

Association of dietary, circulating, and supplement fatty acids with coronary risk

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ABSTRACT

Background Guidelines advocate changes in fatty acid consumption to promote cardiovascular health.

Purpose To summarize evidence about associations between fatty acids and coronary disease.

Data Sources MEDLINE, Science Citation Index, and Cochrane Central Register of Controlled Trials through July 2013.

Study Selection Prospective, observational studies and randomized, controlled trials.

Data Extraction Investigators extracted data about study characteristics and assessed study biases.

Data synthesis There were 32 observational studies (512420 participants) of fatty acids from dietary intake; 17 observational studies (25721 participants) of fatty acid biomarkers; and 27 randomized, controlled trials (105085 participants) of fatty acid supplementation. In observational studies, relative risks for coronary disease were 1.03 (95%CI, 0.98 to 1.07) for saturated, 1.00 (CI, 0.91 to 1.10) for monounsaturated, 0.87 (CI, 0.78 to 0.97) for long-chain omega-3 polyunsaturated, 0.98 (CI, 0.90 to 1.06) for omega-6 polyunsaturated, and 1.16 (CI, 1.06 to 1.27) for trans fatty acids when the top and bottom thirds of baseline dietary fatty acid intake were compared. Corresponding estimates for circulating fatty acids were 1.06 (CI, 0.86 to 1.30), 1.06 (CI, 0.97 to 1.17), 0.84 (CI, 0.63 to 1.11), 0.94 (CI, 0.84 to 1.06), and 1.05 (CI, 0.76 to 1.44), respectively. There was heterogeneity of the associations among individual circulating fatty acids and coronary disease. In randomized, controlled trials, relative risks for coronary disease were 0.97 (CI, 0.69 to 1.36) for alpha-linolenic, 0.94 (CI, 0.86 to 1.03) for long-chain omega-3 polyunsaturated, and 0.86 (CI, 0.69 to 1.07) for omega-6 polyunsaturated fatty acid supplementations

Limitations Potential biases from preferential publication and selective reporting.

Conclusion Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats.

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INTRODUCTION

Dietary fats mainly comprise triacylglycerols consisting of three individual fatty acids, each linked by an ester bond to a glycerol backbone (1-2). Based on the number of double bonds they contain, fatty acids are classified as saturated, monounsaturated, and polyunsaturated. Specific fatty acids within these categories tend to have different biological effects and physical properties (3). To promote cardiovascular health (4-5), nutritional guidelines have generally encouraged low consumption of saturated fats, high consumption of omega-3 polyunsaturated fatty acids from fish or plant sources, and avoidance of *trans* fats, particularly those from partially-hydrogenated fat. There is, however, considerable variation in international guidelines concerning optimum amounts and types of fatty acids consumption (6-11). This variation reflects, at least in part, uncertainties in the available evidence. For example, prospective observational studies have questioned whether there really are associations between saturated fat consumption and cardiovascular disease (12). However, interpretation has been complicated by potential misclassification in the self-report questionnaires used to assess fatty acid consumption (13-15), which also lack the ability to compute intake of specific fatty acids (16). By contrast, fatty acid biomarkers may provide more accurate assessment of consumption, such as for polyunsaturated fatty acids (17), and/or metabolism, such as for saturated and monounsaturated fatty acids (17-20). However, earlier analyses have generally not assessed the consistency between findings from dietary self-report and biomarker measures of fatty acids in coronary disease. With respect to randomised trials of fatty acid supplements for preventing coronary disease, interpretation of results has been complicated by the differences in dietary habits of various trial populations, the absence or presence (and type) of pre-existing vascular disease at entry, the composition of supplementation regimens, trial duration and power, and apparent differences in reported efficacy for coronary prevention. Furthermore, previous meta-analyses of randomised trials were only focused on omega-3 and omega-6 supplementations(21-22)and did not include more recent and larger trials.

To help clarify the evidence, we have conducted a systematic review and meta-analysis of data from long-term prospective observational studies of a broad range of both dietary and biomarker fatty acid measures in coronary disease. To put the observational evidence into context, we have examined associations with coronary outcomes in the randomised trials of fatty acids supplementation.

METHODS

Data Sources and Searches

This review was conducted using a predefined protocol and in accordance to the MOOSE and PRISMA guidelines (**Appendix 1 and 2**). Studies published before 1 July 2013 were identified, without any language restriction, through electronic searches using MEDLINE, Science Citation Index databases, Cochrane Central Register of Controlled Trials and supplemented by scanning reference lists of articles identified for all relevant studies and review articles (including meta-analyses), by hand searching of relevant journals, and by correspondence with authors of included studies. The computer-based searches combined search terms related to the exposure (eg, *fatty acids, unsaturated fatty acids etc*) and coronary disease (eg, *myocardial infarction, atherosclerosis, coronary heart disease, coronary stenosis*) without language restriction (**Appendix 3**).

