

Omega-3 Polyunsaturated Fatty Acid Biomarkers and Risk of Type 2 Diabetes, Cardiovascular Disease, Cancer, and Mortality: A Systematic Review and Meta-analysis

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Abstract

Background: Considerable attention has focused on omega-3 polyunsaturated fatty acids (PUFA) role in protect against the development of cardiometabolic diseases, which has led to dietary recommendations to increase omega-3 fatty acid intake.

Methods: MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and reference lists were searched for articles from inception to May 2020. Random-effects model was used to estimate the pooled relative risk (RR) and 95% confidence intervals (CIs) for the association of omega-3 PUFAs, including α -linoleic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA), with risk of developing type 2 diabetes (T2D), cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, cancer, and mortality.

Results: 66 prospective studies comprised of 211,600 participants were identified. Individual omega-3 PUFAs showed divergent associations with the study outcomes of interest. An inverse association with risk of T2D was observed comparing extreme categories of ALA concentration (RR,0.91;95%CI,0.83-0.99), but not for the marine-origin omega-3 fatty acids biomarkers. The marine-origin omega-3 fatty acids biomarkers, but not ALA, were significantly associated with lower risks of total CVD, CHD, and overall mortality, with RRs ranging from 0.70 for DHA-CHD association to 0.85 for EPA-CHD association. Lower risk of colorectal cancer was observed at higher levels of DPA (RR,0.76;95%CI:0.59-0.98) and DHA (RR,0.80;95%CI:0.65-0.99). In dose-response analyses, inverse linear associations were observed between EPA, DPA, and DHA biomarkers and CVD or CHD risk, except for DHA-CVD association which showed a nonlinearity association.

Conclusion: Higher concentrations of marine-derived omega-3 PUFA biomarkers were associated with a significantly reduced risk of total CVD, CHD, certain types of cancer, and total mortality. Levels of ALA were inversely with a lower risk of T2D but not CVD-related outcomes. These data support the dietary recommendations advocating the role of omega-3 PUFAs in maintaining an overall lower risk of developing cardiovascular disease and premature deaths.

Background

Increasing polyunsaturated fatty acid (PUFA) consumption, especially seafood-derived omega-3 PUFAs, has been considered as a key component of prevention strategy in tackling the current epidemic of chronic disorders [1,2]. Dietary guidelines of the American Heart Association recommend a daily consumption of 250 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for decreasing the risk of cardiac deaths among individuals with and without pre-existing cardiovascular disease (CVD) [2]. Accumulating evidence from experimental studies has demonstrated that omega-3 PUFAs have multiple critical health benefits including inhibiting inflammation, regulating lipid metabolism, reducing arrhythmias, and improving endothelial function and insulin sensitivity [3,4]. Recently, the efficacy of marine-derived omega-3 PUFA supplementation for CVD risk reduction has been demonstrated in the

Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) and the Vitamin D and Omega-3 Trial (VITAL) which consistently reported a beneficial effect of these fatty acids on reducing coronary heart disease (CHD) risk in the overall population or subgroups [5,6]. However, whether these effects can be extrapolated to general populations with lower habitual intake of omega-3 PUFAs or to other related health conditions is unclear.

Existing prospective cohort studies have examined associations of dietary omega-3 PUFAs with the incidence of major chronic diseases and mortality in free-living individuals, and findings of these studies were mixed [7,8]. Some studies showed that intake of plant-derived fatty acid, such as α -linolenic acid (ALA), was associated with decreased risk of T2D, whereas others have reported no such association [9-11]. The conflicting results might be related to variation in different population characteristics, different background diet, measurement errors of dietary assessments, as well as bioavailability of these fatty acids [12]. Meaningful amounts of omega-3 PUFAs could also be obtained from various fortified foods, making an accurate assessment of these fatty acids intake more challenging [13]. Biomarkers of omega-3 PUFAs are valuable when evaluating the associations between the intake of these PUFAs and disease risk because they are free of reporting bias and other measurement errors intrinsic to questionnaire-based assessments [14,15]. Previous researches to date have focused mainly on the association with CVD risk and most suggested inverse associations [16-18]. Compared with the literature on CVD, less evidence exists regarding the associations of omega-3 PUFA fatty acid biomarkers and other chronic conditions, such as T2D, cancer or mortality. In addition, much existing evidence surrounds EPA and DHA, with relatively little evidence generated for the association between other omega-3 PUFAs, such as ALA or docosapentaenoic acid (DPA).

