

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

A Systematic Review and Meta-analysis

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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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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, <i>nt</i>	Participants, <i>n</i>	Coronary Events, <i>n</i>
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

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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).

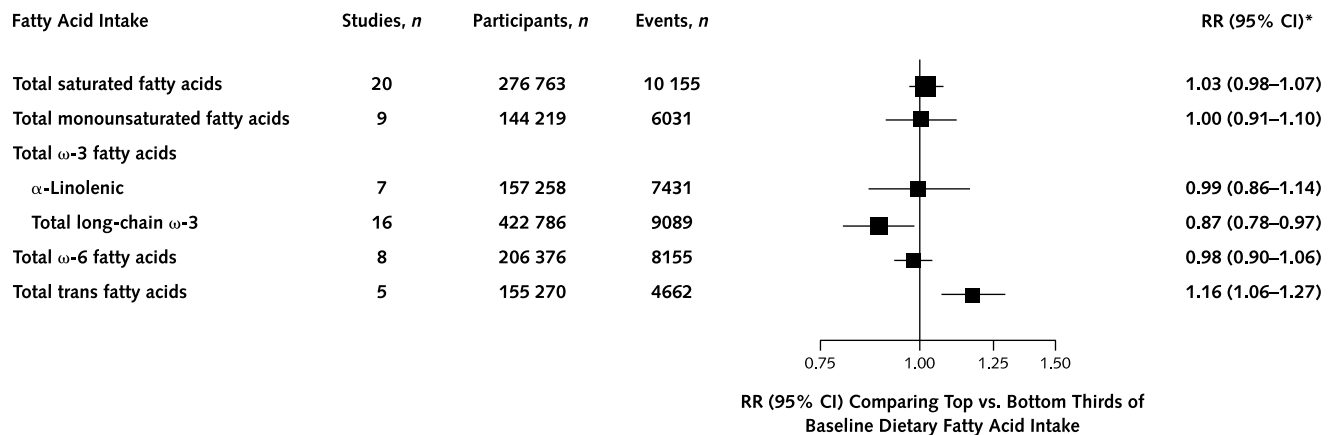
Fatty Acid Biomarkers and Coronary Risk