Study Selection

Observational and intervention studies were included if they had reported on associations of dietary fatty acids intake, fatty acids biomarkers (measured in whole blood, serum, plasma, erythrocyte fraction [ie, circulating fatty acids], or adipose tissue), or fatty acids intervention (dietary or supplements) with risk of coronary disease (defined as fatal or non-fatal myocardial infarction, coronary heart disease, coronary insufficiency, coronary death, angina, angiographic coronary stenosis [where possible sudden cardiac death was not included in the outcome definition]: **Appendix 4** provides study-specific outcomes definition). Observational studies were eligible if they were prospective in design with at least one year of follow-up and involved participants from approximately general populations (ie, participants not selected on the basis of pre-existing disease at baseline) or with stable cardiovascular disease at study entry (defined as a diagnosis made at least 30 days prior to baseline sampling). Intervention studies were eligible for inclusion if they were randomised and recorded coronary outcomes as an endpoint of interest.

Data Extraction and Quality Assessment

Data on the following characteristics were extracted independently by two investigators who used standardised protocols: sample size; study design; sampling population; location (defined as Europe, North America, and the Asia-Pacific region); year of baseline survey; age range of participants at baseline; gender; duration of follow-up; numbers of disease outcomes of interest and reported effect estimates with coronary disease with each marker, degree of statistical adjustment used, cross-sectional correlation coefficients of dietary fatty acids intake and circulating fatty acids (where available). Where appropriate, information on sample type (serum, plasma or adipose tissue), storage temperature, assay methods, dietary assessment tool (diet questionnaire, defined as food frequency or diet history questionnaires; diet records, defined as all open-ended instruments such as 24-hour recall and food diaries), type and formulation of intervention, year of randomisation, allocation concealment, blinding of carers and participants, daily dose of supplementations, and composition of placebo were abstracted. Discrepancies were resolved by discussion and by adjudication of a third reviewer. We used the most up-to-date or comprehensive information in cases of multiple publications. The Newcastle-Ottawa Scale (23) was used for

assessing the quality of observational studies. This scale uses a “star” system (with maximum of nine stars) to assess the quality of a study in three domains: selection of participants; comparability of study groups; and the ascertainment of outcomes of interest. Studies that received a score of nine stars were judged to be of high quality; studies that scored seven or eight stars were considered of medium quality. The Cochrane Collaboration’s tool for assessing risk of bias was used for assessing the validity of randomised trials (24). This tool assesses seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each individual domain, studies were classified into low, unclear and high risk of bias.

Data Synthesis and Analysis

Analyses involved only within-study comparisons (ie, cases and controls were only directly compared within each cohort) to limit potential biases. To enable a consistent approach to meta-analysis and interpretation of findings in this review, relative risk estimates for association of fatty acids and coronary disease that were often differently reported by each study (e.g. per unit change, or per 1-SD change, or comparing quintiles, quartiles, thirds, and other groupings) were transformed to consistently correspond to comparison of the top vs. bottom third of fatty acid distribution in each study, using methods previously described (25). Briefly, log risk estimates were transformed assuming a normal distribution, with the comparison between top and bottom thirds being equivalent to 2.18 times the log risk ratio (RR) for a 1 standard deviation increase (or equivalently, as 2.18/2.54 times the log RR for a comparison of extreme quarters). Standard errors of the log RRs were calculated using published confidence limits and were transformed in the same way (**Appendix 5** provides details of the statistical methods used). Where studies reported RRs with differing degrees of adjustment for other risk factors, the multivariable adjusted estimate that did not include adjustment for blood lipids and/or circulating fatty acids was used (as circulating lipids may act as potential mediators for the associations between fatty acids and coronary disease (26)). For randomised intervention trials we used reported RR or calculated study-specific unadjusted RR for the main outcomes of interest. Hazard ratios and odds ratios were assumed to approximate the same measure of relative risk. Summary RRs were calculated by pooling the study-specific estimates using a random-effects model that included between-study heterogeneity (parallel analyses used fixed-effect models). Correlations of dietary fatty acids intake and circulating fatty acids were estimated by pooling Spearman’s study-specific correlation coefficients using random effects meta-analysis. Consistency of findings across individual studies was assessed by standard χ^2 tests and the I^2 statistic (27). Heterogeneity between observational cohorts was assessed by comparing results from studies grouped according to pre-specified study-level characteristics (such as location, gender, year of baseline survey, duration of follow-up, numbers of outcomes recorded, outcome definition, degree of statistical adjustment used, assay characteristics and dietary assessment) and to the Newcastle-Ottawa Scale score using meta-regression. A similar method was used to assess heterogeneity between randomised trials by constructing groups according to pre-specified trial characteristics (such as type and formulation of intervention, year of randomisation, allocation concealment, blinding of carers and participants, daily dose of supplementations, and composition of

placebo) and to the risk of bias in each individual domain defined by the Cochrane Collaboration's tool for assessing risk of bias. Evidence of publication bias across studies was assessed using funnel plots and Egger test (28). All statistical tests were two-sided and used a significance level of $p < 0.05$. All analyses were performed using Stata release 11 (StataCorp, College Station, Texas).

