REVIEW | Annals of Internal Medicine

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk

A Systematic Review and Meta-analysis

Rajiv Chowdhury, MD, PhD; Samantha Warnakula, MPhil*; Setor Kunutsor, MD, MSt*; Francesca Crowe, PhD; Heather A. Ward, PhD; Laura Johnson, PhD; Oscar H. Franco, MD, PhD; Adam S. Butterworth, PhD; Nita G. Forouhi, MRCP, PhD; Simon G. Thompson, FMedSci; Kay-Tee Khaw, FMedSci; Dariush Mozaffarian, MD, DrPH; John Danesh, FRCP*; and Emanuele Di Angelantonio, MD, PhD*

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 (512 420 participants) of fatty acids from dietary intake; 17 observational studies (25 721 participants) of fatty acid biomarkers; and 27 randomized, controlled trials (105 085 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 ω-3 polyunsaturated, 0.98 (CI, 0.90 to 1.06) for ω-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 α-linolenic, 0.94 (CI, 0.86 to 1.03) for long-chain ω-3 polyunsaturated, and 0.86 (CI, 0.69 to 1.07) for ω-6 polyunsaturated fatty acid supplementations.

Limitation: 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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For author affiliations, see end of text.

* Ms. Warnakula and Dr. Kunutsor contributed equally to this work. Drs. Danesh and Di Angelantonio also contributed equally to this work.

Dietary fats mainly comprise triacylglycerols consisting of 3 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, or polyunsaturated. Specific fatty acids within these categories tend to have different biological effects and physical properties (3). Nutritional guidelines generally encourage low consumption of saturated fats, high consumption of ω-3 polyunsaturated fatty acids from fish or plant sources, and avoidance of trans fats, particularly those from partially hydrogenated fat, to promote cardiovascular health (4, 5). However, there is considerable variation in international guidelines about optimum amounts and types of fatty acid 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). 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). In contrast, fatty acid biomarkers may provide more accurate assessment of consumption, such as for polyunsaturated fatty acids (17), and of 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 relation to coronary disease. With respect to randomized 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 preexisting 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 randomized trials were only focused on ω-3 and ω-6

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supplementation (21, 22) and did not include more recent and larger trials.

To help clarify the evidence, we 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 examined associations with coronary outcomes in the randomized trials of fatty acid supplementation.

Methods

Data Sources and Searches

This review was conducted using a predefined protocol and in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (**Tables 1** and **2** of **Supplement 1**, available at www.annals.org). Studies published before 1 July 2013 were identified, without any language restriction, through electronic searches of MEDLINE, Science Citation Index, and Cochrane Central Register of Controlled Trials. The search was supplemented by scans of reference lists of articles identified for all relevant studies and review articles (including meta-analyses) through hand-searching of relevant journals and correspondence with authors of included studies. The computer-based searches combined search terms related to the exposure (such as "fatty acids" and "unsaturated fatty acids") and coronary disease (such as "myocardial infarction," "atherosclerosis," "coronary heart disease," and "coronary stenosis") without language restriction (**Supplement 2**, available at www.annals.org).

Study Selection

Observational and intervention studies were included if they reported on associations of dietary fatty acid intake, fatty acid biomarkers (measured in whole blood, serum, plasma, erythrocyte fraction [that is, circulating fatty acids], or adipose tissue), or fatty acid intervention (dietary or supplements) with risk for coronary disease (defined as fatal or nonfatal 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]) (**Table 3** of **Supplement 1** provides study-specific outcome definitions). Observational studies were eligible if they were prospective in design with at least 1 year of follow-up and involved participants from general populations (that is, participants not selected on the basis of preexisting disease at baseline) or with stable cardiovascular disease at study entry (defined as a diagnosis made at least 30 days before baseline sampling). Intervention studies were eligible for inclusion if they were randomized and recorded coronary outcomes as an end point of interest.