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

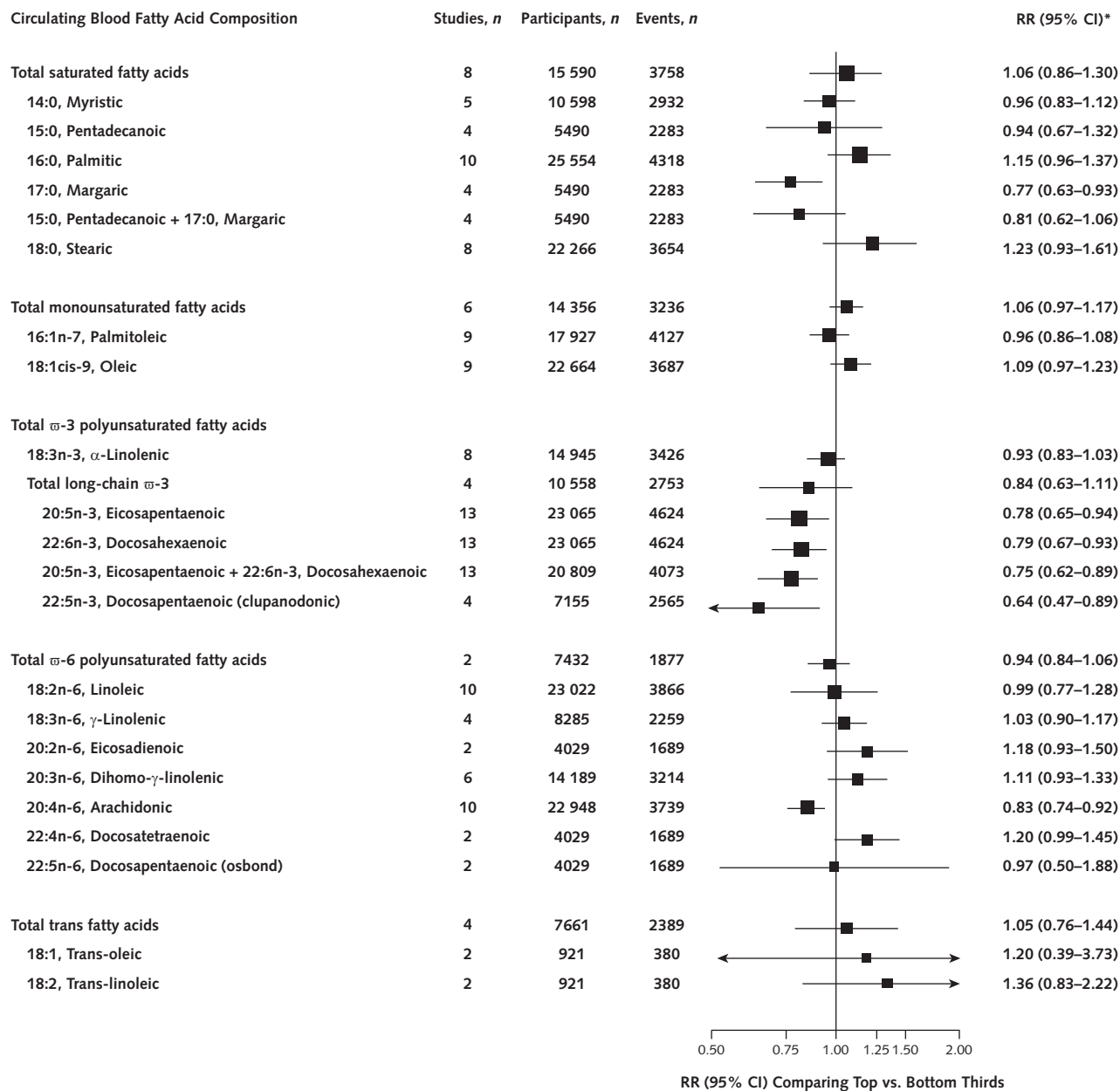
Figure 1. RRs for coronary outcomes in prospective cohort studies of dietary fatty acid intake.



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.



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]), eicosadi-

enoic (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 gener-

ation 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).

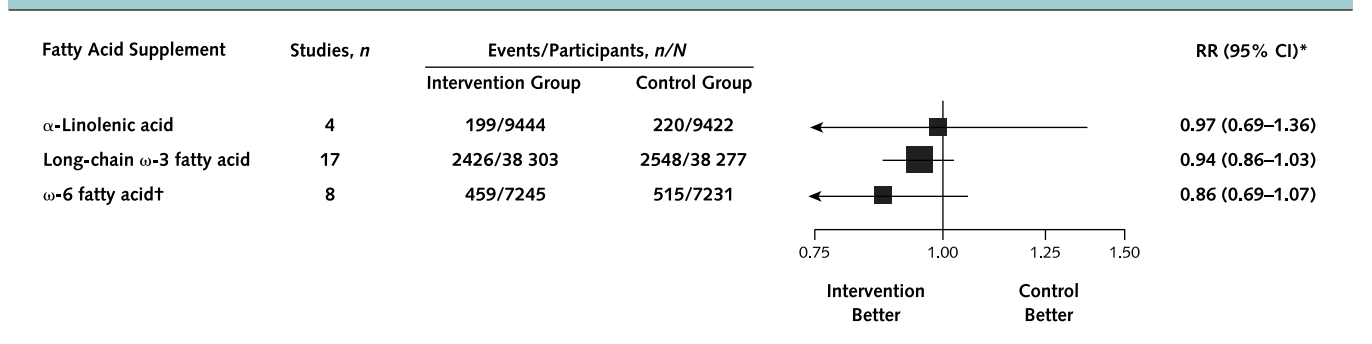
Assessment of Publication Bias

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.