Role of the funding sources

The study was conducted and analysed independently from its funders.

RESULTS

Overall, seventy-two unique studies were identified (**Table 1**, **eFigure 1**, and **Appendix 6** provide study details and references). Nineteen studies were based in North America, 42 studies in Europe, 9 studies in the Asia-Pacific and 2 studies were multinational. Forty-five studies were prospective observational cohorts and 27 were randomised trials (one trial also reported data as an observational cohort on blood fatty acids). Forty studies involved initially healthy populations, ten studies recruited individuals with elevated cardiovascular risk factors, and 22 recruited people with cardiovascular disease at baseline.

Dietary fatty acids intake and coronary risk

Thirty-two prospective cohort studies reported on self-reported dietary fatty acids intake (512,420 participants, 15,945 incident coronary outcomes, average follow-up ranging from 5 to 23 years: **eTable 1**), of which 21 recorded information using diet questionnaires and 11 using diet records. All studies reported adjustment for at least several non-blood based vascular risk factors (eg, age, sex, smoking, history of diabetes, and blood pressure). Thirteen studies were judged to be of high quality and 19 of medium quality, while no studies were rated as low quality (**eTable 2**). Of the medium quality studies, all showed a potential bias in the participant selection and 6 further lacked objective confirmation of self-reported dietary intake of fatty acids by structured face-to-face interview. RRs for coronary disease, comparing participants in the top third versus those in the bottom third of dietary fatty acids, are presented in **Figure 1**. In these studies the pooled RRs (95%CIs) were: 1.03 (95%CI, 0.98 to 1.07) for total saturated fatty acids, 1.00 (CI, 0.91 to 1.10) for total monounsaturated fatty acids, and 1.16 (1.06-1.27) for total *trans* fatty acids (**Figure 1** and **eFigure 2**). Corresponding RRs for total dietary polyunsaturated fatty acids intake were 0.99 (0.86-1.14) for total alpha-linolenic acid, 0.87 (CI, 0.78 to 0.97) for total long-chain omega-3 polyunsaturated fatty acids, and 0.98 (CI, 0.90 to 1.06) for total omega-6 polyunsaturated fatty acids (**Figure 1** and **eFigure 3**). In studies of dietary fatty acid intake, there was some evidence of heterogeneity between studies according to number of events recorded ($p=0.009$ for saturated and $p=0.006$ for monounsaturated fatty acids) and geographical location ($p=0.020$ for long-chain omega-3 polyunsaturated fatty acid studies; **eFigure 4**). There was no material difference in the combined RRs according to gender, year of baseline survey, dietary assessment tool, duration of follow-up, outcome definition or degrees of statistical adjustment (**eFigure 4**).

Fatty acids biomarkers and coronary risk

Information on fatty acids biomarkers was available from 19 prospective studies (**eTables 3** and **4**). Seventeen reported on circulating fatty acids composition (25,721 participants, 5,519 incident coronary outcomes, mean follow-up ranged from 1.3 to 30.7 years: **eTable 3**), and 2 on adipose tissue fatty acid composition (6,586 participants, 1,663 incident coronary events: **eTable 4**). Of those reporting on circulating fatty acids composition, 14 used liquid chromatography, 2 used calorimetric, and one used an enzymatic method to measure fatty acids. Six studies were judged to be of high quality, 9 of medium quality, and 2 were rated as low quality (**eTable 5**). Of the medium quality studies, 8 showed potential bias in participant selection and one did not control for any