Data Extraction and Quality Assessment

Using standardized protocols, 2 investigators independently extracted data on several study characteristics, including sample size, study design, sampling population, location, year of baseline survey, participant characteristics (age and sex), 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 acid 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, and diet records, defined as all open-ended instruments, such as 24-hour recall and food diaries), type and formulation of intervention, year of random assignment, allocation concealment, blinding of caregivers and participants, daily dose of supplementation, and composition of placebo was abstracted. Discrepancies were resolved by discussion and by adjudication of a third reviewer. We used the most up-to-date or comprehensive information when there were several publications. The Newcastle-Ottawa Scale (23) was used to assess the quality of observational studies. This scale uses a "star" system (with a maximum of 9 stars) to assess the quality of a study in 3 domains: selection of participants, comparability of study groups, and ascertainment of outcomes of interest. Studies that scored 7 or 8 stars were considered medium-quality. We used the Cochrane Collaboration's tool for assessing risk of bias to evaluate the validity of randomized trials (24). For each of 7 individual domains in this tool, studies were classified into low, unclear, or high risk of bias.

Data Synthesis and Analysis

Analyses involved only within-study comparisons (that is, case and control participants were only directly compared within each study) 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 (such as per-unit or per–1-SD change or comparing quintiles, quartiles, thirds, and other groupings) were transformed, using methods previously described (25). These transformed estimates consistently corresponded to the comparison of the top versus bottom third of fatty acid distribution in each study. In brief, log risk estimates were transformed assuming a normal distribution, with the comparison between the top and bottom thirds being equal to 2.18 times the log relative risk (RR) for a 1-SD increase (or 2.54 times the log RR for a comparison of extreme quarters). We calculated SEs of the log RRs using published confidence limits and transformed the SEs in the same way (**Supplement 2**, available at www.annals.org, provides details of the statistical methods used). Studies that reported RRs with differ-

Table. **Summary of Data Included in Current Review***

Data Resource	Studies, *n*†	Participants, *n*	Coronary Events, *n*
Prospective cohort studies of dietary fatty acid intake			
All studies	32	512 420	15 945
Dietary questionnaire‡	21	463 038	11 157
Diet record§	11	49 382	4788
Prospective cohort studies of fatty acid biomarkers			
All studies	19	32 307	7182
Circulating fatty acid composition	17	25 721	5519
Adipose tissue fatty acid composition	2	6586	1663
RCTs of fatty acid supplementation	27	105 085‖	6229¶

RCT = randomized, controlled trial.
* Details of all individual studies are included in **Supplement 1** (available at www.annals.org).
† Five 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-h recall and food diaries.
‖ Includes 52 588 and 52 497 total participants in intervention and control groups, respectively.
¶ Includes 3017 and 3212 coronary events in intervention and control groups, respectively.

ing degrees of adjustment for other risk factors used the most adjusted estimate that did not include adjustment for blood lipids or circulating fatty acids (because circulating lipids may act as potential mediators for the associations between fatty acids and coronary disease [26]). We used reported RR or calculated study-specific unadjusted RR for the main outcomes of interest for randomized intervention trials. Hazard ratios and odds ratios were assumed to approximate the same measure of relative risk. We calculated summary RRs by pooling the study-specific estimates using a random-effects model that included between-study heterogeneity (parallel analyses used fixed-effects models). We estimated correlations of dietary fatty acid and circulating fatty acid intake by pooling study-specific Spearman correlation coefficients using random-effects meta-analysis. Consistency of findings across individual studies was assessed by standard chi-square tests and the I^2 statistic (27). We assessed heterogeneity between observational cohorts by comparing results from studies grouped according to prespecified study-level characteristics (such as location, sex, year of baseline survey, duration of follow-up, numbers of outcomes recorded, outcome definition, degree of statistical adjustment used, assay characteristics, dietary assessment, and categories of study quality score) using meta-regression. We used a similar method to assess heterogeneity between randomized trials by constructing groups according to prespecified trial characteristics (such as type and formulation of intervention, year of random assignment, allocation concealment, blinding of caregivers and participants, daily dose of supplementation, composition of placebo, and risk of bias). We assessed evidence of publication bias across studies by using funnel plots and Egger tests (28). All statistical tests were 2-sided and used a significance level of $P < 0.05$. All analyses were done using Stata, version 11 (StataCorp, College Station, Texas).

Role of the Funding Source

This study was funded by the British Heart Foundation, Medical Research Council, Cambridge National Institute for Health Research Biomedical Research Centre, and Gates Cambridge. The funding sources had no role in conducting, analyzing, or interpreting study results or in the decision to submit the manuscript for publication.

