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Fish consumption, omega-3 fatty acids and risk of heart failure: a meta-analysis

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Abstract

Background and Aims—While marine omega-3 fatty acids have been associated with a lower mortality in heart failure patients, data on omega-3 and incident heart failure are inconsistent. We systematically reviewed the evidence on the association of omega-3 fatty acids and fish intake with the incidence of heart failure in this meta-analysis.

Methods—We identified relevant studies by searching MEDLINE and EMBASE databases up to August 31, 2011 without restrictions and by reviewing reference lists from retrieved articles.

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Results—A total of 176,441 subjects and 5,480 incident cases of heart failure from 7 prospective studies were included in this analysis. Using random effect model, the pooled relative risk for heart failure comparing the highest to lowest category of fish intake was 0.85 (95% CI; 0.73–0.99), p=0.04; corresponding value for marine omega-3 fatty acids was 0.86 (0.74–1.00), p=0.05. There was no evidence for heterogeneity across studies of fish consumption (I^2=8%). In contrast, there was modest heterogeneity for omega-3 fatty acid analysis (I^2= 44%). Lastly, there was no evidence for publication bias.

Conclusions—This meta-analysis is consistent with a lower risk of heart failure with intake of marine omega-3 fatty acids. These observational findings should be confirmed in a large randomized trial.

Keywords

Heart failure; epidemiology; diet; nutrition; omega-3 fatty acids; risk factors

Heart failure (HF) remains a major public health burden[1–4]. Despite medical progress, mortality after onset of HF remains high, ranging from 20% to 50%[5–8]. With a rising prevalence of obesity[9] and diabetes[10], and improved treatment of and survival from myocardial infarction and hypertension, the prevalence of HF is expected to increase in the coming years. Coronary heart disease (CHD) and hypertension are major contributors to HF incidence[11–15], suggesting that lowering the risk of CHD and hypertension might reduce the incidence of HF. The DASH trial[16] demonstrated beneficial effects of healthy diet on the risk of hypertension. Accumulating evidence suggest that marine omega-3 fatty acids may reduce the risk of CHD deaths[17]. However, their association with non-fatal CHD[18–21] or blood pressure[22–24] has been inconsistent. In animal experimental and short-term human clinical trials, marine omega-3 fatty acids improved hemodynamics[25], left ventricular structure and function[26–28], and inflammation[29–31], and thereby play an important role in the development of HF. However, few studies have examined the association between omega-3 fatty acids and HF risk. While some studies have reported a lower risk of HF with consumption of baked or broiled fish[32–34] as well as higher plasma of dietary EPA/DHA[35], such findings have not been consistent across studies. The observational arm of the Women's Health Initiative[36] reported a lower risk of HF with fish consumption but no association between dietary EPA/DHA and incident HF. Given the inconsistency in the literature on the role of omega-3 fatty acids and HF risk, it is important to clarify whether marine omega-3 fatty acids confer a lower risk of HF. Hence, we conducted a meta-analysis to review current evidence on the association of fish consumption and marine omega-3 (EPA and DHA) with the incidence of HF.

Materials and Methods

We followed the guidelines published by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group[37] to complete the meta-analysis.

Study selection

All relevant cohort studies published in English-language journals from 1966 to August 2011, that evaluated the association between fish consumption or omega-3 fatty acids and HF, were identified by searching EMBASE, MEDLINE, Web of Science and CABI abstracts. We used the terms "fish," "seafood," "n-3 fatty acids, "animal products," "omega-3 fatty acids," in combination with "congestive heart failure," and "heart failure." In addition, we also manually reviewed the references of all retrieved articles and recent reviews to identify relevant studies. Two of our investigators (LD and AOA) independently conducted the search, reviewed all relevant articles and identified eligible studies. We

resolved any discrepancy by group discussion. Overall, we included any paper that provided multivariable adjusted relative risks (RRs) and their corresponding 95% confidence intervals for HF, comparing categories of fish consumption, dietary intake or blood concentrations of EPA and DHA. If a study reported RR and 95% CI for men and women separately, and the effect of fish or EPA/DHA intake on the risk of HF was modified by sex, we treated the results by sex as 2 separate studies in the meta-analysis. Finally, where more than one study was published from the same cohort, we only included data from the report with biomarker assessment of marine omega-3 fatty acids or study with more incident heart failure.