We therefore conducted a comprehensive dose-response meta-analysis of data from prospective studies to evaluate associations of omega-3 PUFA biomarkers with incident of T2D, total CVD, CHD, stroke, cancer and mortality.

Methods

Search strategy and selection criteria

The study was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Additional file 1: Appendix S1) [19]. PubMed, EMBASE, Web of Science, and Cochrane Library were searched for relevant published articles from inception to May 2020. Three investigators (HJ, LNW, and MW) independently searched and further assessed the eligibility of all identified citations. Further details on the literature search, data extraction is described in Additional file 1: Appendix S2-S3.

Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: (1) study design was prospective (prospective cohort, nested case-control, and case-cohort study) with a follow-up more than one year; (2) the exposures of interest were omega-3 PUFA concentration (ALA, and total or individual marine-derived omega-3 fatty acids) in any type of tissue (circulating blood or adipose tissue); (3) the endpoints of interest included incident T2D, total CVD, CHD, stroke, cancer, all-cause mortality, and cause-specific mortality; (4) the risk estimate with corresponding 95% confidence intervals (CIs) or standard error was presented.

Quality assessment

Study quality was scrutinized by the same authors following the validated Newcastle-Ottawa scale, which awards 0-9 points and incorporates information on selection, comparability, and outcome assessment. We defined studies as low, moderate, and high quality for those scored 0-3, 4-6, and 7-9, respectively [20].

Data synthesis and statistical analysis

Methods previously described were used to derive estimates of associations corresponding to the comparison between the top and bottom thirds of omega-3 PUFA distributions [21]. When studies used multiple measures as biomarker, the overall risk estimate was based on different duration of intake reflection according to the following list: adipose tissue, erythrocyte phospholipids, plasma phospholipids, total plasma or serum, and cholesterol esters. For each included study, the most fully adjusted estimates of rate, hazard, or odds ratios from prospective studies were all valid estimates of the RR. Studies that reported results by sex or other subgroups separately were pooled to derive a single effect size for the study. When CHD and stroke outcomes were separately provided in the same study, we did not combine it to obtain total CVD risk estimates, and therefore, the CVD analysis only considered studies that examined total CVD incidence.

Random-effects model was used to calculate summary RR and 95% CIs. Heterogeneity across study effects was assessed using Q test and I^2 statistic. When statistically significant heterogeneity was detected, meta-regression analyses were performed to explore sources of heterogeneity, including study design, sex, geographical location, duration of follow-up, assessment method, biological sample type, number of cases, and study quality.

Dose-response analyses were assessed using the method proposed by Greenland and Longnecker to calculate study linear trends and 95% CIs from the natural logs of the RRs and CIs across categories of omega-3 PUFA exposure [22]. The dose-response outcomes were limited to studies that reported circulating omega-3 PUFA due to the small number of included studies with other exposures. Sensitivity analyses were performed to further evaluate the robustness of the conclusions. Potential publication bias was examined by Begg's and Egger's tests, as well as the trim and fill method. All analyses were

performed using Stata, version 10.2 (Stata Corp, Texas), and $P < 0.05$ was considered statistically significant. Details of the statistical methods is available in Additional file 1: Appendix S2.

Results

Study characteristics

Figure 1 summarizes the literature search and selection process. We identified 17,339 citations in the primary search, of which 162 were retrieved for full text evaluation after the initial screening of abstracts and titles. 12 studies were identified through manual examination of reference lists. Overall, a total of 66 analyses reported in 64 articles were included in our main analysis (Additional file 1: Appendix S4-9).

The included studies comprised of 25 prospective cohort studies, nine case-cohort studies, one nested case-cohort study, and 30 nested case-control studies. Twenty-five studies were conducted in Europe, 28 in the United States, seven in Asia, and five in Australia. Mean age of participants in the individual studies ranged from 41.1 to 80.5 years. For the measurements of omega-3 PUFA levels, 51 studies used gas chromatography (GC) analytic approach, 13 used gas-liquid chromatography, and one used GC-tandem mass spectrometry.

The Additional file 2: Appendix S1 shows the mean (standard deviation [SD]) proportion of each objective omega-3 PUFA relative to the total fatty acid contents in blood compartments or tissues. Fifty-eight studies were deemed to be of high quality, and the others judged as having a moderate quality (Additional file 1: Appendix S10-S11).