RESULTS

Seventy-two unique studies were identified (**Figure 1** of **Supplement 1** and the **Table**). Nineteen were based in North America, 42 in Europe, and 9 in the Asia-Pacific region; 2 were multinational. There were 45 prospective, observational cohort studies and 27 randomized, controlled trials (1 trial also reported data as an observational cohort on circulating fatty acids). Forty studies involved initially healthy populations, 10 recruited persons with elevated cardiovascular risk factors, and 22 recruited persons with cardiovascular disease at baseline.

Dietary Fatty Acid Intake and Coronary Risk

Thirty-two prospective cohort studies reported on self-reported dietary fatty acid intake (512 420 participants, 15 945 incident coronary outcomes, and an average follow-up ranging from 5 to 23 years) (**Table 4** of **Supplement 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 (such as age, sex, smoking, history of diabetes, and blood pressure). Thirteen were high-quality, 19 were medium-quality, and none were low-quality (**Table 5** of **Supplement 1**). Of the medium-quality studies, all showed a potential bias in the participant selection and 6 lacked objective confirmation of self-reported dietary intake of fatty acids by structured face-to-face interview.

Figure 1 shows RRs for coronary disease, comparing participants in the top third versus those in the bottom third of dietary fatty acids. In these studies, the pooled RRs 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 (CI, 1.06 to 1.27) for total trans fatty acids (**Figure 2** of **Supplement 1** and **Figure 1**). Corresponding RRs for total dietary polyunsaturated fatty acid intake were 0.99 (CI, 0.86 to 1.14) for total α-linolenic acid, 0.87 (CI, 0.78 to 0.97) for total long-chain ω-3 polyunsaturated fatty acids, and 0.98 (CI, 0.90 to 1.06) for total ω-6 polyunsaturated fatty acids (**Figure 3** of **Supplement 1** and **Figure 1**). 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 geographic location ($P = 0.020$ for long-chain ω-3 polyunsaturated fatty acid studies) (**Figure 4** of **Supplement 1**). There was no material difference in the combined RRs according to sex, year of baseline survey, dietary assessment tool, duration of follow-up, outcome definition, or degrees of statistical adjustment (**Figure 4** of **Supplement 1**).

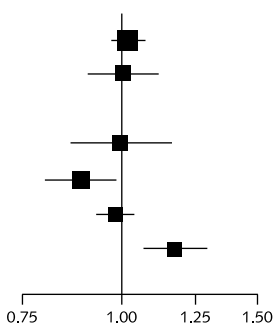
Fatty Acid Biomarkers and Coronary Risk

Information on fatty acid biomarkers was available from 19 prospective studies (**Tables 6** and 7 of **Supplement 1**). Seventeen reported on circulating fatty acid composition (25 721 participants and 5519 incident coronary outcomes; mean follow-up ranged from 1.3 to 30.7 years) (**Table 6** of **Supplement 1**), and 2 reported on adipose tissue fatty acid composition (6586 participants and 1663 incident coronary events) (**Table 7** of **Supplement 1**). Of those reporting on circulating fatty acid composition, 14 used liquid chromatography, 2 used calorimetric methods, and 1 used an enzymatic method to measure fatty acids. Six studies were judged as high-quality, 9 as medium-quality, and 2 as low-quality (**Table 8** of **Supplement 1**). Of the medium-quality studies, 8 showed potential bias in participant selection and 1 did not control for any potential risk factor in its 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 (such as age, sex, smoking, history of diabetes, and blood pressure).

Studies tended to report on a variable number of individual fatty acid isomers (**Table 9** of **Supplement 1**). The mean proportion of each individual circulating fatty acid relative to the total is presented in **Figure 5** of **Supplement 1**. Among studies with available data, there were moderate positive correlations between dietary intake and circulating composition of total ω-3 and ω-6 polyunsaturated fatty acids and weak positive correlations for total saturated and monounsaturated fatty acids (**Table 10** of **Supplement 1**). Relative risks for coronary outcomes (typically adjusted for non–blood-based vascular risk factors) comparing the top third versus bottom third of composite and individual circulating fatty acid composition at baseline are presented in **Figures 6** to **11** of **Supplement 1** and **Figure 2**. For the circulating total fatty acid composition, combined RRs were 1.06 (CI, 0.86 to 1.30) for total saturated fatty acids, 1.06 (CI, 0.97 to 1.17) for total monounsaturated fatty acids, 0.93 (CI, 0.83 to 1.03) for α-linolenic acid, 0.84 (CI, 0.63 to 1.11) for total long-chain ω-3 polyunsaturated fatty acids, 0.94 (CI, 0.84 to 1.06) for total ω-6 polyunsaturated fatty acids, and 1.05 (CI, 0.76 to 1.44) for total trans fatty acids. Among individual saturated and monounsaturated fatty acids, RRs for palmitic, stearic, and oleic

