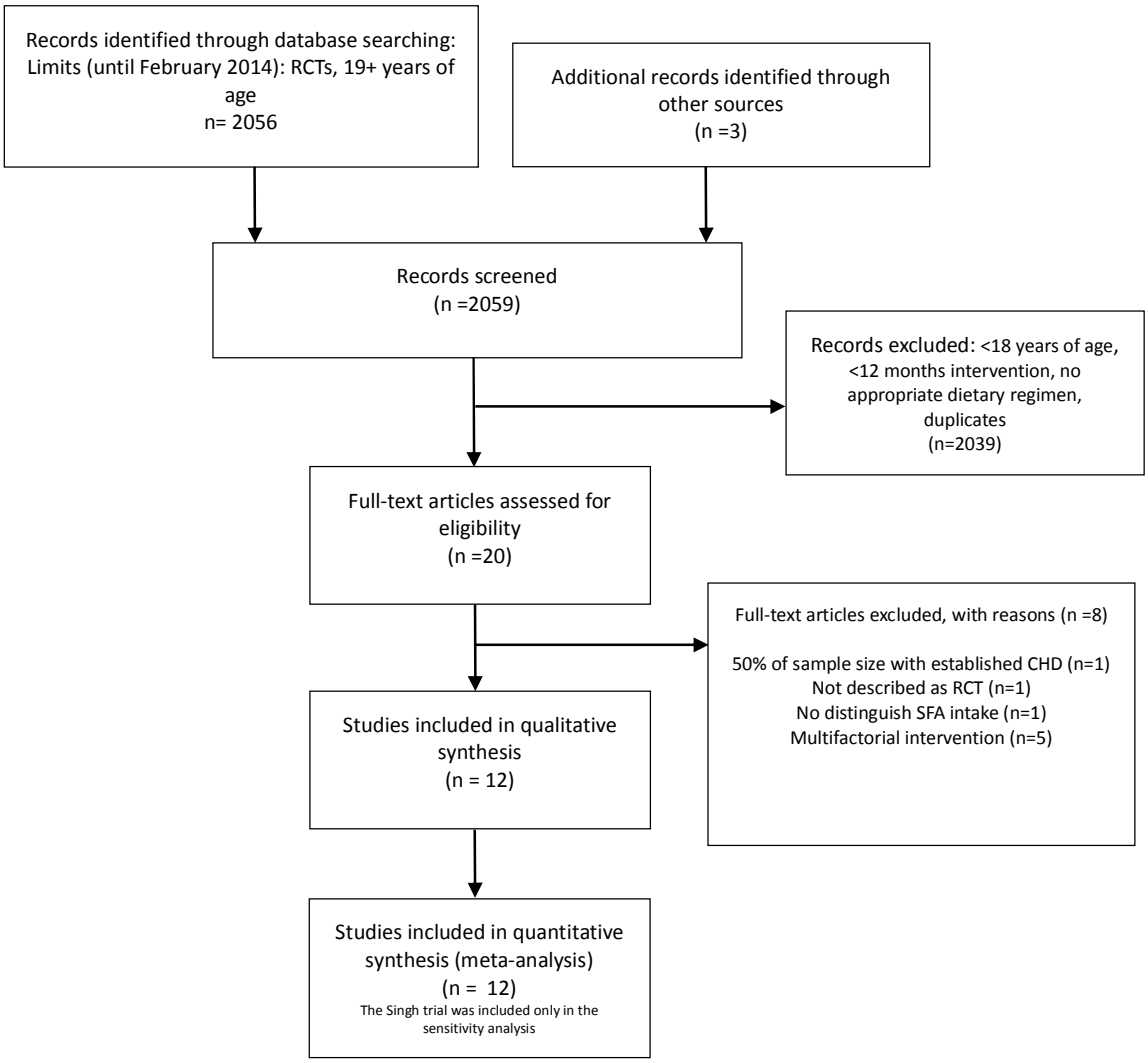
Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression

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



CHD, coronary heart disease; RCT, randomized controlled trial; SFA, saturated fat;

Reference	Detailed Dietary Advise	Dietary Assessment	Smoking cessation Smoking status	Drug intakes
Ball et al. 1965	**I:** 40g fat daily (14g butter, 84g of meat, 1 egg, 56g cottage cheese, and skimmed milk. The nature of the fat consumed was not altered, nor were any additional unsaturated fats given. The main objections were to the skimmed milk, to the small butter ration which was especially hard on those who took sandwiches to work, and to the restriction on biscuits and cakes. **I+C:** Those patients who were overweight were given reducing diets, irrespective of their group. In the control group this was done as far as possible by reducing carbohydrates rather than fats.	Record the weight of all food consumed on a different day each week for the first seven weeks after admission to the trial, and thereafter on the first day of each month. In addition an independent dietitian interviewed a number of patients in each group	n.d	n.d
Burr et al. 1989	**I:** fat advice, designed to reduce fat intake to 30% of total energy and to increase the PUFA/SFA ratio to 1.0.	The dietitian visited and telephoned regularly to reinforce their initial required. Food questionnaires from 7 day weighed intake records	All smokers were strongly advised to stop smoking and ex-smokers were encouraged not to relapse. no difference in care I: 61.2% C: 62.7%	ß-blocker: I: 30.6%, C: 28.2%; Other antihypertensive: I: 33.4%, C: 34% Antiangina: I: 47.7%, C: 45.9%; Anticoagulant: I: 6.2%, C: 5.5%; Aspirin/Antiplatelet: I: 10.5%, C: 10%; Digoxin/antiarrhythmic: I: 8.9%, C: 10.2%
de Lorgeril et al. 1994	**I:** <35% of energy from total lipids, and <10% SFA. The intake of 18:2 n-6 (linoleic acid) was restricted to ≤4%. Intake of 18:3 n-3 (linolenic acid) was to compose ≥0.6%, and the PUFA: SFA was to be ≤0.8%. The six dietary commandments: more bread, more vegetables and legumes, more fish, less meat (beef, lamb, pork), and replaced by poultry; no day without fruit; no more butter and cream, to be replaced by a special margarine. In this study, an erucic acid-free (canola) oil-based margarine was supplied, to the families of all subjects of the experimental group. The oils recommended for salads and food preparation were rapeseed without erucic acid and olive oils exclusively. Moderate alcohol consumption, mainly in the form of red wine, was allowed or recommended at meals.	Compliance with the dietary intervention was maintained by checking the amount of margarine consumed by the family, a dietary survey performed at each patient visit (the survey included a 24-h recall and a food frequency questionnaire), and fatty acid analysis of plasma total lipids performed at each visit.	No difference in care I: 7.6% C: 4.9%	Anticoagulant agents: I: 29.4%, C: 26.4%; Antiplatelet agents: I: 62.6%, C: 64.8%; ß-blockers: I: 60.2%, C: 63.4%; Calcium-channel blockers: I: 20.4%, C: 21.7%; ACE-inhibitors: I: 9.3%, C: 6.1%;
Howard et al. 2006	**I:** The intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy intake (in kilocalories) by increasing intake of vegetables and fruits to at least 5 servings daily and of grains to at least 6 servings daily. The intervention did not include total energy reduction or weight loss goals. Although not a separate focus of the intervention, it was presumed that by reducing total fat intake to 20% kcal, intake of saturated fat would also be reduced (7% energy intake). The intensive behavioral modification program involved 18 group sessions in the first year and quarterly maintenance sessions thereafter, led by specially trained and certified nutritionists. Each participant was assigned her own fat-gram goal, calculated on the basis of height. Participants self-monitored total fat-gram intake and also servings of vegetables, fruits, and grains. No formal intervention regarding saturated fat, cholesterol, trans fatty acids, or other known atherogenic factors was provided. **C:** Women in the comparison group received a copy of the Dietary Guidelines for Americans	All participants completed an FFQ designed specifically for the study at baseline and 1 year. Thereafter, one third of the participants completed the FFQ each year in a rotating sample;	No difference in care I: 6.6% C: 6.8%	Hypertension treated: I: 42.5% C: 43.2% History of hypercholesterolemia requiring medication: I: 11.8% C: 12.1% Treated for diabetes: I: 4.4% C: 4.6%
Leren et al. 1966	**I:** Protein (92g), Fat (104g), CHO (269 g) and dietary cholesterol 264 mg; Daily intake of calories was 2387; Calories derived from fat constituted 39%. The sources of fat were: soy bean oil (72%), fish fat (11.6%), animal fat (8.8%), cereal fat (5%), and fat from other sources (2.6%). Of the mean dietary fat, 21.6% was saturated, 25.7% monounsaturated, and 52.7% polyunsaturated.	Adherence to the diet was controlled by close personal contact, the physician being assisted by a full time, experienced dietician who worked in the homes	Smoking habits were about the same in the two groups at entry and showed practically no change	n.d

		of the patients. The degree of adherence was quantified by means of a detailed questionnaire used six times during the period of observation.	during the first 5 years	
MRC 1968	**I:** as far as possible, SFA were removed from the diet. Patients were instructed to take 85g of soya bean oil daily. The oil was chosen because it is highly unsaturated and, when used previously in a similar diet, had been shown to cause satisfactory fall in serum-cholesterol. At least 43g of soya-bean oil daily had to be taken unheated, and it was often drunk with fruit juice. In 10 patients who develop intolerance to the oil. Such as nausea and diarrhea, corn oil was substituted. Up to 35g of other fat per day was also allowed. 14g of this was taken as a moderately unsaturated margarine. Foods allowed daily included lean meat (up to 85g), any fish, skimmed milk, and clear soups. Foods forbidden included butter, other margarines, cooking-fat, other oils, fat meat, whole milk, cheese, egg yolk, and most biscuits, and cakes. **C:** ate the diet they would ordinarily have taken.	Patients were issued with scales and diet sheets, and asked to record the weight of all food consumed on a different day each week for the first seven weeks after admission to the trial, and thereafter on the first day of each month. These records were used as the basis of the dietary supervision and analysis. An independent dietitian interviewed a sample of patient´s wives in each group on one occasion.	No difference in care I: 81% C: 84%	n.d
Michalsen et al. 2006	**I:** The intervention for the MG lasted 12 months with decreasing intensity. The program began with a 3-day nonresidential retreat, followed by weekly 3-h meetings for 10 weeks. Thereafter, 2-h meetings took place every other week for 9 months. The meetings were held in groups of 10–13 subjects. The lifestyle program addressed diet and stress management. MG participants were extensively informed about the Mediterranean diet as adapted from the Lyon Diert heart Study (de Lorgeril et al., 1999) by nutritional information, repetitive group discussions, cooking classes and group meals. If necessary, the dietary instructions were customized in an individual 1-hour-long session, considering the patients' readiness for behavioural change according to the concept of stages of change (Prochaska and Velicer, 1997). All instructions had to be detailed and compatible with the way of living. The general aim of the dietary recommendations was to provide subjects in the MG with a diet rich in alinolenic acid (ALA), marine n-3 polyunsaturated fatty acids (PUFA), monounsaturated fats (MUFA), phytochemicals, and low in saturated fats (SFA). In brief, the instructions to the MG were to consume at least five portions of fruits and vegetables daily, with an emphasis on root and green vegetables with a high content of ALA, and more than two portions of fatty fish per week. They were further asked to consume preferably whole-grain bread, pasta and rice. The intake of flaxseed and walnuts was strongly recommended. The intakes of meat and sausage should be limited to three servings per week, and beef, lamb and pork were to be replaced by poultry, fish or vegetarian dishes. Both olive oil and canola oil, and, for some dishes, walnut and flaxseed oil, were strongly recommended as the only oils for all food preparations. The intake of margarine was discouraged, with the exception of one margarine based primarily on olive oil and commercially available at that time. (When designing the study, no margarine with a defined high content of ALA was available in Germany). Modest regular alcohol consumption in the form of red wine to the meals was recommended. **C:** Patients in the AG received only written and less detailed information about the dietary principles of the Mediterranean diet, and some general advice about stress reduction by means of leaflets that were mailed shortly after randomization.	Before and after the 1-year period, the patients completed a 7-day record of food intake. Food records were converted into nutrients intake by using the EBIS software dietary analysis program, which is based on the national database of the German nutrition report. The subject's dietary intake was compared with a validated food frequency questionnaire of the German Institute of Nutrition. For each patient, we compared the calculated intakes of nutrients of both methods.	No difference in care I: 8% C: 4%	Statins: I: 84.4%, C: 79.2%; ß-blockers: I: 75%, 77.3%; ACE-inhibitors: I: 50%, C: 49.5%;
Rose et al. 1965	**I:** Patients in both oil groups were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes (except	Dietary assessment were performed	n.d	n.d