Omega-3 PUFA biomarkers and type 2 diabetes

Eleven studies comprised of 15,595 T2D incidence and 53,642 participants investigated the relationship between the concentrations of omega-3 PUFA biomarkers and T2D risk. Compared with participants in the lowest tertile, those in the highest tertile of ALA levels had a lower risk of T2D (RR,0.91;95%CI,0.83–0.99; $P_{\text{heterogeneity}}=0.26$; Fig. 2 and Additional file 2: Appendix S2). No significant associations were found for levels of EPA (RR,0.87;95% CI: 0.75–1.00; $P_{\text{heterogeneity}}<0.001$; Fig. 2), DPA (RR,0.87;95%CI,0.76–1.00; $P_{\text{heterogeneity}}=0.001$; Fig. 2), DHA (RR,0.92;95%CI,0.78–1.10; $P_{\text{heterogeneity}}=0.001$; Fig. 2) or the sum of EPA + DPA + DHA (RR,0.81;95%CI,0.60–1.09; $P_{\text{heterogeneity}}=0.15$; Fig. 2) with T2D risk (Additional file 2: Appendix S3-6 and Additional file 1: Appendix S12). The result of subgroup analyses did not substantially alter the association between level of omega-3 PUFA biomarkers and T2D risk. In dose-response analyses, a linear association was found between ALA biomarker and T2D risk (Additional file 2: Appendix S7). The RR of T2D for each 1-SD increase in concentrations of ALA was 0.91 (95%CI,0.83–0.99).

Omega-3 PUFA biomarkers and CVD

Association of omega-3 PUFA levels with total CVD was assessed in 12 studies, which included a total of 5,503 cases among 35,581 participants. When comparing the extreme tertiles, the risk of total CVD was

significantly lower by 19% for EPA (RR,0.81;95%CI,0.72–0.91; $P_{\text{heterogeneity}}=0.30$; Fig. 2), 23% for DPA (RR,0.77;95%CI,0.69, 0.85; $P_{\text{heterogeneity}}=0.94$; Fig. 2), 25% for DHA (RR,0.75;95%CI,0.65–0.87; $P_{\text{heterogeneity}}=0.01$; Fig. 2), and by 55% for the sum of EPA + DPA + DHA (RR,0.45;95%CI,0.27–0.74; $P_{\text{heterogeneity}}=0.15$; Fig. 2) (Additional file 3: Appendix S1-S4 and Additional file 1: Appendix S13). No association was observed between ALA and risk of CVD when comparing the highest with lowest categories (RR,1.09;95%CI,0.99–1.21; $P_{\text{heterogeneity}}=0.65$; Fig. 2 and Additional file 3: Appendix S5). Results from the dose-response analyses showed a significant linear decrease in the risk of CVD of individuals with increasing values of circulating EPA and DPA concentration, and per 1-SD increment was associated with 9% (RR,0.91;95%CI,0.86–0.96) and 11% (RR,0.89;95%CI,0.85–0.93) lower risk of CVD, respectively (Fig. 3). A potential nonlinear dose-response curve was detected for DHA-CVD association in that the CVD risk did not decrease until the DHA levels exceeded about 2% ($P_{\text{non-linearity}}=0.02$; Fig. 3).

Omega-3 PUFA biomarkers and CHD

The association between omega-3 PUFA biomarker levels and CHD was evaluated in 13 studies, which consisted of 7,626 cases and 27,814 participants. The overall effect estimates of CHD comparing the top tertile compared with bottom tertile was 0.98 for ALA (95%CI,0.95–1.02; $P_{\text{heterogeneity}}=0.89$; Fig. 2), 0.85 for EPA (95%CI,0.77–0.95; $P_{\text{heterogeneity}}=0.41$; Fig. 2), 0.83 for DPA (95%CI,0.76–0.92; $P_{\text{heterogeneity}}=0.84$; Fig. 2), 0.70 for DHA (95%CI,0.58–0.84; $P_{\text{heterogeneity}}=0.02$); Fig. 2, and 0.67 for the sum of EPA + DPA + DHA (95%CI,0.47–0.96; $P_{\text{heterogeneity}}=0.34$; Fig. 2) (Additional file 4: Appendix S1-S5 and Additional file 1: Appendix S13). For the dose-response analyses, a linear association was observed for marine-derived omega-3 PUFA biomarkers and risk of CHD. For every 1-SD increase in levels of EPA, DPA, and DHA in circulating, the RR: of CHD decreased by 8% (RR,0.92;95% CI,0.88–0.97), 17% (RR,0.83;95%CI,0.74–1.06), and 16% (RR:0.84;95%CI,0.77–0.93), respectively (Fig. 3).