Figure 1. **RRs for coronary outcomes in prospective cohort studies of dietary fatty acid intake.**

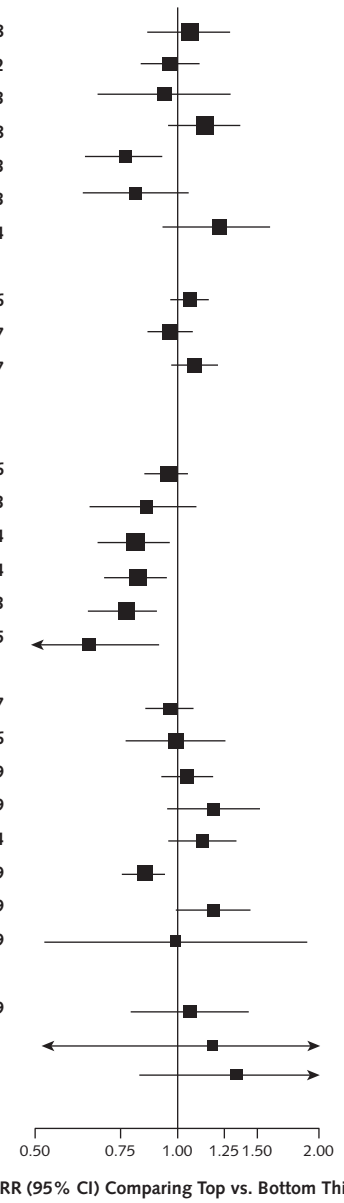
Fatty Acid Intake	Studies, *n*	Participants, *n*	Events, *n*	RR (95% CI)*
Total saturated fatty acids	20	276 763	10 155	1.03 (0.98–1.07)
Total monounsaturated fatty acids	9	144 219	6031	1.00 (0.91–1.10)
Total ω-3 fatty acids				
α-Linolenic	7	157 258	7431	0.99 (0.86–1.14)
Total long-chain ω-3	16	422 786	9089	0.87 (0.78–0.97)
Total ω-6 fatty acids	8	206 376	8155	0.98 (0.90–1.06)
Total trans fatty acids	5	155 270	4662	1.16 (1.06–1.27)



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 estimates, and pooled RRs based on fixed-effects meta-analysis are provided in **Supplement 1**, available at www.annals.org.

Figure 2. **RRs for coronary outcomes in prospective cohort studies of circulating fatty acid composition.**

Circulating Blood Fatty Acid Composition	Studies, *n*	Participants, *n*	Events, *n*	RR (95% CI)*
Total saturated fatty acids	8	15 590	3758	1.06 (0.86–1.30)
14:0, Myristic	5	10 598	2932	0.96 (0.83–1.12)
15:0, Pentadecanoic	4	5490	2283	0.94 (0.67–1.32)
16:0, Palmitic	10	25 554	4318	1.15 (0.96–1.37)
17:0, Margaric	4	5490	2283	0.77 (0.63–0.93)
15:0, Pentadecanoic + 17:0, Margaric	4	5490	2283	0.81 (0.62–1.06)
18:0, Stearic	8	22 266	3654	1.23 (0.93–1.61)
Total monounsaturated fatty acids	6	14 356	3236	1.06 (0.97–1.17)
16:1n-7, Palmitoleic	9	17 927	4127	0.96 (0.86–1.08)
18:1cis-9, Oleic	9	22 664	3687	1.09 (0.97–1.23)
Total ϖ-3 polyunsaturated fatty acids				
18:3n-3, α-Linolenic	8	14 945	3426	0.93 (0.83–1.03)
Total long-chain ϖ-3	4	10 558	2753	0.84 (0.63–1.11)
20:5n-3, Eicosapentaenoic	13	23 065	4624	0.78 (0.65–0.94)
22:6n-3, Docosahexaenoic	13	23 065	4624	0.79 (0.67–0.93)
20:5n-3, Eicosapentaenoic + 22:6n-3, Docosahexaenoic	13	20 809	4073	0.75 (0.62–0.89)
22:5n-3, Docosapentaenoic (clupanodonic)	4	7155	2565	0.64 (0.47–0.89)
Total ϖ-6 polyunsaturated fatty acids	2	7432	1877	0.94 (0.84–1.06)
18:2n-6, Linoleic	10	23 022	3866	0.99 (0.77–1.28)
18:3n-6, γ-Linolenic	4	8285	2259	1.03 (0.90–1.17)
20:2n-6, Eicosadienoic	2	4029	1689	1.18 (0.93–1.50)
20:3n-6, Dihomo-γ-linolenic	6	14 189	3214	1.11 (0.93–1.33)
20:4n-6, Arachidonic	10	22 948	3739	0.83 (0.74–0.92)
22:4n-6, Docosatetraenoic	2	4029	1689	1.20 (0.99–1.45)
22:5n-6, Docosapentaenoic (osbond)	2	4029	1689	0.97 (0.50–1.88)
Total trans fatty acids	4	7661	2389	1.05 (0.76–1.44)
18:1, Trans-oleic	2	921	380	1.20 (0.39–3.73)
18:2, Trans-linoleic	2	921	380	1.36 (0.83–2.22)