	plain sponge), etc. Milk, eggs, and butter were restricted. An oil supplement of 80 g/day was prescribed, to be taken in three equal doses at meal-times. The general nature and purpose of treatment were explained, together with the fact that different patients were receiving different kinds of oil. C: No advice on dietary fat was given to control patients.	on those patients still in the trials during the second year of follow-up, using a self-administered questionnaire		
Singh et al. 1992	**I+ C:** In both diets meat, eggs, hydrogenated oils, butter, and clarified butter were replaced with vegetarian meat substitutes and soya bean, sunflower, and ground nut oils so as to provide a prudent diet reflecting the recommendations of the American Heart Association. Group A patients were also advised to eat fruit, vegetables, pulses, nuts, and fish. The goal was to provide at least 400 g/day of fruits and vegetables. In both groups, patients had a mainly vegetarian diet, eating eggs 4-5 times a week and meat 1-2 times a week. Other health related advice, such as stopping smoking, reducing alcohol intake, counseling to relieve mental stress and on physical activity, was given to both groups. However, though patients in group A had the advice regularly reinforced, those in group B were left to usual care after the initial advice.	Dietary intake before admission to hospital was estimated in both groups by taking a detailed history of pre-study food intake from spouses. Information from the questionnaires was quantified by a formula. A total score of 1 indicated 100% adherence to the recommended changes in the diet, smoking, alcohol intake, and weight and 0 indicated no adherence. Patients who consumed more than our minimum recommendation of 400 g/day of fruit and vegetables scored greater than 1. The scores were multiplied by 100 to convert into percentages.	No difference in care: I: 36% C: 35%	Propranolol: I: 46%, C: 44%; Verpamil: I: 25%, C. 27%; Nitrates: I: 98%, C: 97%; Frusemide: I: 14%, C: 18%;
Sondergaard et al. 2003	**I:** was given dietary advice by a master of science in clinical nutrition and a specially trained research nurse. In general, the patients were advised to eat at least 600 grams of fruits and vegetables daily, to modify the intake of fat, especially saturated fat from meat and dairy produce, to eat fatty fish at least once a week and preferably several times a week, to eat plenty of bread and cereals, and to replace refined, hard, animal margarine products with vegetable oils, preferably canola oil. The first session was performed as a thorough interview lasting for at least 1 hour and using the 24-hour recall method. **C:** The control group was offered booklets about heart-healthy diets that are usually delivered to patients in the coronary care unit. They were also offered a single visit to a dietitian who was not participating in the study. The patients were examined every third month at clinical control sessions, but without follow-up on dietary advice. The control group was asked to perform a single diary after 1 year, and the results were entered and analyzed in the same database.	Every patient had to describe the intake of foods and beverages for the past 24 hours, and the dietary advice was adjusted individually and repeated every third month. The patients were asked at every control session to prepare a written 4-day diary of foods and beverages consumed. They were asked not to weight the foods but to describe in ordinary words the size of the single ingredients (eg, a small, medium, or large apple) or size of portions of food; furthermore, they were asked to describe in detail fat percentages, especially in dairy produce and minced meat. Also, the patients were asked to note their hot meals. The food diaries were returned to the study nurse, who	No difference in care I: 43% C: 52% Non-significant baseline smoking status	ß-blockers: I: 56%; C: 68%; Calcium antagonists: I: 22%, C: 17%; ACE inhibitors: I: 15%, C: 22%; Long-acting nitrates: I: 6%, C: 19% (significant difference between groups; p=0.04)

		thoroughly reviewed the contents; in case of doubt, the diary was returned to the patient with appropriate clarifying questions.		
Watts et al. 1992	**I:** Total fat intake was reduced to 27% of dietary energy, SFA content 8-10%, and dietary cholesterol to 100mg/1000 kcal; omega-6 and omega-3 PUFA were increased to8%, and plant derived soluble fiber (chiefly pectin) intake was increased to the equivalent of 3.6g polygalacturonate/1000 kcal. Intake of alcohol was permitted at the patient´s habitual level. Patients were instructed by a dietitian after a detailed history was obtained as a guide to energy requirements; choice of food was adapted to individual preferences. For patients with a BMI below 25 kg/m^2 an isocaloric diet was prescribed; overweight patients were prescribed a diet that contained 1000-1200 kcal daily to achieve a BMI of 25 kg/m^2. **C:** received, in common with both intervention groups, cardiological supervision and treatment, repeated counseling against smoking, and antihypertensive treatment if appropriate. All participants were advised about a suitable level of daily exercise. Patients in the control group with a BMI above 25 kg/m^2 were advised to lose weight but did not receive formal dietary counseling.	At each follow-up visit the clinician inquired about dietary compliance and provided encouragement.	No difference I: 26.9% C: 29.2%	n.d
Woodhill et al. 1978	**I:** were advised and tutored individually to reduce SFA intake to approximately 10% and dietary cholesterol to 300 mg or less per day. They were encouraged to use food containing PUFA to 15% or more of daily calories.	The diets of all participants were assessed by interview and/or food log three times during the first year and twice yearly thereafter.	No difference in care I+C: 38%	n.d

STable 1: Specific study characteristics

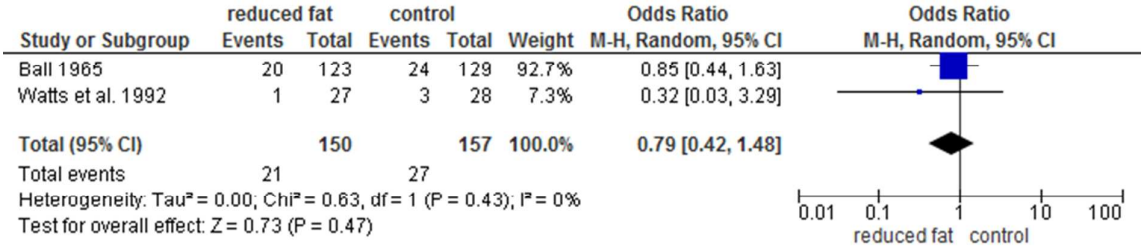


Figure S2. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 2 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the shaded square reflects the relative weight of the study in the respective meta-analysis.

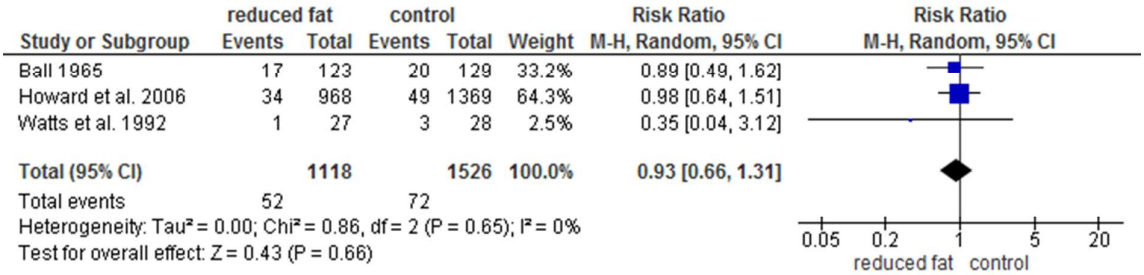


Figure S3. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 3 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits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

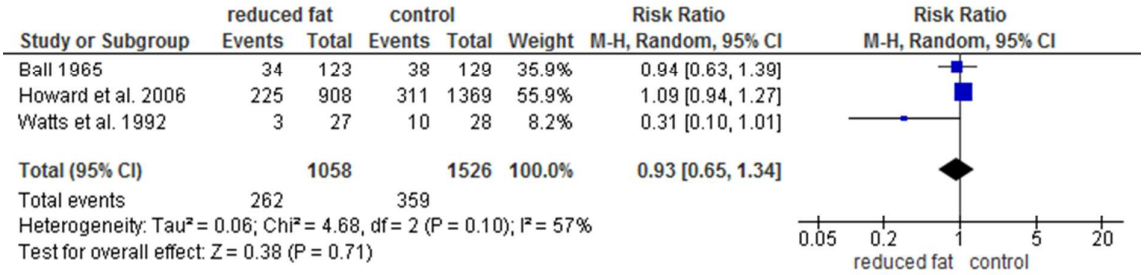


Figure S4. Forest plot showing pooled relative risks (RRs) with 95% CI for combined cardiovascular events for 3 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper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

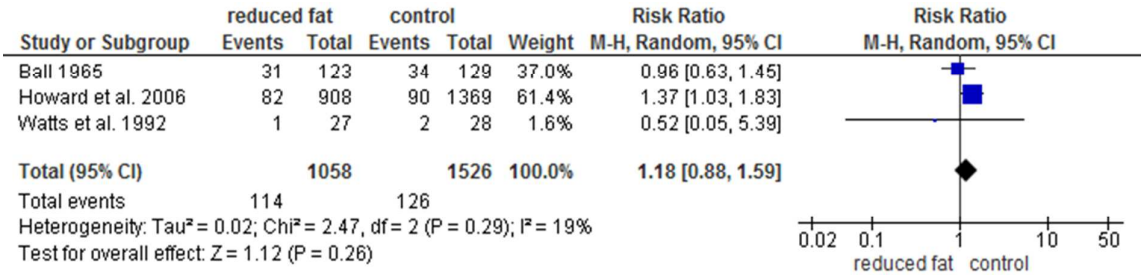


Figure S5. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 3 randomized controlled reduced diet groups. For each reduced fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits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

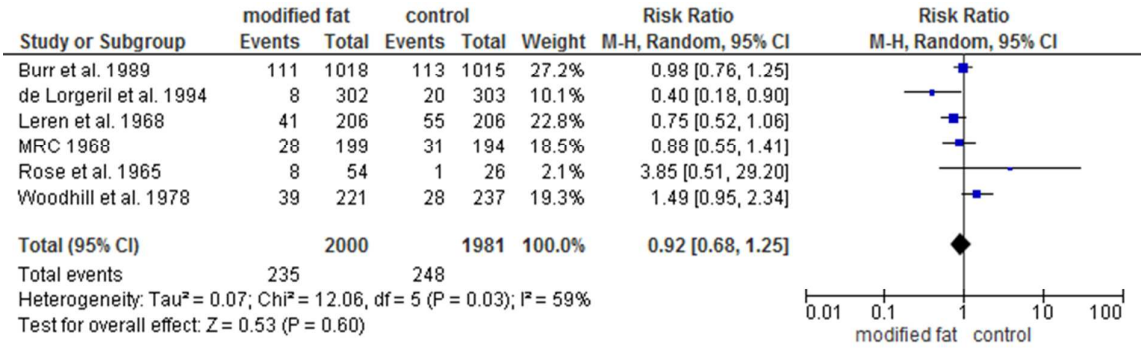


Figure S6. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 6 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits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

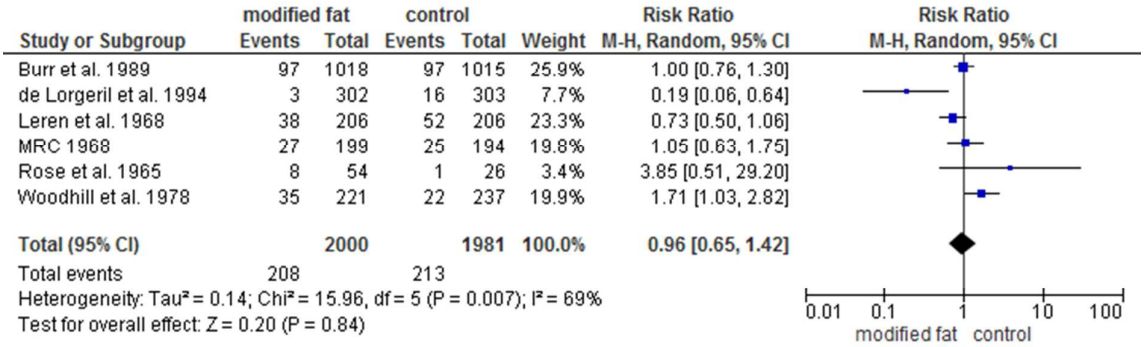


Figure S7. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 6 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper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