Omega-3 PUFA biomarkers and stroke

Twelve studies provided information on omega-3 PUFA levels and the subsequent risk of stroke, including a total of 7,036 events in 77,163 participants. The pooled estimate indicated that high DHA status was associated with a lower risk of stroke (RR,0.84;95%CI,0.72–0.99; $P_{\text{heterogeneity}}=0.03$; Fig. 2), while there was no significant association for biomarkers of ALA, EPA, DPA, or the sum of EPA + DPA + DHA (Fig. 2, Additional file 5: Appendix S1-S5 and Additional file 1: Appendix S14). A linear relation was noted between DHA biomarker and stroke in the dose-response analysis (Additional file 5: Appendix S6), and the RR: was 0.91 (95%CI,0.83–0.99) for each 1-SD increment of DHA concentration in circulating.

Omega-3 PUFA biomarkers and cancer

Twenty-one studies were included in the analysis of omega-3 PUFA biomarker status and colorectal, breast, or prostate cancers. For colorectal cancer ($n = 3$), in comparison with the lowest category, the highest level category of DPA and DHA were associated with 24% (RR,0.76;95%CI,0.59–0.98; $P_{\text{heterogeneity}}=0.87$; Fig. 2) and 20% (RR,0.80;95%CI,0.65–0.99; $P_{\text{heterogeneity}}=0.56$; Fig. 2) reduced risk of colorectal cancer, respectively (Additional file 6: Appendix S1-S2). ALA and EPA biomarker had a non-

significant association with incident colorectal cancer (Additional file 6: Appendix S3-S4). No association was observed between ALA, EPA, DPA, and DHA concentrations and incidence of breast cancer (n = 9) or prostate cancer (n = 9) (Fig. 2 and Additional file 6: Appendix S5-S12 and Additional file 1: Appendix S15).

Omega-3 PUFA biomarkers and total mortality

Eight studies investigated the relation of omega-3 PUFA biomarker levels with mortality with a total of 7,558 deaths from 23,484 participants. Pooled RR for the comparison of extreme tertiles was 0.80 for EPA (95%CI,0.71–0.90; $P_{\text{heterogeneity}}=0.02$; Fig. 2), 0.81 for DPA (95%CI,0.73–0.90; $P_{\text{heterogeneity}}=0.59$; Fig. 2), and 0.84 for DHA (95%CI,0.76–0.94; $P_{\text{heterogeneity}}=0.07$; Fig. 2) (Additional file 7: Appendix S1-S3 and Additional file 1: Appendix S16). Nonsignificant association was observed for ALA biomarker (RR,1.00;95%CI,0.93–1.08; $P_{\text{heterogeneity}}=0.64$; ; Fig. 2 and Additional file 7: Appendix S4).

Sensitivity analysis and publication bias

In sensitivity analyses omitting one study at a time from each analysis, the combined estimate did not substantially change for most omega-3 PUFA biomarkers, except for the studies that evaluated the association between DHA level and prostate cancer: the pooled RR (95% CI) was strengthened to 1.14 (95%CI,1.00-1.30) when the study by Chavarro et al. was removed [23]. No indication of substantial publication bias was found for most outcomes with either Egger's test or Begg's test ($P > 0.05$ for both tests; Additional file 7: Appendix S5-S7).

Discussion

This comprehensive meta-analysis demonstrated robust inverse associations between marine-derived omega-3 PUFA in circulation or adipose tissue and lower risk of total CVD, CHD and overall mortality. Furthermore, a high level of DPA and DHA were inversely associated with colorectal cancer risk. In contrast, the associations between ALA and disease outcomes are less clear except an inverse association for T2D. The results largely persisted in dose-response meta-analyses or sub-group analyses. These findings therefore suggest that omega-3 PUFAs have important implications in chronic diseases prevention.

Results from large-scale randomized controlled trials (RCTs) that investigated the effects of omega-3 PUFA supplementation on composite cardiovascular end points have shown conflicting results. Data from a previous meta-analysis of 10 RCTs (77,917 patients with existing cardiovascular conditions) reported no significant adverse or beneficial effects of omega-3 fatty acid supplements on CHD and major vascular events risk for a mean of 4.4 years treatment [24]. However, two recent randomized trials, which were conducted among individuals who were free of pre-existing CVD, suggested cardiovascular benefits by omega-3 fatty acid supplementation. According to the REDUCE-IT report, supplementation with pure EPA at 4g/day decreased the risk of ischemic events by 19–30% during a median of 4.9 y among 8,179 patients with elevated CVD risk or diabetes [5]. Results from the VITAL also showed a significant 39% reduction in myocardial infarction (MI) risk by 1 g/day EPA + DHA supplementation over a

median 5.3 years period [6]. In agreement with the results of these two trials, we also found a significant, lower risk of developing CHD and CVD with higher levels of EPA, DPA, and DHA biomarkers among largely healthy individuals, which lends further support for the role of these nutrients in the primary prevention of CHD and CVD.