potential risk factor in their analyses. The 2 low quality studies included participants drawn from selected populations and also did not control for potential covariates in their analyses. All studies reported adjustment for standard non-blood based vascular risk factors (eg, age, sex, smoking, history of diabetes, and blood pressure). Studies tended to report on a variable number of individual fatty acid isomers (**eTable 6**). The mean proportion of each individual circulating fatty acid relative to the total is presented in **eFigure 5**. Among studies with available data, there were moderate positive correlations between dietary intake and circulating composition of total omega-3 and omega-6 polyunsaturated fatty acids, and weak positive correlations for total saturated and monounsaturated fatty acids (**eTable 7**). RRs for coronary outcomes, typically adjusted for non-blood based vascular risk factors, comparing top third versus bottom third of composite and individual circulating fatty acid composition at baseline are presented in **Figures 2** and **eFigures 6-11**. For the circulating total fatty acids composition, combined RRs were: 1.06 (0.86-1.30) for total saturated fatty acids, 1.06 (0.97-1.17) for total monounsaturated fatty acids, 0.93 (0.83-1.03) for *alpha*-linolenic acid, 0.84 (0.63-1.11) for total long-chain omega-3 polyunsaturated fatty acids, 0.94 (0.84-1.06) for total omega-6 polyunsaturated fatty acids, and 1.05 (0.76-1.44) for total *trans* fatty acids. Among individual saturated and monounsaturated fatty acids, RRs for palmitic, stearic and oleic acids were 1.15 (0.96-1.37), 1.23 (0.93-1.61) and 1.09 (0.97-1.23). By contrast, margaric acid was significantly associated with lower risk (0.77 [0.63-0.93]; **Figure 2** and **eFigures 6-7**). Among specific polyunsaturated fatty acids, eicosapentaenoic (0.78 [0.65-0.94]), docosahexaenoic (0.79 [0.67-0.93]), and arachidonic (0.83 [0.74-0.92]) acids were associated with lower risk; and dihomo-gamma linolenic (1.11 [0.93-1.33]), eicosadienoic (1.18 [0.93-1.50]), and docosatetrahexanoic (1.20 [0.99-1.45]) acids tended towards a positive, albeit nonsignificant, association with coronary disease (**Figure 2**, **eFigures 8-10**). Only two studies with a total of <500 cases reported on individual circulating *trans* fatty acids composition (**eFigure 11**). For circulating total saturated fatty acid, there were some evidence of heterogeneity between studies according to outcome definition (fatal vs non-fatal) and duration of follow-up for ($p=0.003$ for both). For circulating eicosapentaenoic+docosahexaenoic fatty acids composition, there was some evidence of heterogeneity between studies according to outcome definition (fatal vs non-fatal, $p=0.004$), duration of follow-up for ($p<0.001$), number of events recorded ($p<0.001$), gender ($p=0.014$) and fasting or non-fasting sampling state ($p=0.037$; **eFigure 12**). There was no material difference in the combined RRs according to year of baseline survey, population baseline risk, geographical location, assay characteristics (such as sample type, lipids fraction used or storage temperature), or degrees of statistical adjustment. In 2 studies that measured adipose tissue fatty acid composition, there were generally non-significant associations across total and specific fatty acids (**eFigure 13**).

Effects of fatty acids supplementation on coronary outcomes

Overall, 27 randomised controlled trials reported on fatty acids supplementation, including a total of 105,085 participants among whom 6,229 had an incident coronary outcome (mean follow-up ranged from 0.1 to 8 years: **eTable 8**). Eighteen trials recruited individuals with cardiovascular disease at baseline, 8 recruited individuals with elevated cardiovascular risk factors and one involved initially healthy participants. Four studies reported on alpha-linolenic acid supplementation (dose ranging

from 2 to 5.5 grams/day where dietary oil was the principal form of supplementation); 17 on long-chain omega-3 polyunsaturated fatty acids supplementation (dose ranging from 0.3 to 6 grams/day where capsule was the principle form of supplementation), and 8 on omega-6 polyunsaturated fatty acids supplementation (2 using linoleic acid specific and 6 with mixed polyunsaturate intervention where dietary supplementation consisted principally of linoleic acid). No data were available on interventions related to saturated or monounsaturated fatty acids. Risk of bias assessment in each trial is reported in **eTable 9**. All trials had low risk of bias for the random sequence generation and the incomplete outcome data domains. One trial had an unclear risk of bias for allocation concealment and 7 for blinding of outcome assessment. Eight trials had a high risk of bias for blinding of participants and personnel, and 3 for selective reporting. Risk of other bias was unclear in 6 trials and high in 3. RRs for coronary outcomes comparing individuals in the intervention group versus those in the control group were: 0.97 (0.69-1.36) for alpha-linolenic acid, 0.94 (0.86-1.03) for total long-chain omega-3 polyunsaturated fatty acids, and 0.86 (CI, 0.69 to 1.07) for omega-6 polyunsaturated fatty acids (**Figure 3** and **eFigure 14**). There was no significant evidence of heterogeneity according to several trial characteristics, such as baseline population risk, geographical location, length of follow-up, outcome definition, and number of ascertained coronary outcomes (**eFigure 15**). Furthermore, overall effects of the fatty acid supplementations on coronary disease were generally similar in the trials that had appropriate allocation concealment or blinded its participants and carers (**eFigure 15**). Subsidiary analyses by excluding trials that had recorded less than 50 coronary disease outcomes did not materially alter the results (**eFigure 16**). However, in a subsidiary analysis, exclusion of one omega-6 trial which used a margarine-based supplementation also high in trans fat, the relative risk for omega-6 polyunsaturated fatty acids was 0.81 (CI, 0.68 to 0.98).