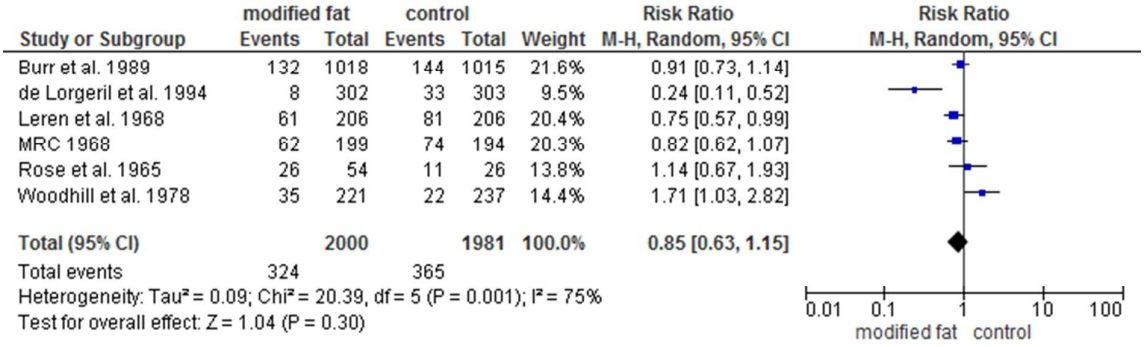


Figure S8. Forest plot showing pooled relative risks (RRs) with 95% CI for combined cardiovascular events for 6 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and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

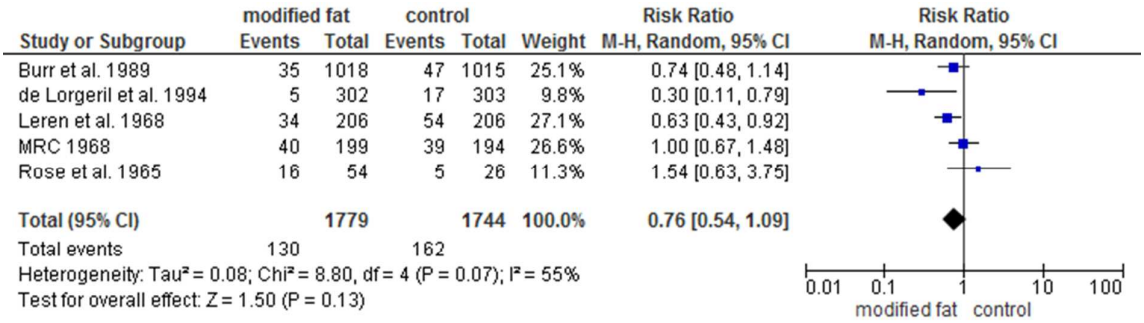


Figure S9. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 5 randomized controlled modified diet groups. For each modified fat study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits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

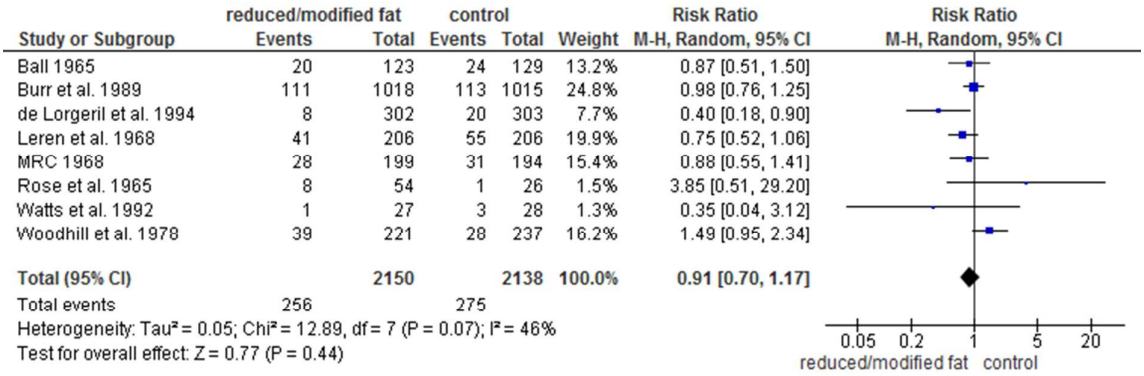


Figure S10. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 8 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and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

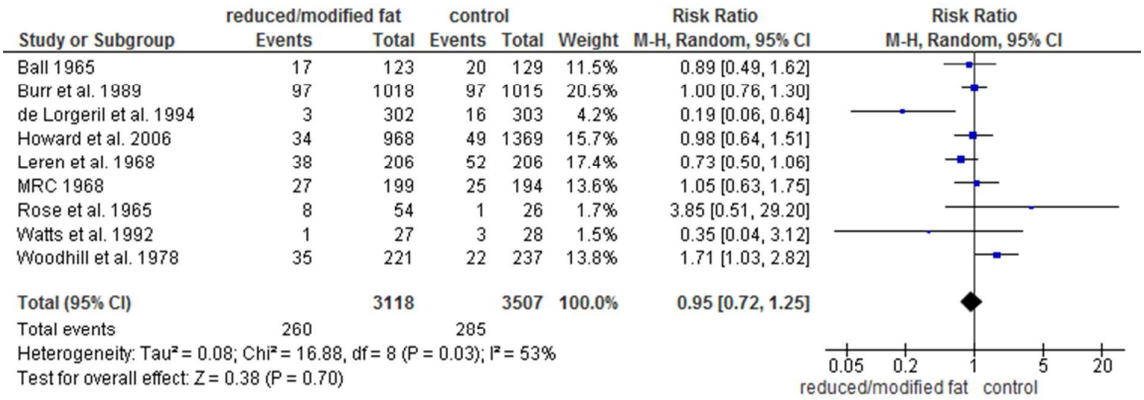


Figure S11. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 9 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower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

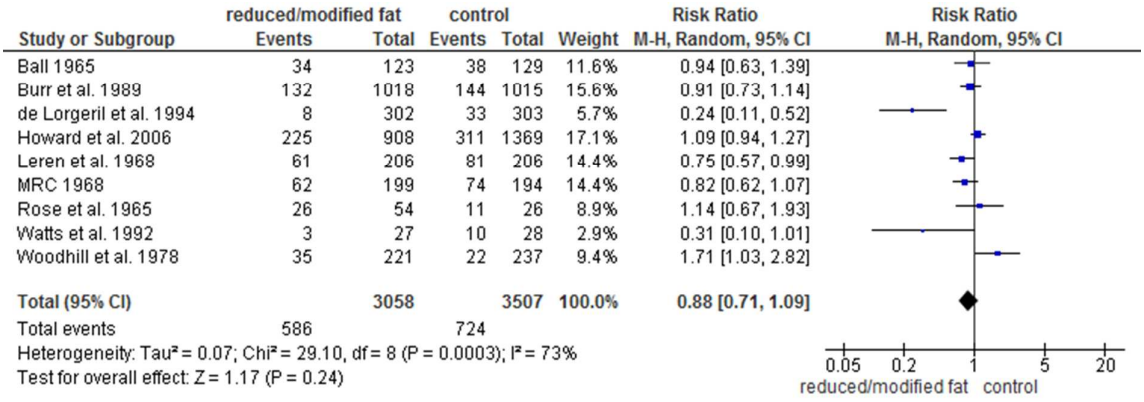


Figure S12. Forest plot showing pooled relative risks (RRs) with 95% CI for total cardiovascular events for 9 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the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

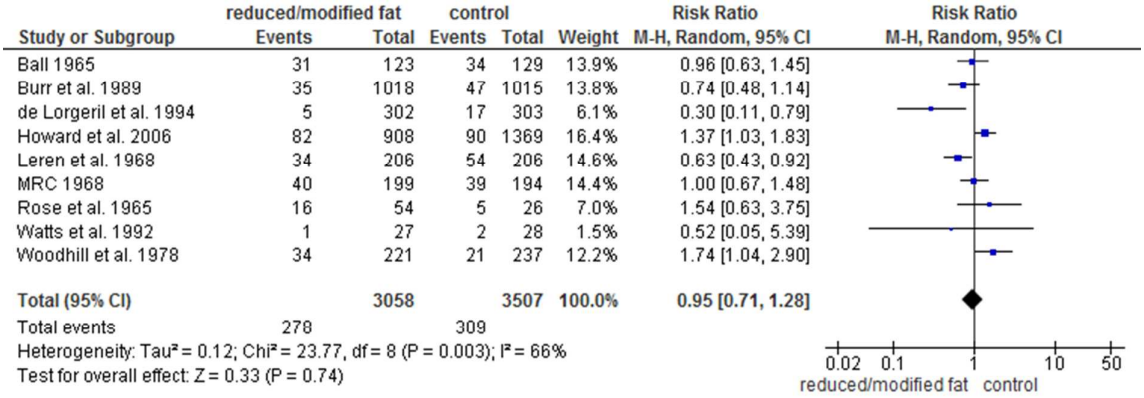


Figure S13. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 9 randomized controlled reduced/modified diet groups. For each reduced/modified study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower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

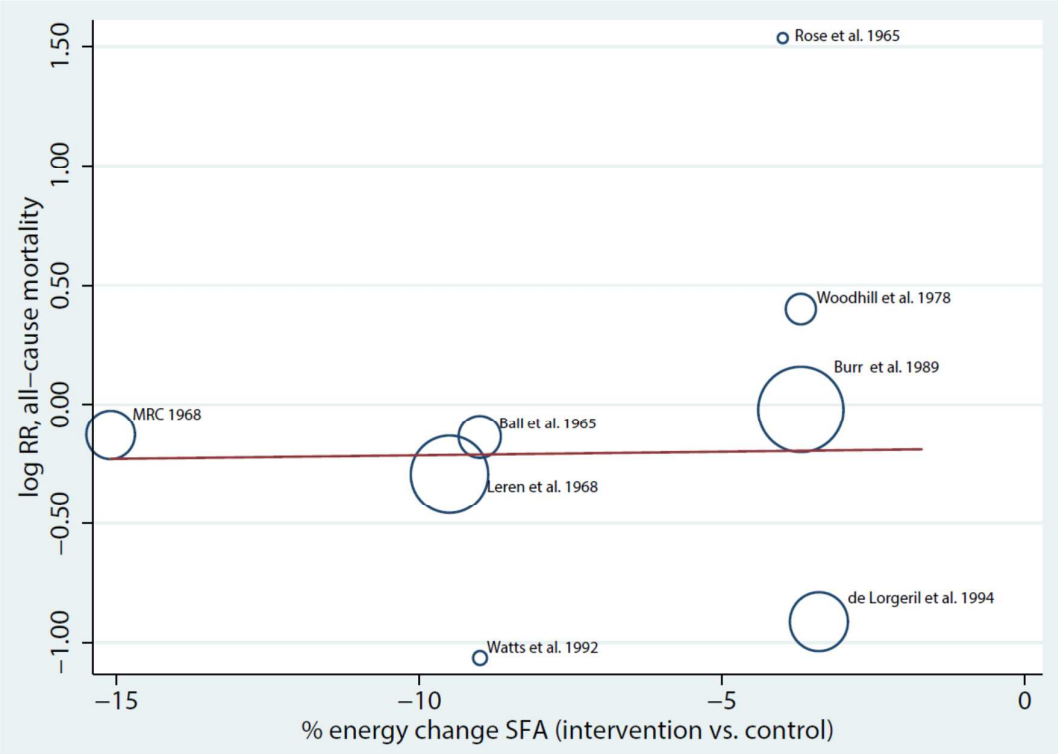


Figure S14. Bubble plot showing the association between % energy change from SFA and all-cause mortality