In contrast with cardiometabolic diseases, no RCT has yet been performed to explore the effects of omega-3 PUFA supplementation on risk of T2D incidence. Existing trials that evaluated the effect of fish oil supplementation and risk markers of T2D yielded mixed results. In a 12-week RCT, Thota et al. detected that marine-derived omega-3 PUFA supplementation produced a significant improvement in insulin resistance among participants at high risk of developing diabetes, impaired fasting glucose or glucose tolerance at baseline [25]. However, Giacco et al. did not observe significant effect on insulin action, β -cell function, or glucose tolerance with omega-3 PUFA supplementations in participants without T2D during a 3 months intervention period [26]. A number of studies that specifically evaluated fish intake (the main source of EPA, DPA, and DHA) and T2D risk have been conducted over the past several decades and few reported protective association [27, 28]. The present study did not find evidence of an association between individual marine-derived omega-3 PUFA biomarkers and the risk of T2D, except for plant-derived ALA, for which an inverse trend was observed. The underlying mechanisms by which ALA may lower T2D risk may be partly due to the improvement in insulin sensitivity. It is likely that ALA could modulate nuclear receptors, such as peroxisome proliferator activated receptor, to improve insulin-like growth factor-I secretion from hepatocytes, which might help enhance whole-body insulin sensitivity and modulate carbohydrate metabolism. Moreover, the favorable effect of ALA to T2D might be also attributed to stimulating insulin secretion [29, 30]. This hypothesis was supported by the evidence from *in vivo* and *ex vivo* studies, in which ALA was capable of stimulating glucose-dependent insulin secretion from pancreatic islets both directly and indirectly through mediating glucagon-like peptide 1 [31]. It is important to mention that circulating or adipose tissue ALA biomarker may not reflect ALA intake as dietary source of ALA was extensively oxidized after ingestion and absorption. In addition, it could convert to EPA and DHA after consumption and absorption, though the proportion is small [32, 33].

With regard to cancer, large intervention trials exploring omega-3 PUFA supplementation in the primary prevention of cancer are scarce. In the VITAL trial, omega-3 PUFA supplementation showed no effect on the incidence of cancer or death from cancer.⁶ However, these results should be interpreted with caution as the number of cases was small in the trial which made it difficult to draw small to modest effects. Observational studies that evaluated the associations of fish and omega-3 PUFA consumption with breast cancer, prostate cancer, or colorectal cancer did not yield consistent findings [34–36]. Results from our study indicated that a higher level of certain marine-derived omega-3 fatty acids was associated with a significant decreased risk of colorectal cancer. However, only a limited number of studies were conducted in this regard and further studies are warranted to substantiate the relationship between omega-3 PUFAs and cancer.

Limitations of study

Several potential limitations should be considered when interpreting the results. First, fatty acid biomarker levels were measured only once at baseline and changes of fatty acid levels over time were not accounted for. However, a recent analysis suggested that the omega-3 PUFA concentrations, with the exceptions of DPA, in serum cholesteryl ester, triglyceride and phospholipid fractions remained fairly stable in 8–10 years [37]. Second, although most included studies in our analysis adjusted for multiple major risk factors, such as sociodemographic, lifestyle, clinical, and other dietary risk factors, we cannot exclude the impact of residual and unmeasured confounding on the observed associations [38]. In particular, participants with high omega-3 PUFA status might be more likely to adhere to a healthier dietary pattern or have a higher socioeconomic status, which might distort the true associations. Third, variation in fatty acids metabolism and *de novo* lipogenesis between individuals and between populations may introduce extraneous heterogeneity to the current analysis. In the era of precision medicine, further studies are needed to incorporate factors that account for individual variation in response to omega-3 PUFA intake and subsequent chronic disease risk. Finally, we cannot exclude the possibility of publication bias, although our trim-and-fill analyses suggested such a bias is likely to be small.