Assessment of publication bias

There was generally no evidence of publication bias among the included observational or intervention studies (**eFigure 17**).

DISCUSSION

Our findings do not clearly support cardiovascular guidelines that promote high consumption of omega-6 polyunsaturated fatty acids and suggest reduced consumption of total saturated fatty acids. First, we saw statistically nonsignificant associations in prospective studies of coronary disease that involved assessment of dietary intake of omega-6 polyunsaturated fatty acids. Conversely, dietary long-chain omega-3 polyunsaturated fatty acids was associated with lower risk of coronary disease. We found heterogeneity of the associations between specific circulating long-chain omega-3 and omega-6 polyunsaturated fatty acid composition and coronary disease, with some evidence that circulating levels of eicosapentaenoic and docosahexaenoic acids (the 2 main types of long-chain omega-3 polyunsaturated fatty acids) and arachidonic acid are each associated with lower coronary risk. However, our meta-analysis of randomized trials of long-chain omega-3 and omega-6 polyunsaturated fatty acid supplements suggests that supplementation with these nutrients does not statistically significantly reduce the risk for coronary outcomes. These updated findings are in line with an earlier meta-analysis that reported limited effect of omega-3 polyunsaturated fatty acid supplements on cardiovascular disease (22). Nonetheless, further trials are warranted because the available evidence is generally limited, especially in initially healthy populations; hence, there is considerable interest in a large randomized trial of long-chain omega-3 polyunsaturated supplements in primary prevention currently in progress (29).

Second, we found essentially null associations between total saturated fatty acids and coronary risk in studies using dietary intake and in those using circulating biomarkers. This apparent lack of association in self-reported dietary studies could at least partially be explained by biases in self-report questionnaires, especially in relation to certain foods, such as common snacks high in saturated fats (30) (however, consumption of both saturated and monounsaturated fats is measured reasonably well by questionnaires [31, 32]). We saw heterogeneity of effect across circulating composition of specific saturated fatty acids. This could, at least in part, reflect biology because circulating saturated fatty acid fractions reflect both consumption and endogenous metabolism and synthesis (33). For example, the influence of metabolism seems particularly relevant for the *de novo* synthesis of even-numbered saturated fatty acids in the body, compositions of which are largely determined by dietary factors, including carbohydrate and alcohol consumption (33–35), and other metabolic pathways (36, 37) rather than direct dietary intake. This is supported indirectly by the positive yet nonsignificant associations seen for circulating blood composition of palmitic and stearic acids (which are synthesized in the body and only weakly correlated with saturated fatty acid consumption [32, 38]) with coronary disease. In contrast, we found a possible inverse association between circulating margaric acid (an odd-chain saturated fatty acid that is moderately correlated with milk and dairy fat consumption [39, 40]) and coronary disease, suggesting that odd-chain saturated fats, which reflect milk or dairy consumption, may have less deleterious effects in risk for coronary heart disease (41).

Third, we saw null associations of total and individual monounsaturated fatty acids with coronary risk in studies using both dietary intake and circulating fatty acid composition. This apparent lack of

association is consistent with available mechanistic data, which remain contradictory about whether monounsaturated fatty acids promote or protect against atherogenesis (42–44). In addition, total dietary trans fatty acid intake was positively associated with coronary disease risk in our meta-analysis, which is in line with the present guidelines that support avoidance of trans fats. However, because only 5 published prospective cohort studies contributed to this analysis, the inclusion of relevant data from other unpublished studies could alter the overall estimate. This association was unclear in studies that assessed circulating trans fatty acid composition, potentially because of a relative paucity of data on trans fatty acid biomarkers and coronary risk. Furthermore, the method used to measure circulating fatty acids in 1 study (41) may not have been sufficient for optimal resolution of the individual trans fatty acid isomers.