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 estimates, and pooled RRs based on fixed-effects meta-analysis are provided in **Supplement 1**, available at www.annals.org.

acids were 1.15 (CI, 0.96 to 1.37), 1.23 (CI, 0.93 to 1.61), and 1.09 (CI, 0.97 to 1.23), respectively. In contrast, margaric acid was significantly associated with lower risk (RR, 0.77 [CI, 0.63 to 0.93]) (**Figures 6** and 7 of **Supplement 1** and **Figure 2**). Among specific polyunsaturated fatty acids, eicosapentaenoic (0.78 [CI, 0.65 to 0.94]), docosahexaenoic (0.79 [CI, 0.67 to 0.93]), and arachidonic ([CI, 0.74 to 0.92]) acids were associated with lower risk. Dihomo-γ linolenic (1.11 [CI, 0.93 to 1.33]), eicosadienoic (1.18 [CI, 0.93 to 1.50]), and docosatetrahexanoic (1.20 [CI, 0.99 to 1.45]) acids tended toward a positive, albeit nonsignificant, association with coronary disease (**Figures 8** to **10** of **Supplement 1** and **Figure 2**). Only 2 studies with fewer than 500 case participants reported on individual circulating trans fatty acid composition (**Figure 11** of **Supplement 1**). For circulating total saturated fatty acids, there was some evidence of heterogeneity between studies according to outcome definition (fatal vs. nonfatal)

and duration of follow-up ($P = 0.003$ for both). For circulating eicosapentaenoic and docosahexaenoic fatty acid composition, there was some evidence of heterogeneity between studies according to outcome definition (fatal vs. nonfatal; $P = 0.004$), duration of follow-up ($P < 0.001$), number of events recorded ($P < 0.001$), sex ($P = 0.014$), and fasting or nonfasting sampling state ($P = 0.037$) (**Figure 12** of **Supplement 1**). There was no material difference in the combined RRs according to year of baseline survey, population baseline risk, geographic 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 nonsignificant associations across total and specific fatty acids (**Figure 13** of **Supplement 1**).