Conclusion

Our meta-analysis of existing prospective evidence indicated that the marine-derived omega-3 PUFAs were associated with a lower risk of developing major chronic diseases, including CVD, CHD, certain types of cancer, and mortality, although associations for other disease outcomes were unclear. These findings further support the current recommendations of increasing intakes of marine-derived omega-3 PUFAs to facilitate the primary and secondary prevention of chronic conditions, especially CVD.

Abbreviations

ALA, α -linoleic acid; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; GC, gas chromatography; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; REDUCE-IT, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; RR, relative risk; SD, standard deviation; T2D, type 2 diabetes; VITAL, the Vitamin D and Omega-3 Trial.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LM and DLW generated the idea for the study, formulated an analytical plan. All authors acquired, analyzed, or interpreted the data. HJ and LNW designed the search strategy, and HJ and LNW, and MW performed the literature search and screened studies for eligibility. HJ, YN, and MW extracted data. WRJ and XL assessed the risk of bias. HJ, JXL, and YL performed data analysis. HJ, MW, LM, and CL interpreted the data analysis and assessed the certainty of evidence. HJ drafted the manuscript and all other authors revised the manuscript. LM supervised the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figures

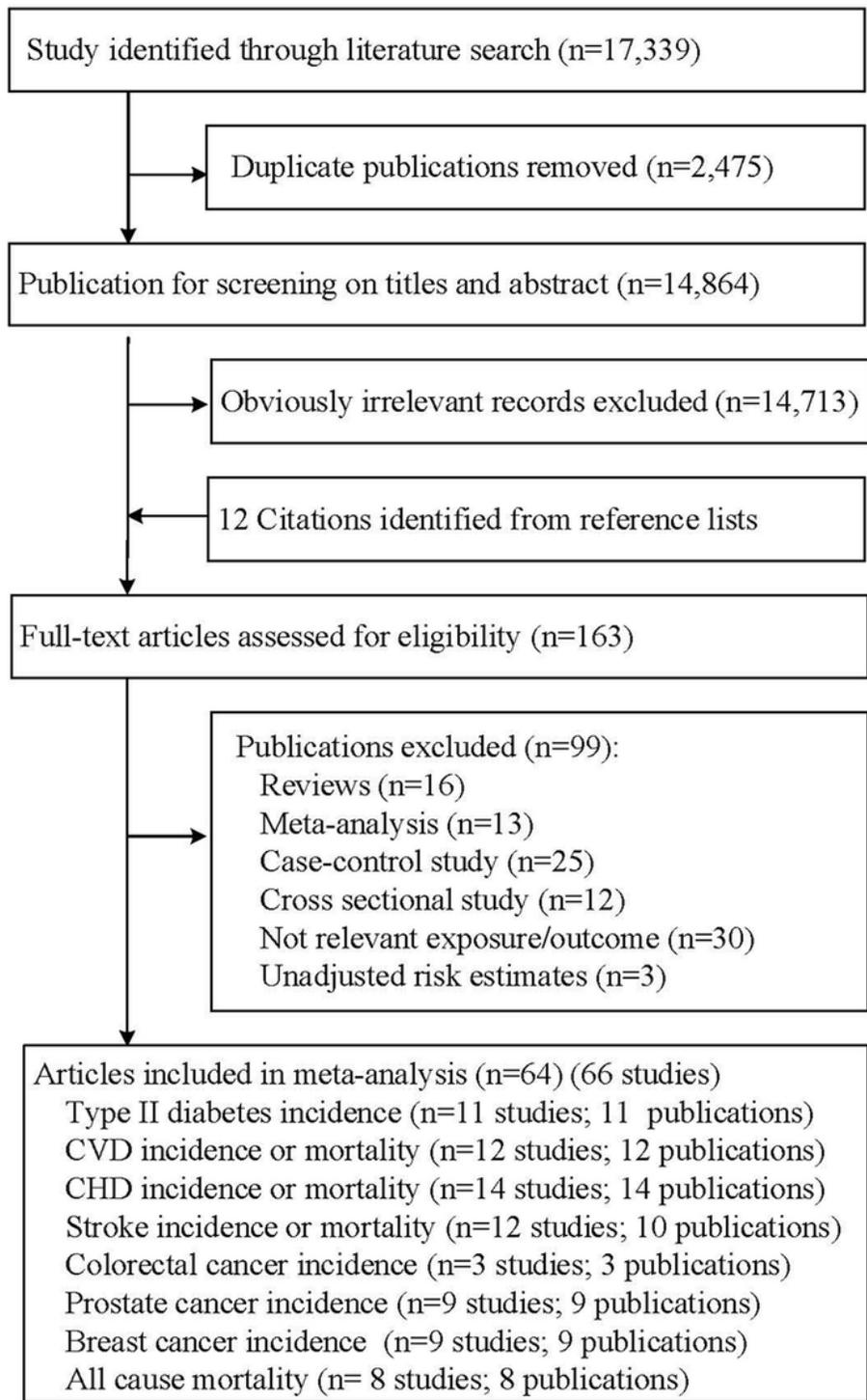


Figure 1

Flow chart of study selection CHD, coronary heart disease; CVD, cardiovascular disease; T2D, type 2 diabetes.

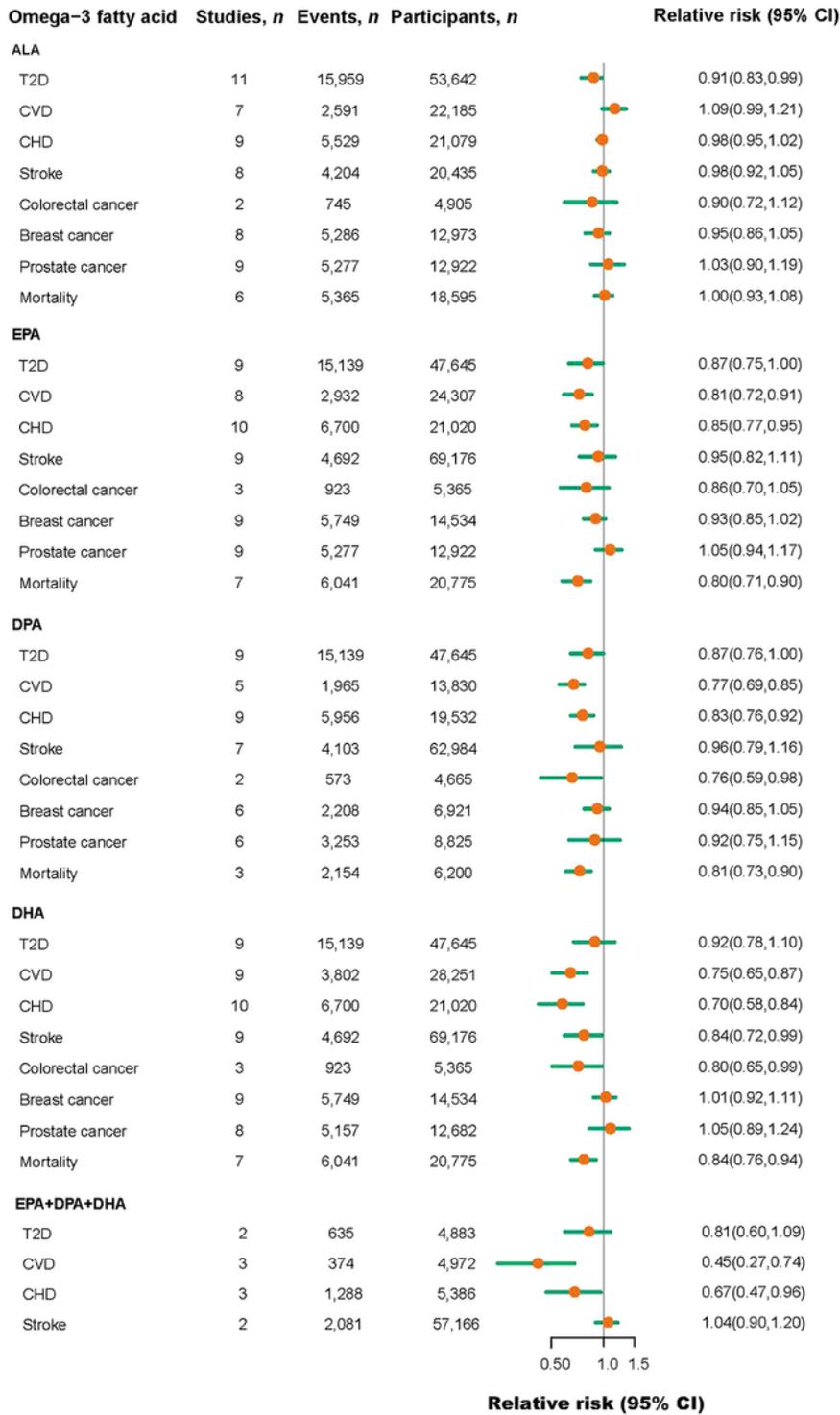


Figure 2

Pooled relative risks (RRs) of T2D, CVD, CHD, stroke, colorectal cancer, prostate cancer, and all-cause mortality comparing the highest with the lowest tertile of omega-3 fatty acids biomarkers. The size of the black squares indicates the relative weight of each estimate, horizontal lines indicate 95% confidence interval (CI), and diamonds indicate summary RR estimates with 95% CIs. ALA, α -linolenic acid; CHD,

coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; RR, relative risk; T2D, type 2 diabetes.