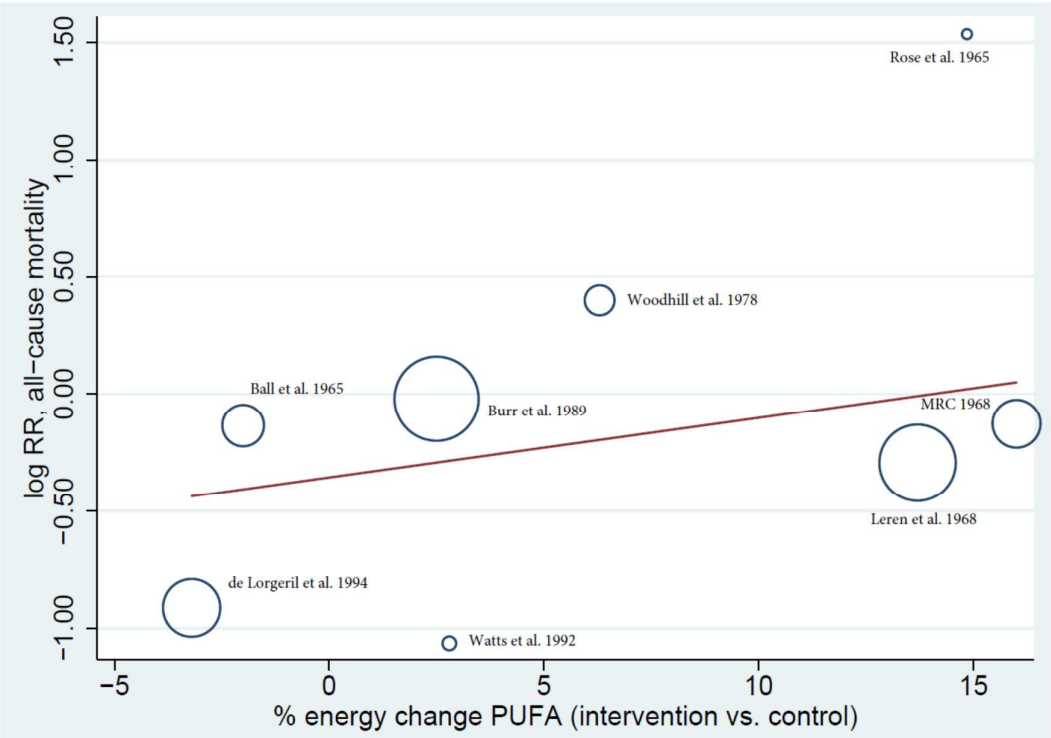


Figure S15. Bubble plot showing the association between % energy change from PUFA and all-cause mortality

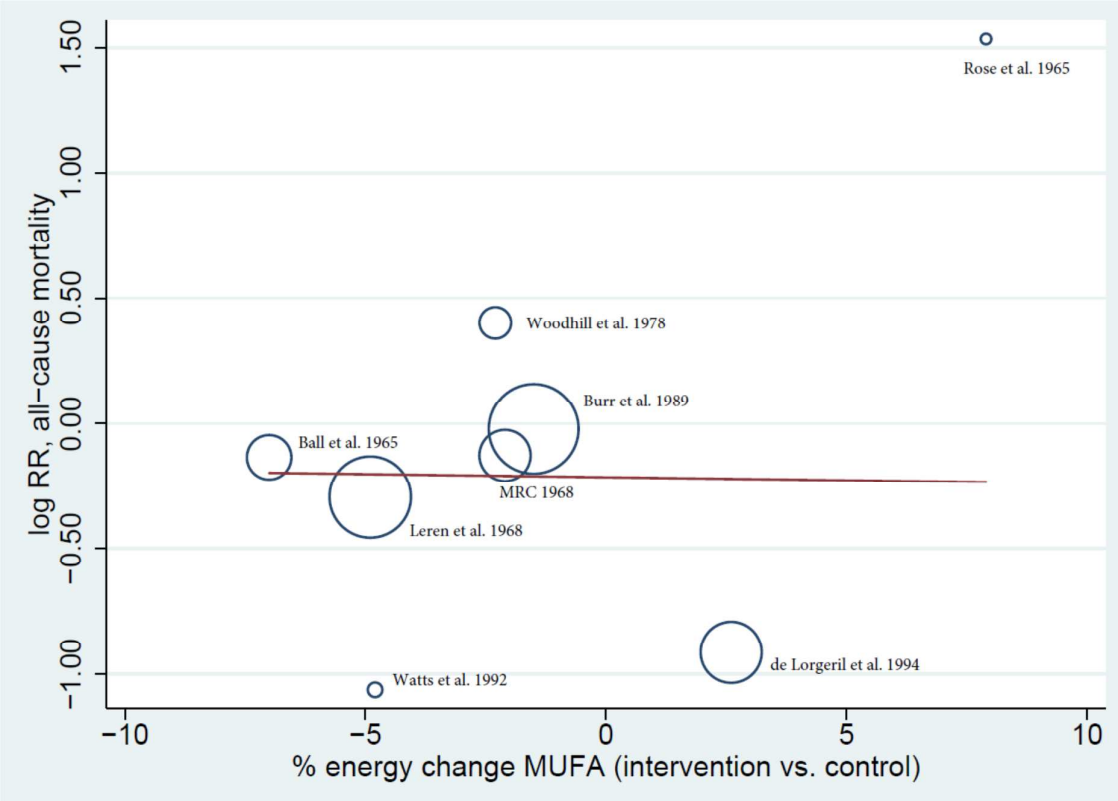


Figure S16. Bubble plot showing the association between % energy change from MUFA and all-cause mortality

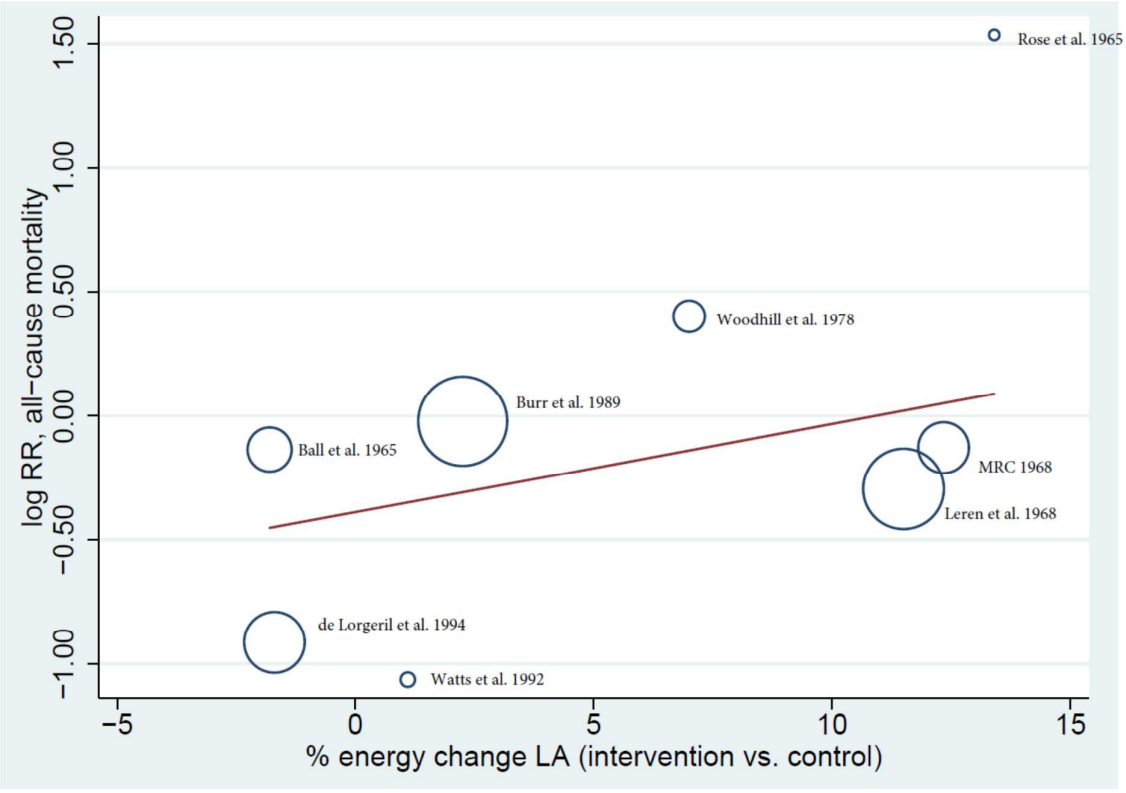


Figure S17. Bubble plot showing the association between % energy change from LA and all-cause mortality

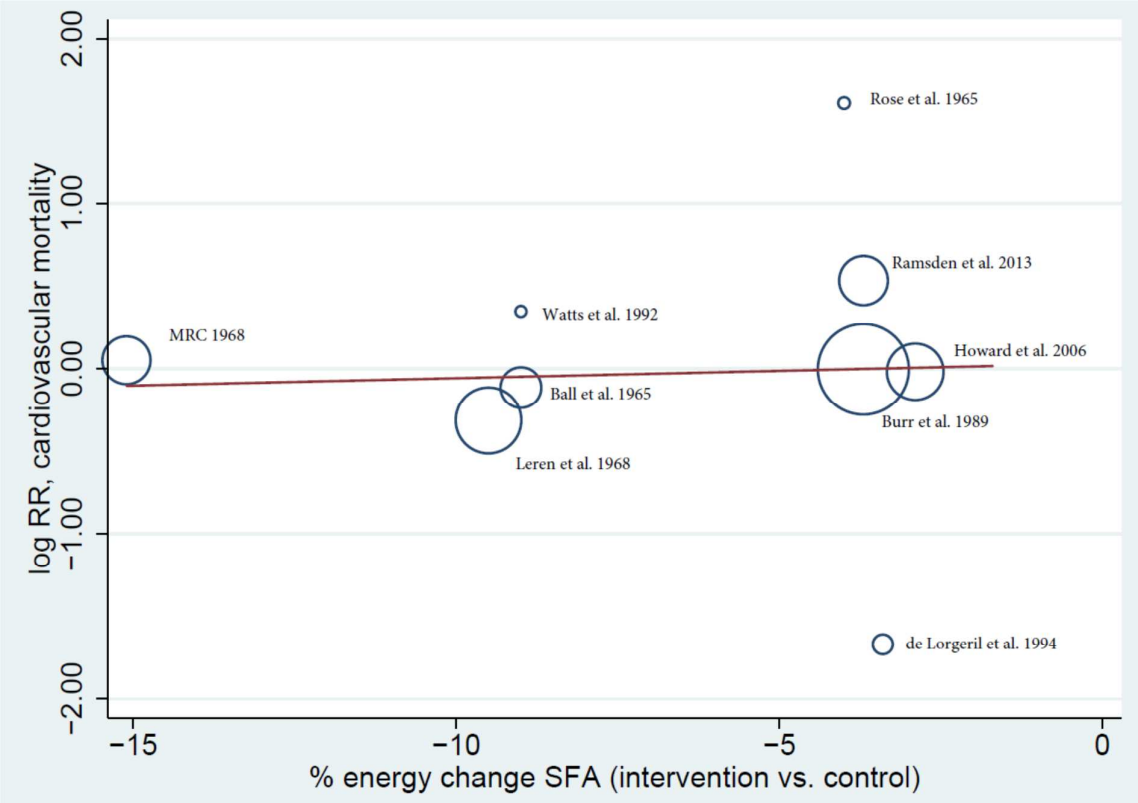


Figure S18. Bubble plot showing the association between % energy change from SFA and cardiovascular mortality