Several strengths and limitations merit careful consideration. The review provides a comprehensive systematic synthesis of available evidence by including data from different sources of evidence and quantifies the risk for coronary disease for a wide range of individual fatty acid isomers and several relevant subgroups in a consistent way. Generalizability was enhanced by the involvement of information from more than 600,000 participants in 18 countries. Most of the observational studies were judged as reasonably high-quality. Limitations include the moderate amount of available data on some specific circulating fatty acids and possible overestimations of associations because of preferential publication of extreme findings or, analogously, by selective reporting of results for particular fatty acids with striking associations. Although selective reporting seems minimal among randomized trials, few observational studies reported on all measured circulating fatty acids. Therefore, selective underreporting may have contributed at least in part to the observational findings in this meta-analysis. Because most studies lacked serial assessment of fatty acids in the same persons, relative risks in published reports may have been prone to underestimation because of “regression dilution bias” (45). Similar considerations apply to self-reported measures of fatty acid consumption. We assumed log-linear associations between fatty acid measures and coronary risk because we lacked access to individual-participant data. Although we used estimates that were unadjusted for potential mediators (such as blood lipids and circulating fatty acids), we could not adjust consistently for potential confounding factors across all studies. In addition, although most trials were rated as having low risk of bias, the findings from these studies should be interpreted with caution because of the relatively small number of trials investigating α -linolenic and omega-6 polyunsaturated fatty acid interventions and the potential differences in design and population characteristics of each trial.

In conclusion, the pattern of findings from this analysis did not yield clearly supportive evidence for current cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of saturated fats.

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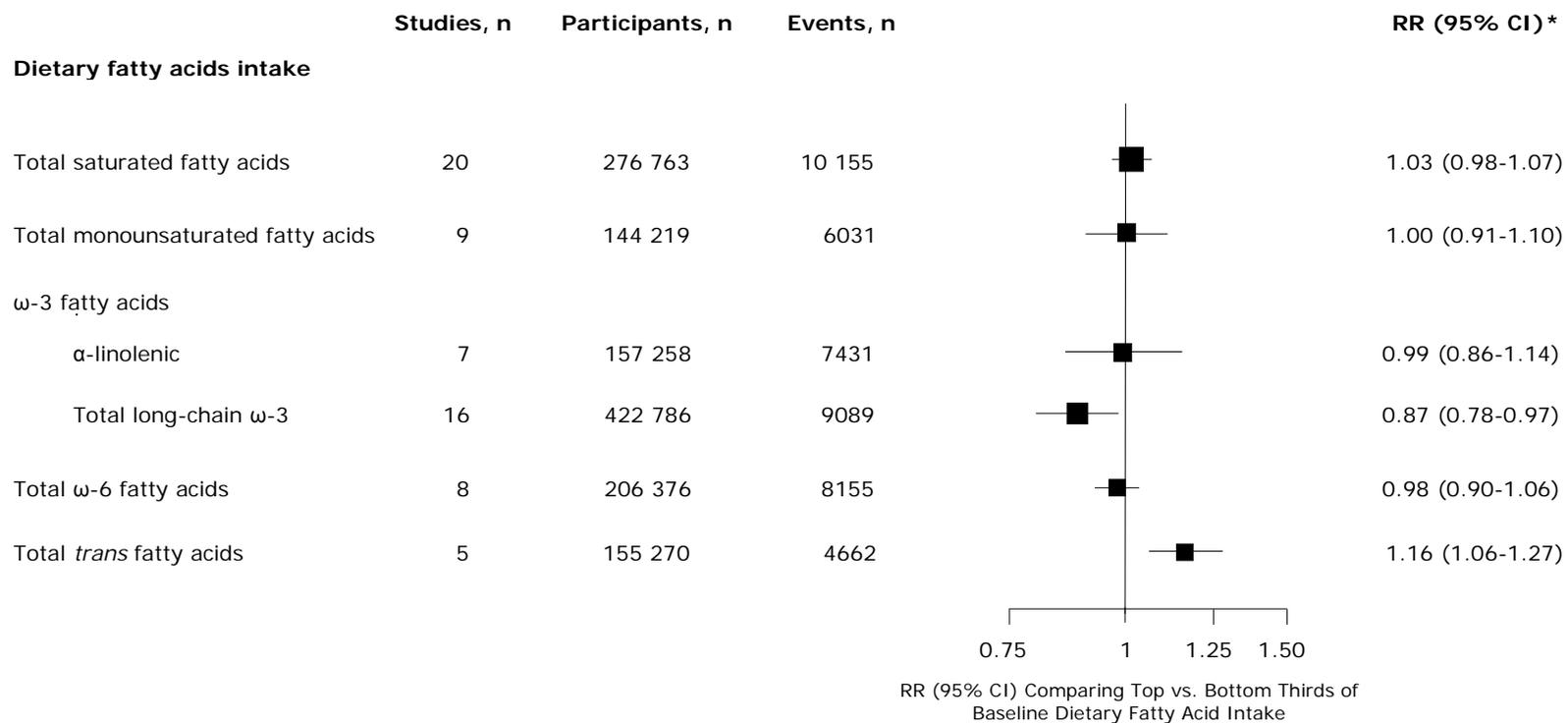
MAIN TABLE AND FIGURES