Effects of Fatty Acid Supplementation on Coronary Outcomes

Twenty-seven randomized, controlled trials reported on fatty acid supplementation and included a total of 105 085 participants, among whom 6229 had an incident coronary outcome (mean follow-up ranged from 0.1 to 8.0 years) (**Table 11** of **Supplement 1**). Eighteen trials recruited participants with cardiovascular disease at baseline, 8 recruited participants with elevated cardiovascular risk factors, and 1 involved initially healthy participants. Four studies reported on α-linolenic acid supplementation (dose ranging from 2.0 to 5.5 g/d where dietary oil was the principal form of supplementation); 17 on long-chain ω-3 polyunsaturated fatty acid supplementation (dose ranging from 0.3 to 6.0 g/d where capsules were the principal form of supplementation), and 8 on ω-6 polyunsaturated fatty acid supplementation (2 using linoleic acid–specific and 6 using 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 **Table 12** of **Supplement 1**. All trials had low risk of bias for the random-sequence generation and incomplete outcome data domains. We found unclear risk of bias for allocation concealment in 1 trial and for blinding of outcome assessment in 7 trials. We found high risk of bias for blinding of participants and personnel in 8 trials and for selective reporting in 3 trials. Risk of other bias was unclear in 6 trials and high in 3. Relative risks for coronary outcomes when persons in the intervention and control groups were compared were 0.97 (CI, 0.69 to 1.36) for α-linolenic acid, 0.94 (CI, 0.86 to 1.03) for total long-chain ω-3 polyunsaturated fatty acids, and 0.86 (CI, 0.69 to 1.07) for ω-6 polyunsaturated fatty acids (**Figure 14** of **Supplement 1** and **Figure 3**). There was no significant evidence of heterogeneity according to several trial characteristics, such as baseline population risk, geographic location, length of follow-up, outcome definition, and number of ascertained coronary outcomes (**Figure 15** of **Supplement 1**). Furthermore, overall effects of the fatty acid supplementation on coronary disease were generally similar in the trials that had appropriate allocation concealment or blinded their participants and caregivers (**Figure 15** of **Supplement 1**). Subsidiary analyses excluding trials that had recorded fewer than 50 coronary disease outcomes did not materially alter the results (**Figure 16** of **Supplement 1**). However, in a subsidiary analysis, exclusion of one ω-6 trial which used a margarine-based supplementation also high in trans fat, the relative risk for ω-6 polyunsaturated fatty acids was 0.81 (CI, 0.68 to 0.98).

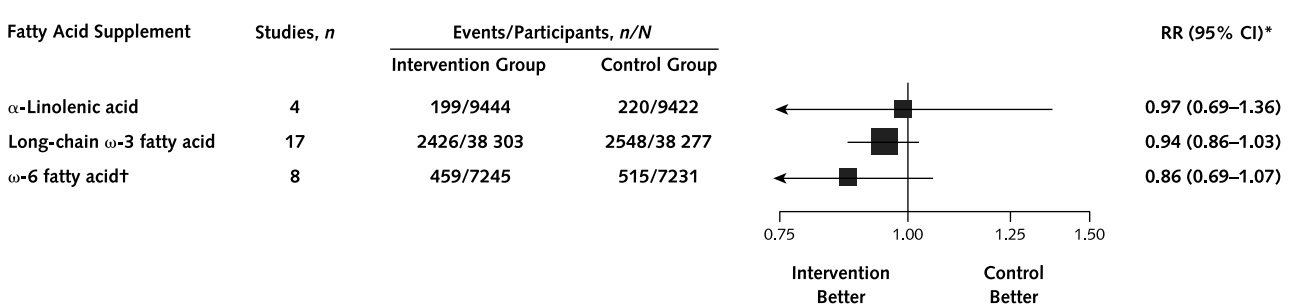
Assessment of Publication Bias

There was generally no evidence of publication bias among the included observational or intervention studies (**Figure 17** of **Supplement 1**).

DISCUSSION

Our findings do not clearly support cardiovascular guidelines that promote high consumption of ω-6 polyunsaturated fatty acids and suggest reduced consumption of

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



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 estimates, and pooled RRs based on fixed-effects meta-analysis are provided in **Supplement 1**, available at www.annals.org.
† Includes studies with ω-6–specific intervention and mixed polyunsaturate interventions with linoleic acid as the primary fatty acid.

total saturated fatty acids. First, we saw statistically nonsignificant associations in prospective studies of coronary disease that involved assessment of dietary intake of ω-6 polyunsaturated fatty acids. Conversely, dietary long-chain ω-3 polyunsaturated fatty acids was associated with lower risk of coronary disease. We found heterogeneity of the associations between specific circulating long-chain ω-3 and ω-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 ω-3 polyunsaturated fatty acids) and arachidonic acid are each associated with lower coronary risk. However, our meta-analysis of randomized trials of long-chain ω-3 and ω-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 ω-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 ω-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 ω-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.

From the University of Cambridge and Medical Research Council, Cambridge, United Kingdom; Harvard School of Public Health, Boston, Massachusetts; University of Oxford, Oxford, United Kingdom; School of Public Health, Imperial College London, London, United Kingdom; Centre for Exercise, Nutrition and Health Sciences, University of Bristol, Bristol, United Kingdom; and Erasmus University Medical Center, Rotterdam, the Netherlands.