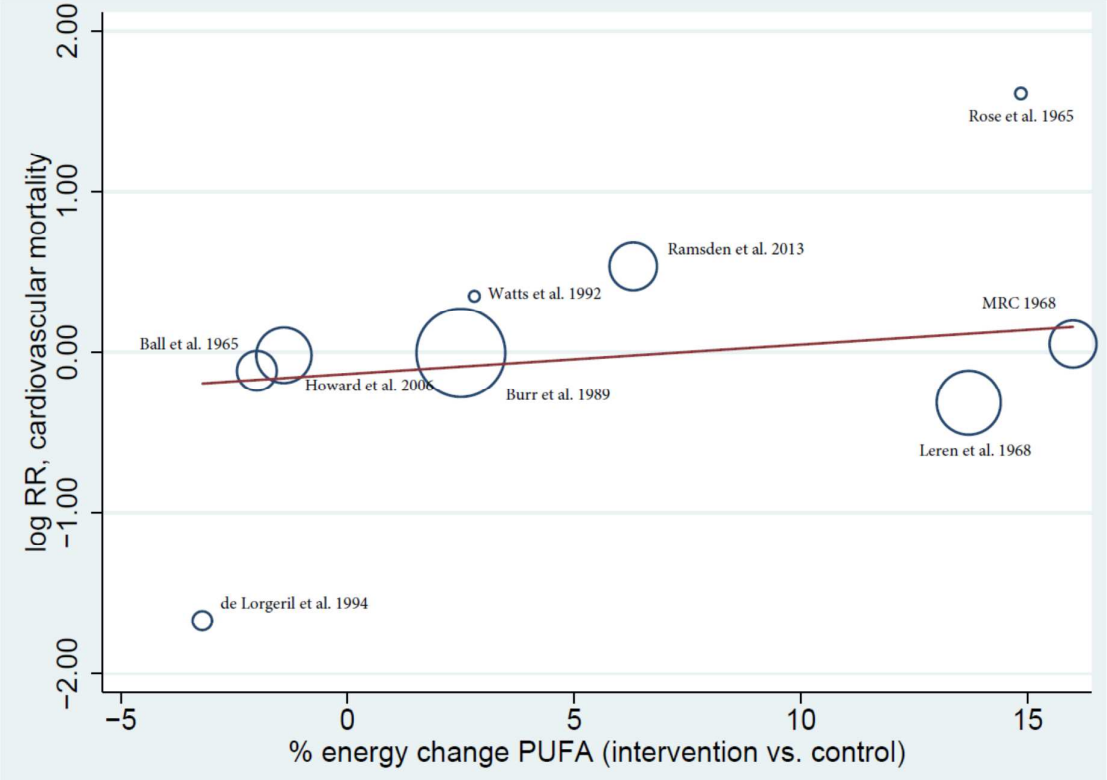


Figure S19. Bubble plot showing the association between % energy change from PUFA and cardiovascular

mortality

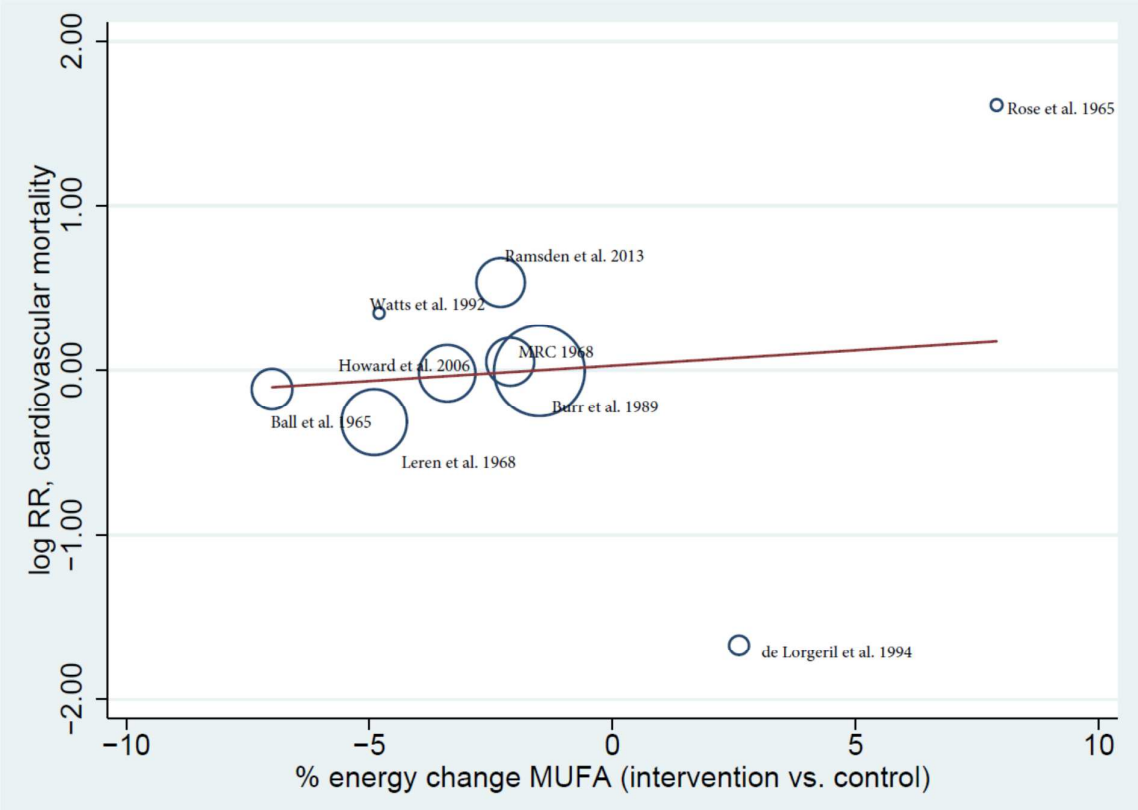


Figure S20. Bubble plot showing the association between % energy change from MUFA and cardiovascular mortality

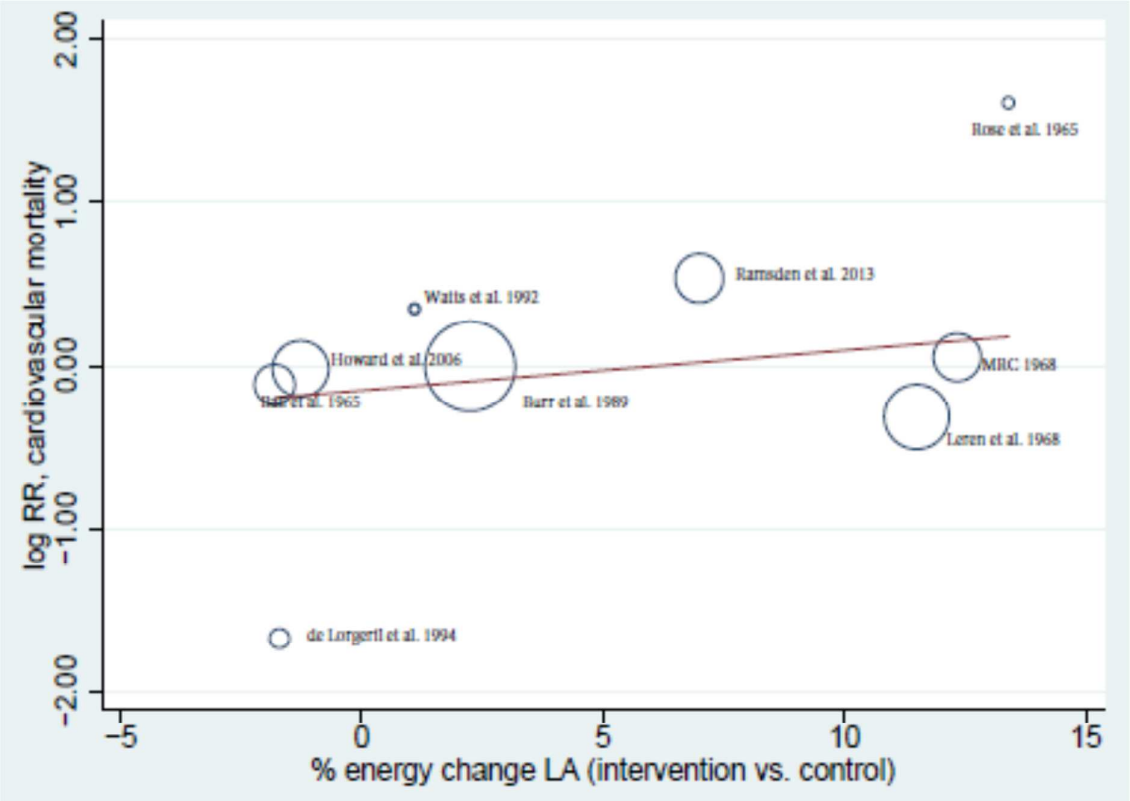


Figure S21. Bubble plot showing the association between % energy change from LA and cardiovascular

mortality

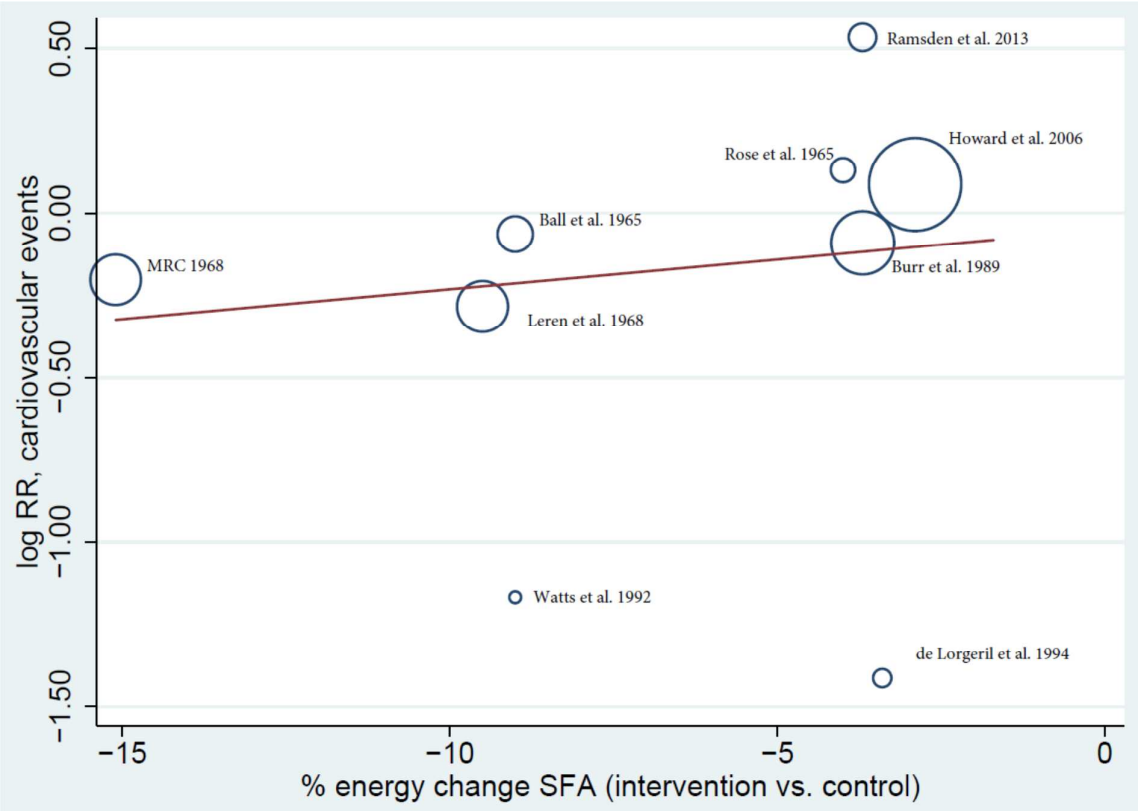


Figure S22. Bubble plot showing the association between % energy change from SFA and cardiovascular events

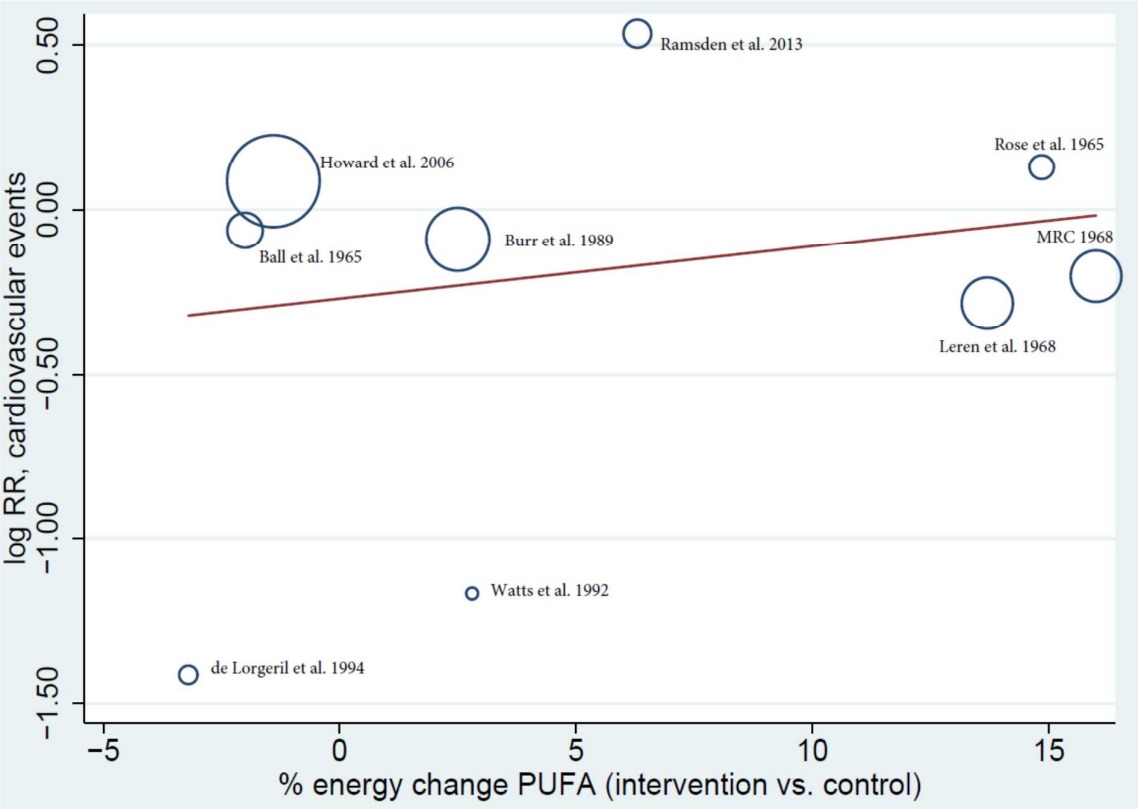


Figure S23. Bubble plot showing the association between % energy change from PUFA and cardiovascular