Table 1. Summary of Data Included in the Current Review

	Number of		
	Studies*	Participants	Coronary events
Prospective cohort studies of dietary fatty acids intake			
All studies	32	512,420	15,945
Dietary questionnaire [¶]	21	463,038	11,157
Diet record [§]	11	49,382	4,788
Prospective cohort studies of fatty acid biomarkers			
All studies	19	32,307	7,182
Circulating fatty acids composition	17	25,721	5,519
Adipose tissue fatty acids composition	2	6,586	1,663
RCTs of fatty acids supplementation	27	105,085 [‡]	6,229 [†]

*5 studies reported on both circulating and diet-based exposures, and 1 study reported on both circulating fatty acids and effect of fatty acid supplementation; ¶ includes food frequency and diet history questionnaires; § includes open-ended instruments such as 24 hour recall and food diaries; ‡ Includes 52,588 and 52,497 total participants in intervention and control groups respectively; † Includes 3,017 and 3,212 coronary events in intervention and control groups respectively; RCT, Randomised controlled trial. Details of all individual studies are included in the Supplementary Material.

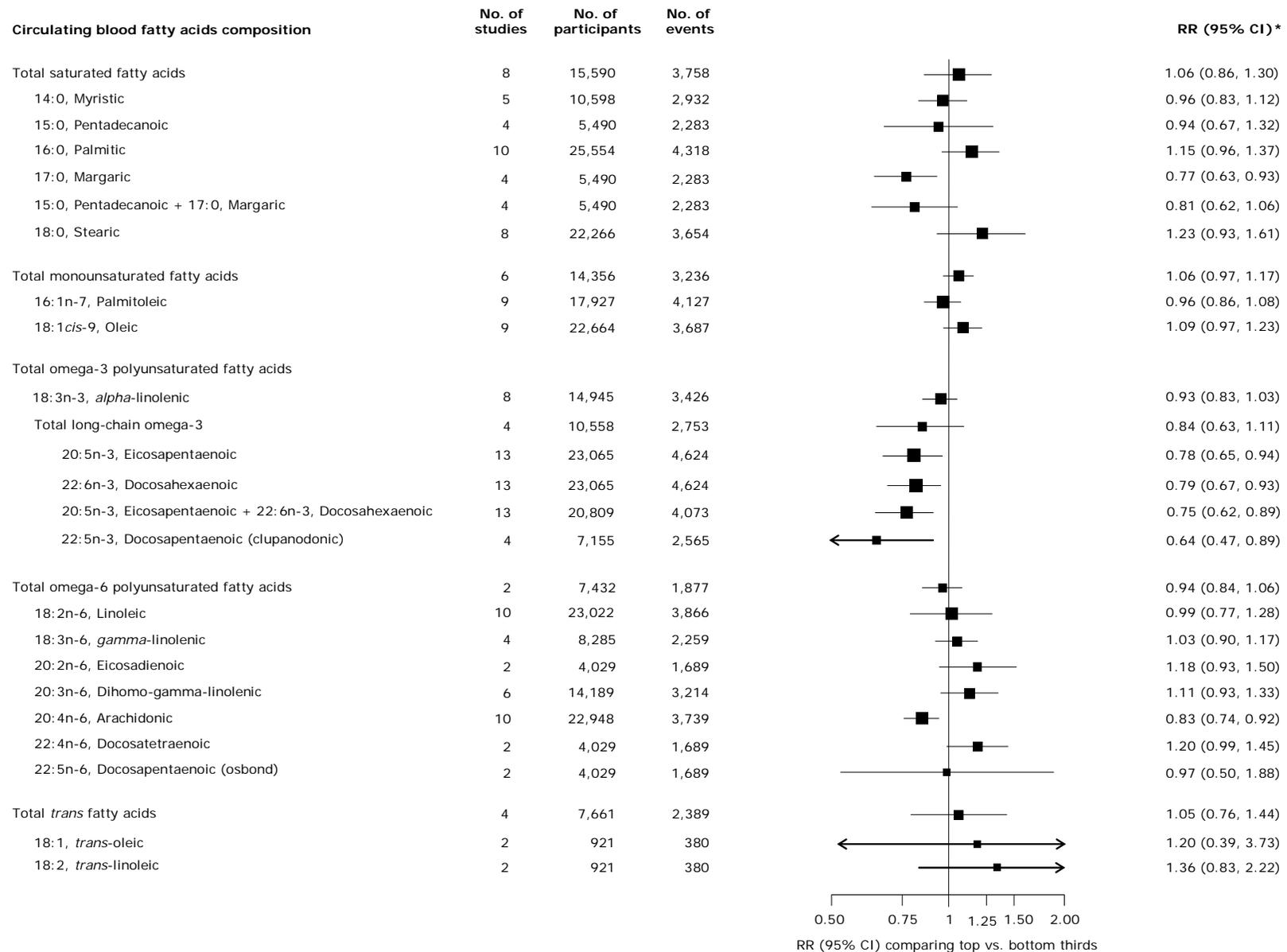
Figure 1. RRs for coronary outcomes, based in prospective cohort studies of dietary fatty acids intake.