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Requests for Single Reprints: Rajiv Chowdhury, MD, PhD, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, 2 Wort's Causeway, Cambridge CB1 8RN, United Kingdom; e-mail, rajiv.chowdhury@phpc.cam.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Chowdhury, Kunutsor, Butterworth, Thompson, Khaw, Danesh, and Di Angelantonio and Ms. Warnakula: Department of Public Health and Primary Care, University of Cambridge, 2 Wort's Causeway, Cambridge CB1 8RN, United Kingdom.
Dr. Crowe: Cancer Epidemiology Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom.
Dr. Ward: Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom.
Dr. Johnson: Centre for Exercise, Nutrition and Health Sciences, University of Bristol, 8 Priory Road, Bristol BS8 1TZ, United Kingdom.
Dr. Franco: Department of Epidemiology, Erasmus University Medical Center, Office Na 29-16, PO Box 2040, 3000 CA Rotterdam, the Netherlands.
Dr. Forouhi: United Kingdom Medical Research Council Epidemiology Unit, Cambridge Box 285, Addenbrookes Hospital, Cambridge CB2 0QQ, United Kingdom.
Dr. Mozaffarian: Department of Epidemiology, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115.

Author Contributions: Conception and design: R. Chowdhury, K. Khaw, J. Danesh, E. Di Angelantonio.
Analysis and interpretation of the data: R. Chowdhury, S. Warnakula, S. Kunutsor, H.A. Ward, O.H. Franco, S.G. Thompson, J. Danesh, E. Di Angelantonio.
Drafting of the article: R. Chowdhury, E. Di Angelantonio.
Critical revision of the article for important intellectual content: R. Chowdhury, S. Warnakula, S. Kunutsor, F. Crowe, H.A. Ward, L. Johnson, O.H. Franco, A. Butterworth, N.G. Forouhi, S.G. Thompson, K. Khaw, D. Mozaffarian, J. Danesh, E. Di Angelantonio.
Final approval of the article: R. Chowdhury, S. Warnakula, S. Kunutsor, F. Crowe, H.A. Ward, L. Johnson, O.H. Franco, A.S. Butterworth, N.G. Forouhi, S.G. Thompson, K. Khaw, D. Mozaffarian, J. Danesh, E. Di Angelantonio.
Statistical expertise: R. Chowdhury, S. Kunutsor, S.G. Thompson, D. Mozaffarian, E. Di Angelantonio.
Obtaining of funding: K. Khaw, J. Danesh.
Administrative, technical, or logistic support: R. Chowdhury, S. Warnakula, K. Khaw.
Collection and assembly of data: R. Chowdhury, S. Warnakula, S. Kunutsor, K. Khaw, E. Di Angelantonio.

Correction

Correction: Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk

A recent meta-analysis (1) contained the following numerical errors. First the summary estimate for total saturated fatty acids in prospective cohort studies of dietary fatty acid intake should be 1.03 (95% CI, 0.98 to 1.07) based on 20 studies, 276 763 participants and 10 155 events. Second the summary estimate for total monounsaturated fatty acids in prospective cohort studies of dietary fatty acid intake should be 1.00 (CI, 0.91 to 1.10) based on 9 studies, 144 219 participants and 6031 events. Third the number of participants included in the analysis of alpha-linoleic in prospective cohort studies of dietary fatty acid intake should be 157 258 participants and 7431 events. Fourth the summary estimate for total long-chain ω-3 fatty acids in prospective cohort studies of dietary fatty acid intake should be 0.87 (CI, 0.78 to 0.97) based on 16 studies, 422 786 participants and 9089 events. Fifth the summary estimate for total ω-6 fatty acids in prospective cohort studies of dietary fatty acid intake should be 0.98 (CI, 0.90 to 1.06) based on 8 studies, 206 376 participants and 8155 events. Sixth the summary estimate for the effect of ω-6 fatty acids in randomized controlled trials should be 0.86 (CI, 0.69 to 1.07) based on 8 studies, 459 events/7245 participants in the intervention group and 515 events/7231 participants in the control group. These corrections, however, do not affect the main conclusions reported in the original article.

These changes have been made on the online version.

Reference

1. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398-406.