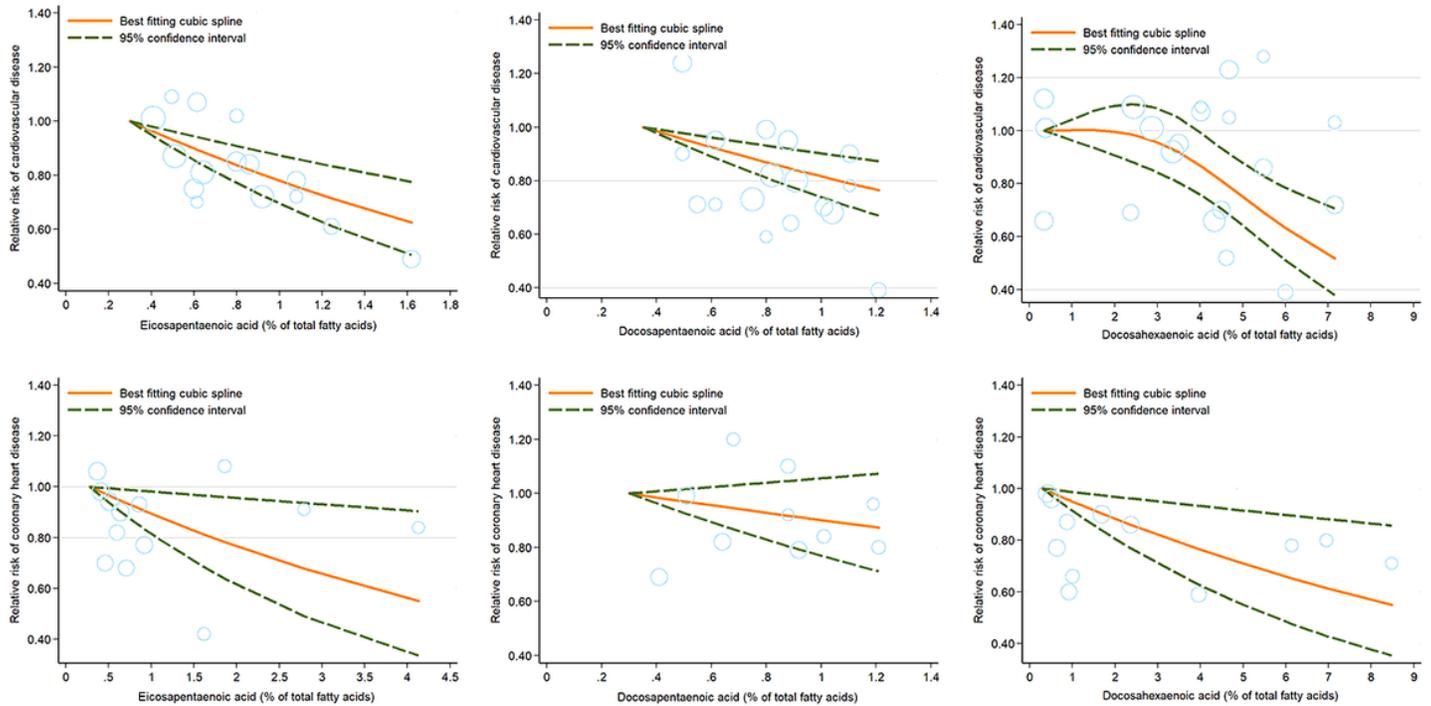


Figure 3

Dose-response analysis for linear or nonlinear association of EPA, DPA, and DHA biomarkers with CVD (A, B, and C) and CHD (D, E, and F) risk. The size of the black squares indicates the relative weight of each estimate, horizontal lines indicate 95% confidence interval (CI), and diamonds indicate summary relative risk (RR) estimates with 95% CIs. CHD, coronary heart disease; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; T2D, type 2 diabetes.

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