events

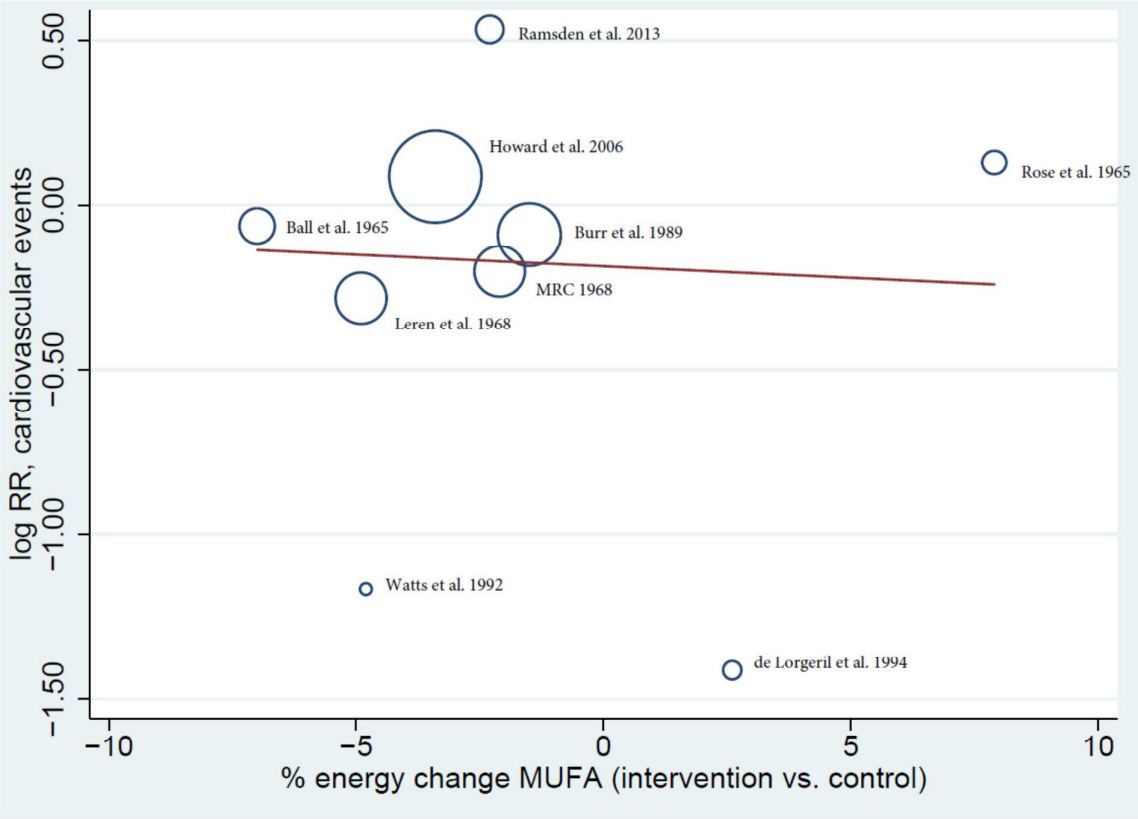


Figure S24. Bubble plot showing the association between % energy change from MUFA and cardiovascular events

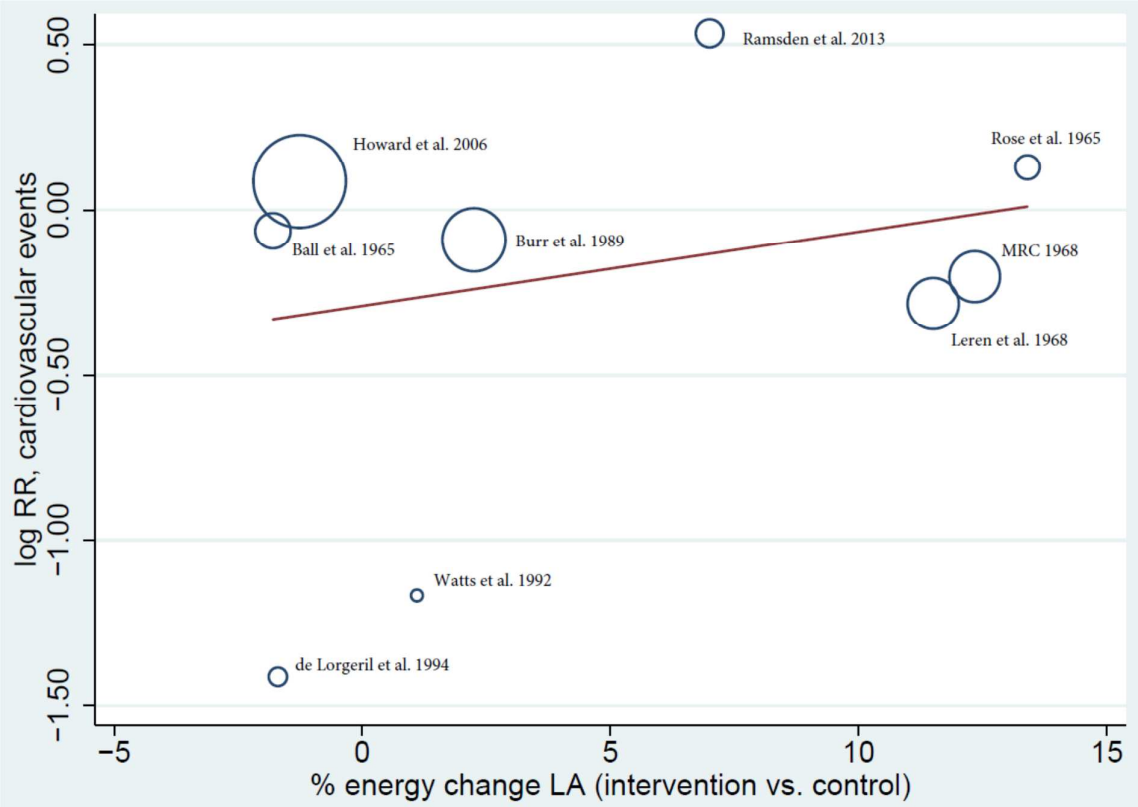


Figure S25. Bubble plot showing the association between % energy change from LA and cardiovascular events

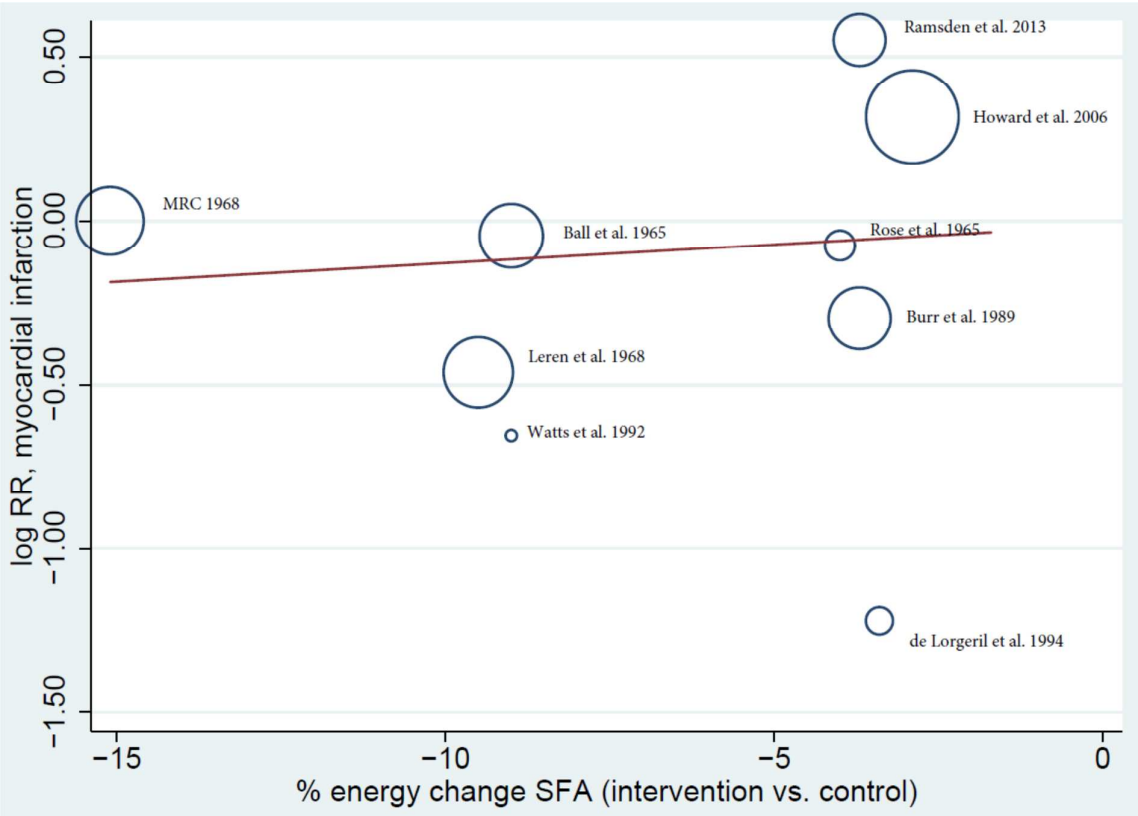


Figure S26. Bubble plot showing the association between % energy change from SFA and myocardial infarction

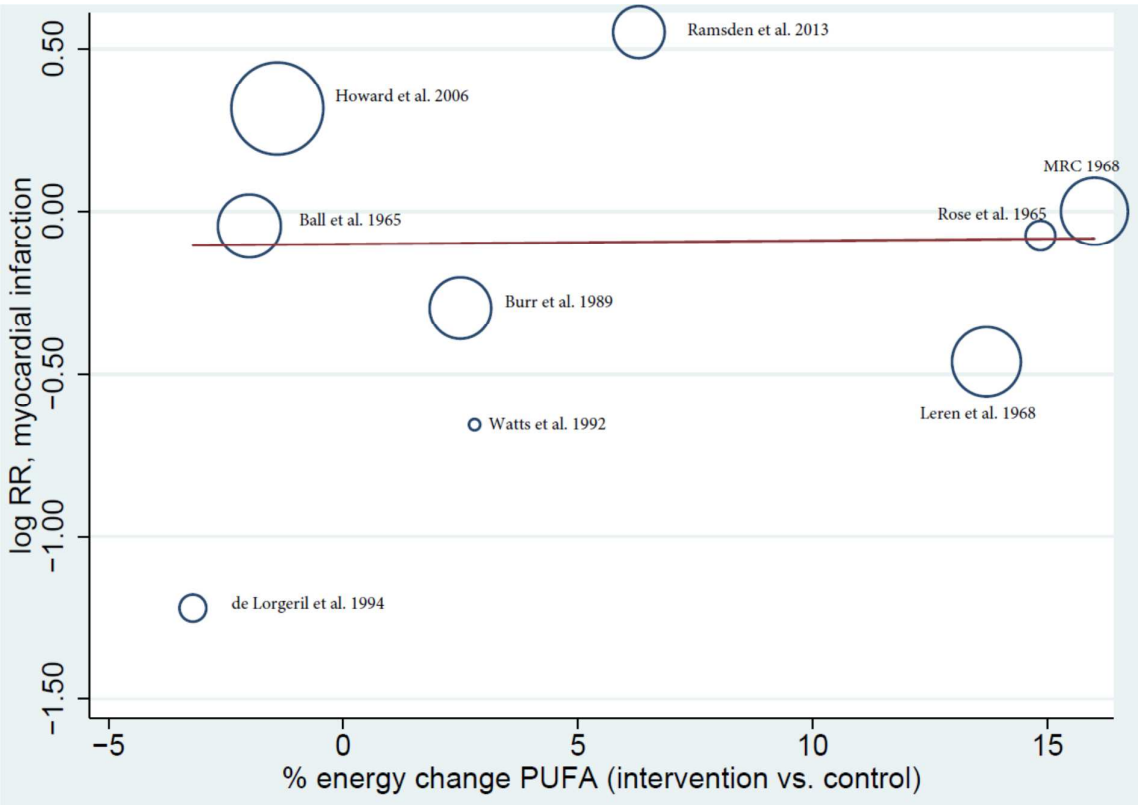


Figure S27. Bubble plot showing the association between % energy change from PUFA and myocardial infarction