Size of the data marker is proportional to the inverse of the variance of the RR. RR=relative risk.

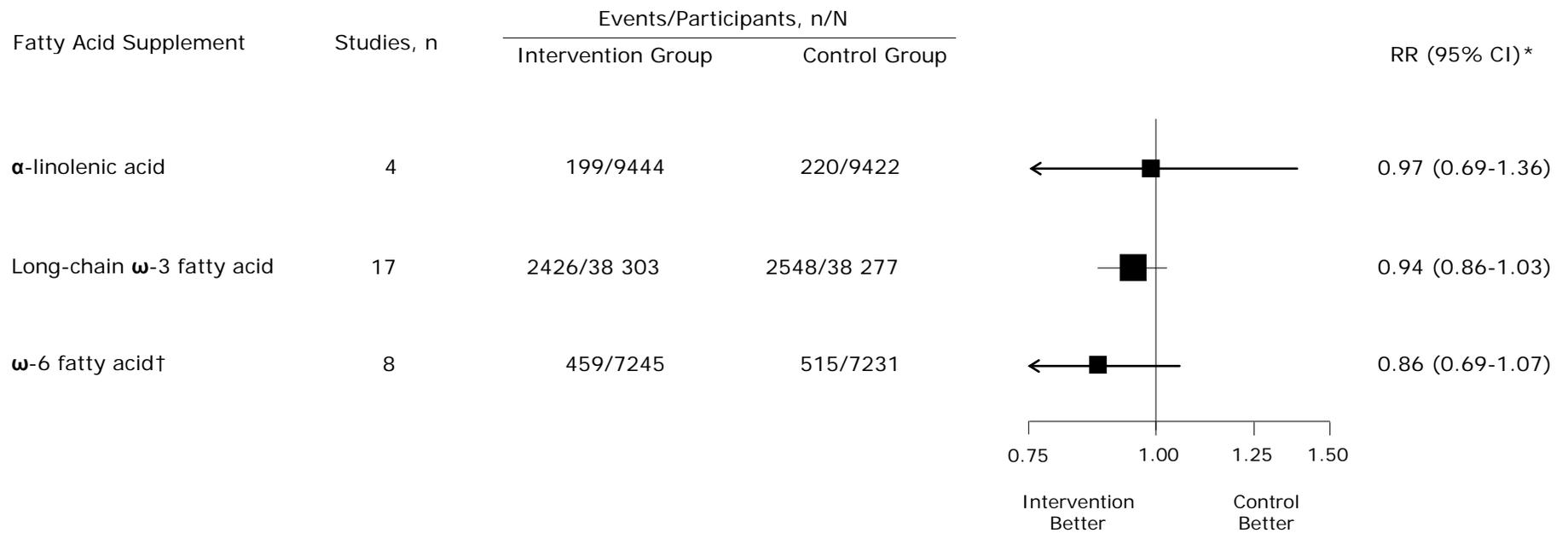
*Pooled estimate based on random effects meta-analysis. Corresponding forest plots, I^2 (95% CI) estimates and pooled RRs based on fixed-effect meta-analysis are provided in **Supplement 1**, available at www.annals.org.

Figure 2. Relative risk for coronary outcomes, in prospective cohort studies of circulating fatty acid composition



*Pooled estimate based on random effects meta-analysis. Size of the data marker is proportional to the inverse of the variance of relative risk (RR) and horizontal line represents 95% confidence interval (CI). Corresponding forest plots, I^2 (95% CI) estimates and RRs from fixed-effect meta-analysis are provided in Supplementary Material

Figure 3. Effect of fatty acid supplementation on risk for coronary event, derived from available randomized, controlled trials.



RR = relative risk. Size of the data marker is proportional to the inverse of the variance of the RR.

*Pooled estimate based on random effects meta-analysis. Corresponding forest plots, I^2 (95% CI) estimates and pooled RRs based on fixed-effect meta-analysis are provided in **Supplement 1**, available at www.annals.org.

†Includes studies with ω -6 specific intervention and mixed polyunsaturrate interventions with linoleic acid as the primary fatty acid.