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References

- McNaught AD, Wilkinson A. *Compendium of Chemical Terminology*. 2nd ed. New York: Blackwell Scientific; 1997.
- Ratnayake WM, Galli C. Fat and fatty acid terminology, methods of analysis and fat digestion and metabolism: a background review paper. *Ann Nutr Metab*. 2009;55:8-43. [PMID: 19752534]
- Campbell MK, Farrell OS. *Biochemistry*. 5th ed. Florence, KY: Cengage Learning; 2006.
- Gidding SS, Lichtenstein AH, Faith MS, Karpyn A, Mennella JA, Popkin B, et al. Implementing American Heart Association pediatric and adult nutrition guidelines: a scientific statement from the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular Disease in the Young, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. *Circulation*. 2009;119:1161-75. [PMID: 19255356]
- Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. *Circulation*. 2008;117:3031-8. [PMID: 18541753]
- EURODIET Core Report. Nutrition & Diet for Healthy Lifestyles in Europe. Accessed at http://ec.europa.eu/health/archive/ph_determinants/life_style/nutrition/report01_en.pdf on 18 July 2013.
- Stanner S, ed. *Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors*. 1st ed. Oxford, United Kingdom: Blackwell Publishing; 2005.
- Joint World Health Organization/Food and Agriculture Organization Expert Consultation. Diet, Nutrition and the Prevention of Chronic Disease. Accessed at http://whqlibdoc.who.int/trs/WHO_TRS_916.pdf on 18 July 2013.
- National Institute for Health and Care Excellence. PH25: Prevention of cardiovascular disease. Accessed at <http://publications.nice.org.uk/prevention-of-cardiovascular-disease-ph25> on 18 July 2013.
- Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635-701. [PMID: 22555213]
- Smit LA, Mozaffarian D, Willett W. Review of fat and fatty acid requirements and criteria for developing dietary guidelines. *Ann Nutr Metab*. 2009;55:44-55. [PMID: 19752535]
- Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr*. 2010;91:535-46. [PMID: 20071648]
- Goris AH, Westerterp-Plantenga MS, Westerterp KR. Underreporting and underrecording of habitual food intake in obese men: selective underreporting of fat intake. *Am J Clin Nutr*. 2000;71:130-4. [PMID: 10617957]
- Hebert JR, Clemow L, Pbert L, Ockene IS, Ockene JK. Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. *Int J Epidemiol*. 1995;24:389-98. [PMID: 7635601]
- Johansson L, Solvoll K, Bjørneboe GE, Drevon CA. Under- and overreporting of energy intake related to weight status and lifestyle in a nationwide sample. *Am J Clin Nutr*. 1998;68:266-74. [PMID: 9701182]
- Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N. Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet*. 2003;362:212-4. [PMID: 12885485]
- Willett WC. Nutritional epidemiology issues in chronic disease at the turn of the century. *Epidemiol Rev*. 2000;22:82-6. [PMID: 10939011]
- Baylín A, Campos H. The use of fatty acid biomarkers to reflect dietary intake. *Curr Opin Lipidol*. 2006;17:22-7. [PMID: 16407712]
- Erkkilä A, de Mello VD, Rísérus U, Laaksonen DE. Dietary fatty acids and cardiovascular disease: an epidemiological approach. *Prog Lipid Res*. 2008;47:172-87. [PMID: 18328267]
- Riboli E, Rönholm H, Saracci R. Biological markers of diet. *Cancer Surv*. 1987;6:685-718. [PMID: 2838169]
- Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney