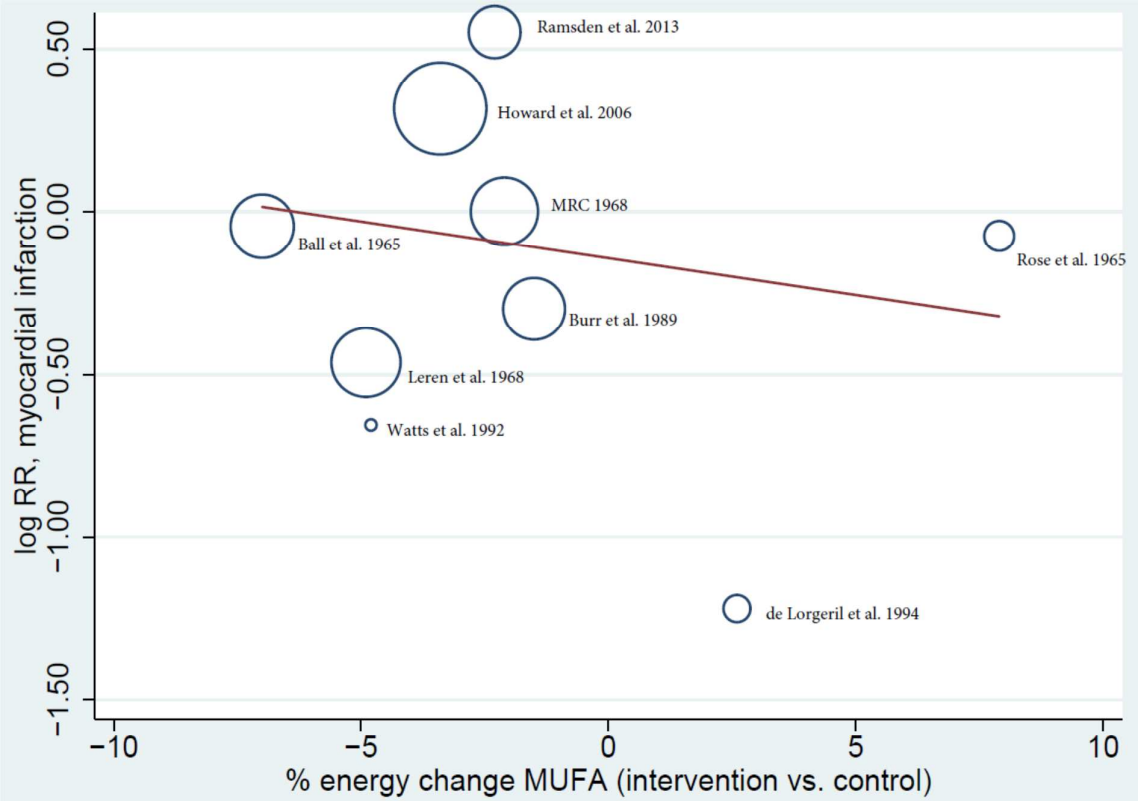


Figure S28. Bubble plot showing the association between % energy change from MUFA and myocardial

infarction

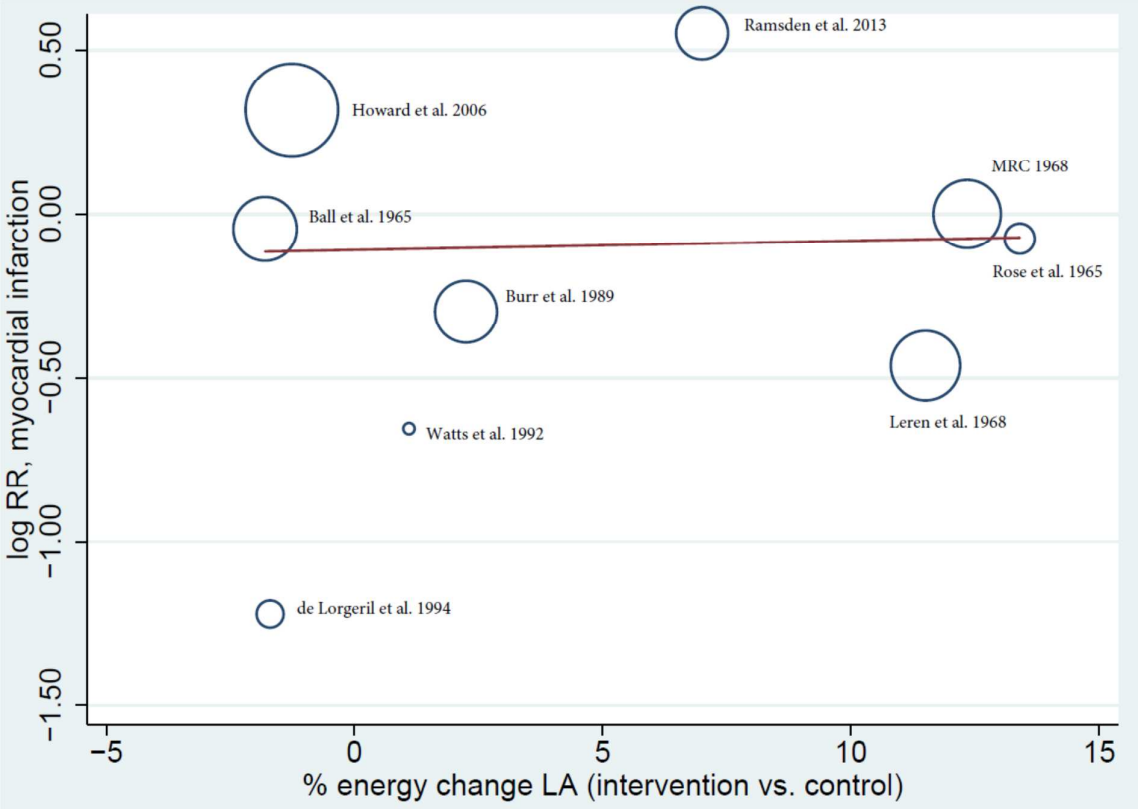


Figure S29. Bubble plot showing the association between % energy change from LA and myocardial infarction

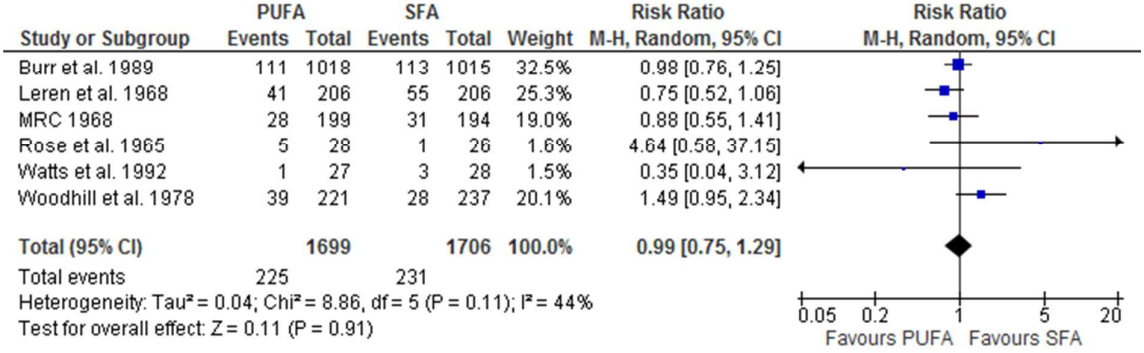


Figure S30. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 6 randomized controlled trials (PUFA vs. SFA).

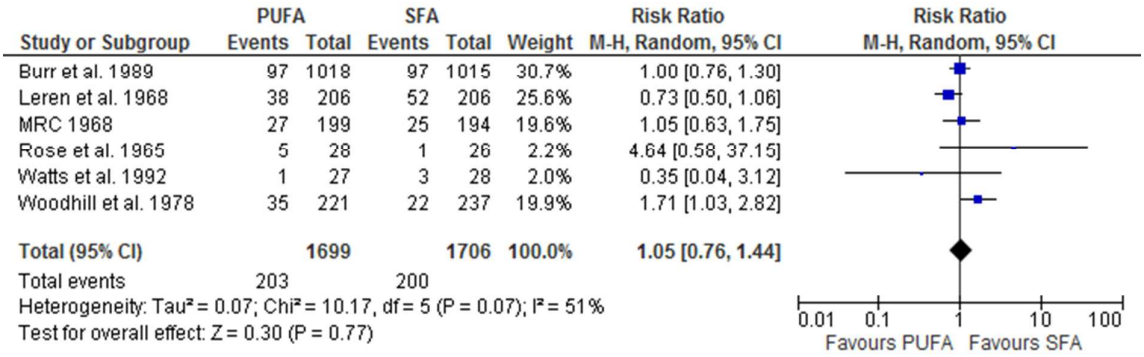


Figure S31. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 6 randomized controlled trials (PUFA vs. SFA).

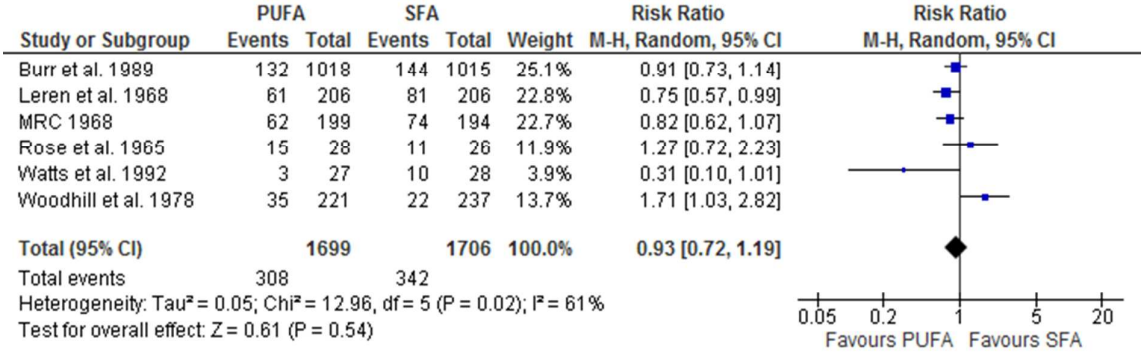


Figure S32. Forest plot showing pooled relative risks (RRs) with 95% CI for total cardiovascular events for 6 randomized controlled trials (PUFA vs. SFA).

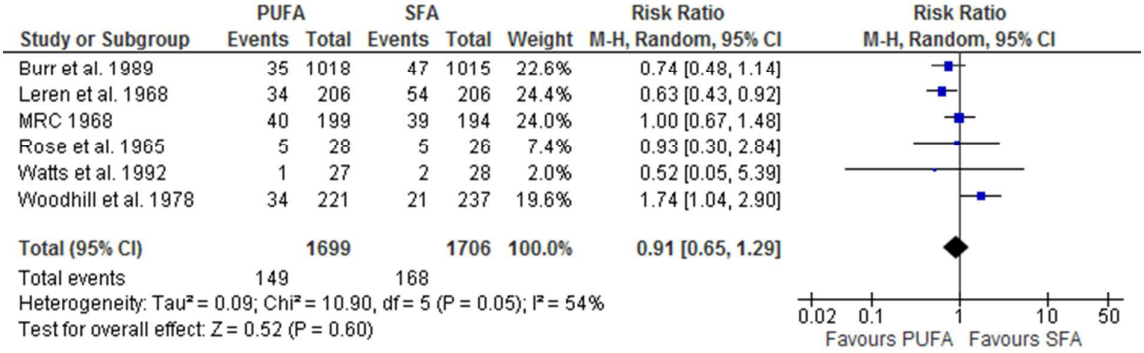


Figure S33. Forest plot showing pooled relative risks (RRs) with 95% CI for myocardial infarction for 6 randomized controlled trials (PUFA vs. SFA).