- Diet Heart Study and updated meta-analysis. *BMJ*. 2013;346:e8707. [PMID: 23386268]
22. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308:1024-33. [PMID: 22968891]
 23. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.htm on 21 October 2013.
 24. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al; Cochrane Bias Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. [PMID: 22008217]
 25. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998;279:1477-82. [PMID: 9600484]
 26. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ*. 1997;314:112-7. [PMID: 9006469]
 27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60. [PMID: 12958120]
 28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34. [PMID: 9310563]
 29. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, et al. The vitamin d and omega-3 trial (vital): Rationale and design of a large randomized controlled trial of vitamin d and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials*. 2012;33:159-71. [PMID: 21986389]
 30. Poppitt SD, Swann D, Black AE, Prentice AM. Assessment of selective under-reporting of food intake by both obese and non-obese women in a metabolic facility. *Int J Obes Relat Metab Disord*. 1998;22:303-11. [PMID: 9578234]
 31. Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Tsugane S; JPHC. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess fatty acid intake: comparison with dietary records and serum phospholipid level. *J Epidemiol*. 2003;13:S64-81. [PMID: 12701633]
 32. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992;135:1114-26; discussion 1127-36. [PMID: 1632423]
 33. Parks EJ, Hellerstein MK. Carbohydrate-induced hypertriglycerolemia: historical perspective and review of biological mechanisms. *Am J Clin Nutr*. 2000;71:412-33. [PMID: 10648253]
 34. Forsythe CE, Phinney SD, Feinman RD, Volk BM, Freidenreich D, Quann E, et al. Limited effect of dietary saturated fat on plasma saturated fat in the context of a low carbohydrate diet. *Lipids*. 2010;45:947-62. [PMID: 20820932]
 35. Merchant AT, Kelemen LE, de Koning L, Lonn E, Vuksan V, Jacobs R, et al; SHARE and SHARE-AP investigators. Interrelation of saturated fat, trans fat, alcohol intake, and subclinical atherosclerosis. *Am J Clin Nutr*. 2008;87:168-74. [PMID: 18175752]
 36. Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM, et al. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. *Lipids*. 2008;43:65-77. [PMID: 18046594]
 37. Siri PW, Krauss RM. Influence of dietary carbohydrate and fat on LDL and HDL particle distributions. *Curr Atheroscler Rep*. 2005;7:455-9. [PMID: 16256003]
 38. Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. *Prog Lipid Res*. 2008;47:348-80. [PMID: 18435934]
 39. Wennberg M, Vessby B, Johansson I. Evaluation of relative intake of fatty acids according to the Northern Sweden FFQ with fatty acid levels in erythrocyte membranes as biomarkers. *Public Health Nutr*. 2009;12:1477-84. [PMID: 19144238]
 40. Wolk A, Vessby B, Ljung H, Barrefors P. Evaluation of a biological marker of dairy fat intake. *Am J Clin Nutr*. 1998;68:291-5. [PMID: 9701185]
 41. Khaw KT, Friesen MD, Riboli E, Luben R, Wareham N. Plasma phospholipid fatty acid concentration and incident coronary heart disease in men and women: the EPIC-Norfolk prospective study. *PLoS Med*. 2012;9:e1001255. [PMID: 22802735]
 42. Degirolamo C, Shelness GS, Rudel LL. LDL cholesteryl oleate as a predictor for atherosclerosis: evidence from human and animal studies on dietary fat. *J Lipid Res*. 2009;50 Suppl:S434-9. [PMID: 19029117]
 43. Gillingham LG, Harris-Janz S, Jones PJ. Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. *Lipids*. 2011;46:209-28. [PMID: 21308420]
 44. Lucas L, Russell A, Keast R. Molecular mechanisms of inflammation. Anti-inflammatory benefits of virgin olive oil and the phenolic compound oleocanthal. *Curr Pharm Des*. 2011;17:754-68. [PMID: 21443487]
 45. Mozaffarian D, Lemaitre RN, King IB, Song X, Spiegelman D, Sacks FM, et al. Circulating long-chain ω -3 fatty acids and incidence of congestive heart failure in older adults: the Cardiovascular Health Study: a cohort study. *Ann Intern Med*. 2011;155:160-70. [PMID: 21810709]

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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.