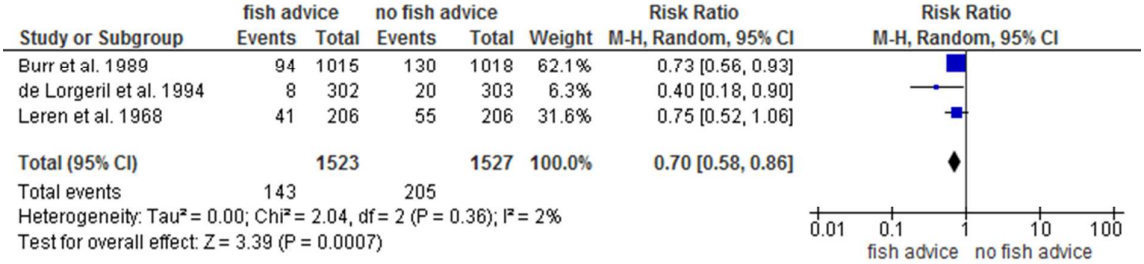


Figure S34. Forest plot showing pooled relative risks (RRs) with 95% CI for all-cause mortality for 3 randomized controlled trials (fish advice vs. no fish advice).

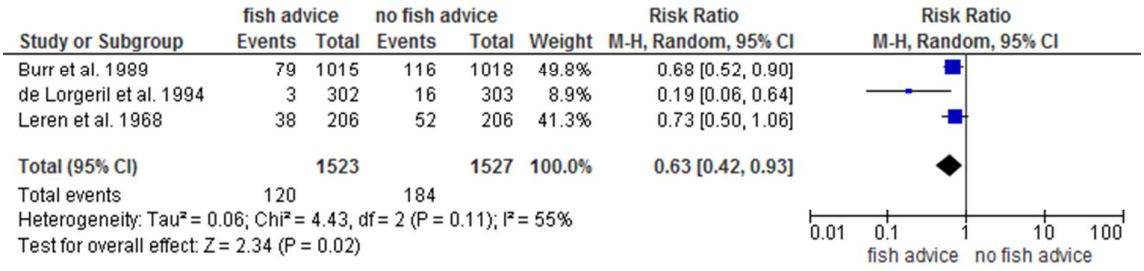


Figure S35. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular mortality for 3 randomized controlled trials (fish advice vs. no fish advice).

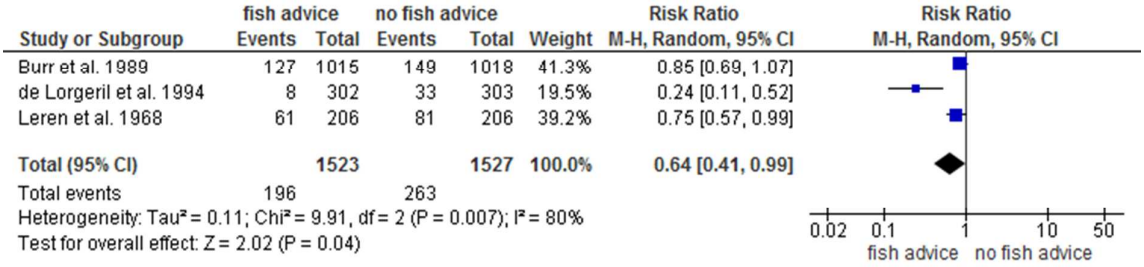


Figure S36. Forest plot showing pooled relative risks (RRs) with 95% CI for cardiovascular events for 3 randomized controlled trials (fish advice vs. no fish advice).

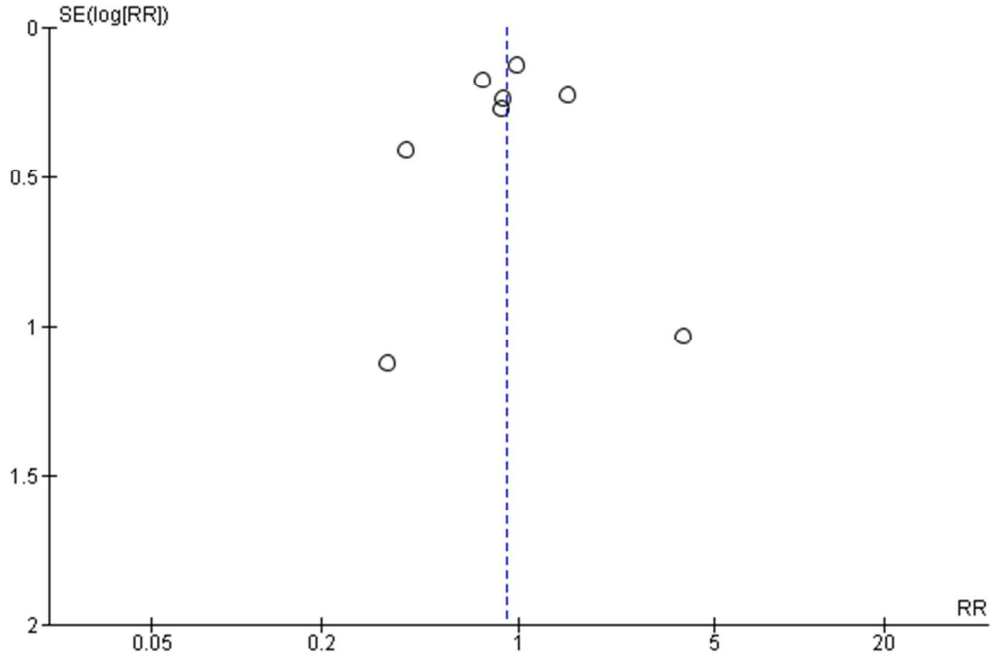


Figure S37. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for all-cause mortality. SE = Standard error

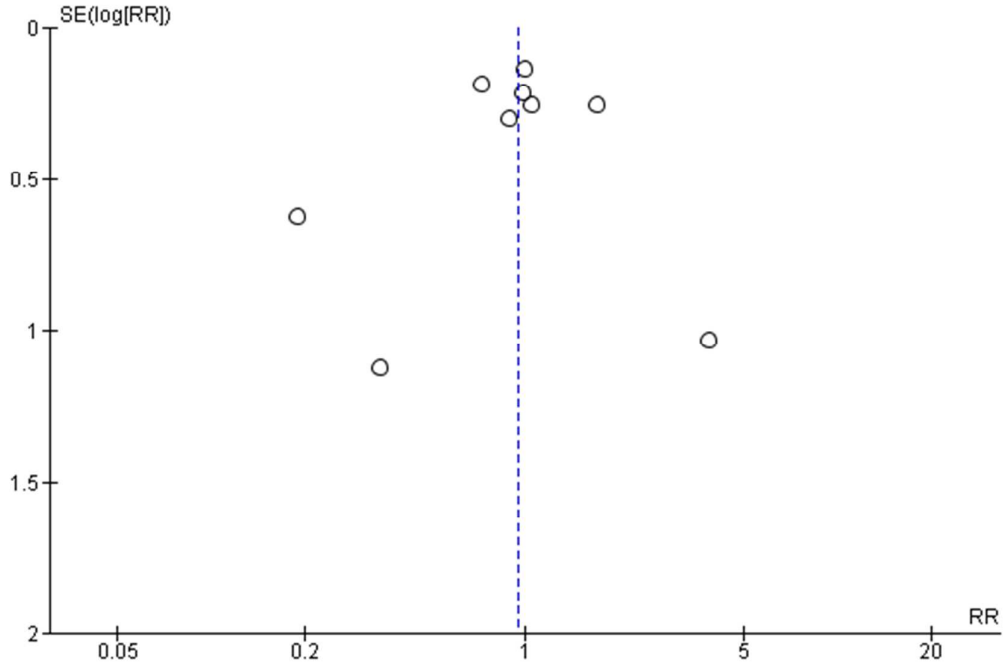


Figure S38. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for cardiovascular mortality. SE = Standard error

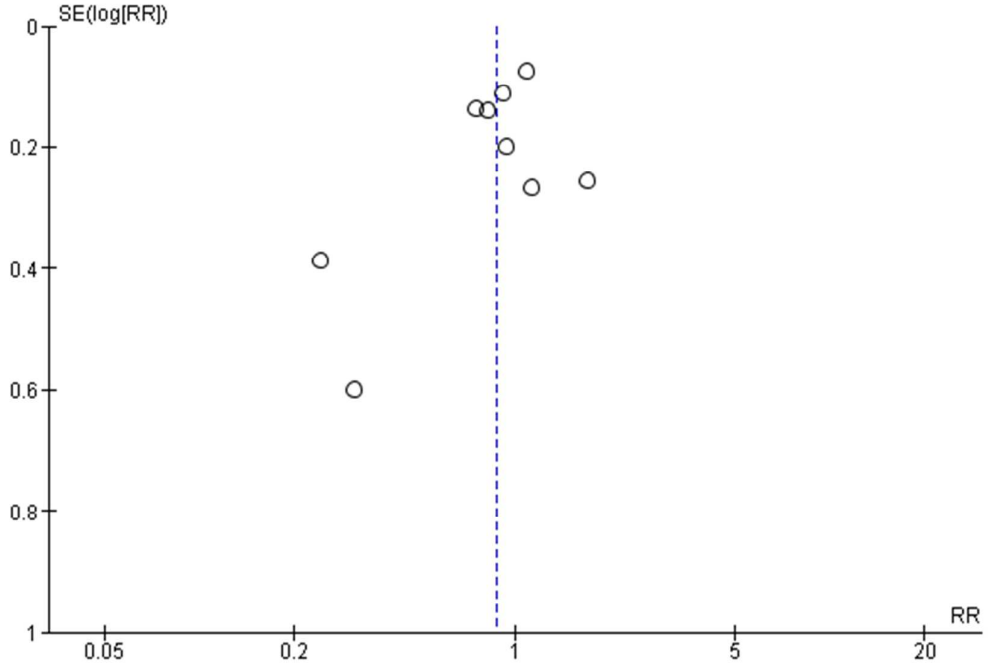


Figure S39. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for combined cardiovascular events. SE = Standard error

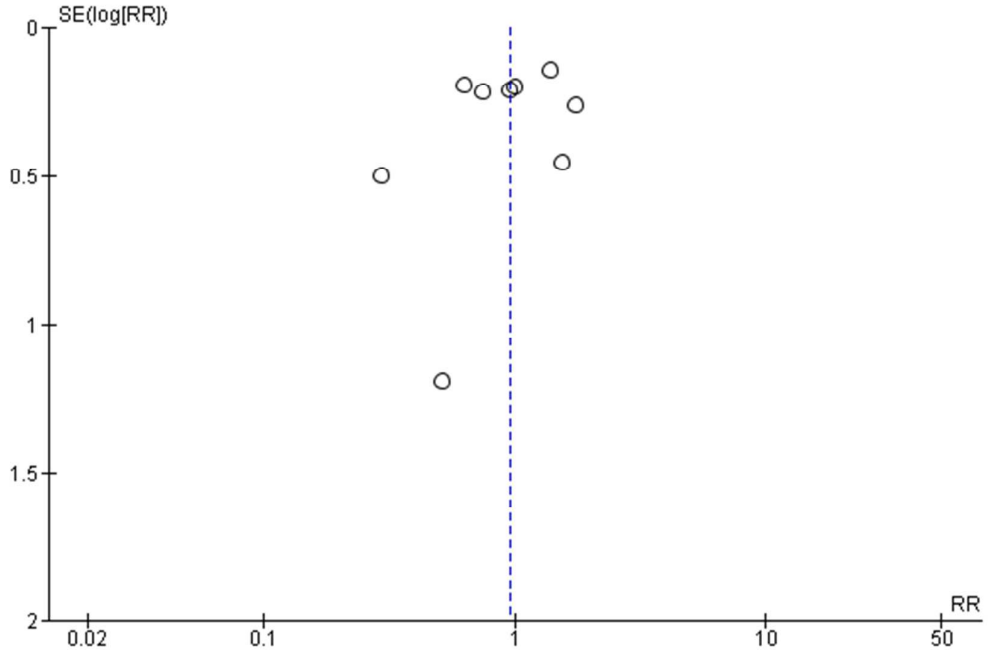


Figure S40. Funnel plot showing study precision against the relative risk effect estimate with 95% CIs for myocardial infarction. SE = Standard error