Data extraction

Two investigators (LD and AOA) independently abstracted data and entered them in a customized data collection form. The data collection's form included the first author's last name, year of publication, country where the study was conducted, duration of follow-up, age range for study participants at baseline, sample size, proportion of men, number of HF events, methods used to assess marine omega-3 fatty acids (measured in plasma, red blood cells, or diet) and fish intake, variables included in the multivariable model. We also recorded median level of exposure, person-years of follow-up, number of cases and the multivariable-adjusted risk estimates and corresponding 95% CI in each exposure category. Dr. Yamagishi[38] kindly provided exposure category-specific median levels of circulating EPA and DHA, which were not previously published.

Study quality evaluation

The quality of each study was assessed using the Newcastle-Ottawa Scale[39]. This scale ranges from 1 to 9 stars and judges each study on three broad categories: selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest. Any disagreement was resolved through discussion with two authors (LD and AOA).

Statistical Analysis and data Synthesis

We used RevMan 5.1.4 software (The Cochrane Collaboration, Oxford, England) and STATA (StataCorp, College Station, TX) for the meta-analysis. We transformed hazard ratios by taking their natural logarithms and calculating standard errors from the corresponding 95% CI as follows: Ln[upper limit of CI] – Ln[lower limit of CI])/3.92. To estimate a pooled effect and corresponding 95% CI for the highest versus lowest levels of consumption, we weighted the logarithm of the hazard ratios by the inverse of their variance. The Q test and I^2 were used to assess heterogeneity among studies[40]. In the presence of relevant heterogeneity (I2 >50%), the used the DerSimonian and Laird random effect model[41] to obtain a pooled estimate of effect. Publication bias was evaluated by visually inspecting funnel plots for asymmetry[42] and by using the Egger's test[43]. In a sensitivity analysis, we use the "leave one out" method[44] to evaluate studies with substantial impact on between-study heterogeneity. Lastly, we assessed potential heterogeneity in study results by geographic location (US vs. Europe).

Description of method for dose-response

The generalized least-squares method for trend estimation of summarized dose-response data was used to calculate relative risks per unit of exposure based on the Greenland and Longnecker method[45]. These analyses were carried out for fish and marine omega-3 fatty acid intake and HF risk only, as there was insufficient data for EPA/DHA biomarkers. To check for significant non-linear associations ($p<0.05$), spline knots were created, using the command MKSPLINE. Piecewise and restricted cubic spline regression models were

constructed to assess non-linear associations and the optimal model selected based on the Akaike Information Criterium. The xblc command was used to create the dose-response plot of the linear and non-linear relationships (Stata Journal, 2011, 11:1). Dose-response analyses were completed using Stata 10.0 (StataCorp, College Station, TX).

Results

Search results

The literature search yielded 449 papers of which seven articles were included in the current analyses after various exclusions (Figure 1). We retained seven prospective studies conducted in the US (n=4) or Europe (n=3) with 176,441 participants in whom 5,480 incident HF occurred. The sample sizes varied across studies from 2,735 in the Cardiovascular Health study[35] to 84,493 in the Women's Health Initiative[36]. The average duration of follow-up was 13.33 years (range 7 to 16 years). Data on fish intake were obtained via food frequency questionnaires and estimates of dietary EPA/DHA intake was derived from nutrients (n=4 studies) [36,4633,34]or plasma phospholipid omega-3 measurements (n=2 studies)[35,47]. All reported relative measures of effect for HF in each study were adjusted for multiple covariates. Details on these seven cohorts are provided in Table 1.

Study quality

The overall quality of studies included in these analyses was good with two studies scoring 8 stars on the Newcastle-Ottawa scale and the remaining 5 scoring 7 stars (Table 1). There was consistency in scoring between the two reviewers (kappa=100%).

Fish intake and risk of HF

Five prospective studies[32–34,36,46] evaluated the association between fish intake and incident HF. In the pooled analysis, a higher intake of fish was associated with a 15% (95% CI: 1% to 27%) lower risk of HF compared with the lowest category of fish intake, Figure 2. There was no evidence for heterogeneity among studies (I^2=8%) or publication bias visual inspection of the funnel plot (Figure 3) and by Egger's test (p = 0.18)

EPA/DHA and risk of HF

A total of six studies[33–36,38,46] examined the association between dietary or plasma levels of EPA/DHA and incident HF. Compared to the lowest category of EPA/DHA, there was a 14% lower risk of HF in the highest category of EPA/DHA (95% CI: 0% to 26%, p=0.05) in the pooled analysis (figure 2). There was no statistically significant evidence for heterogeneity among studies (I^2=44%, p=0.10) and no evidence for publication bias (Egger's test (p = 0.53).

Sensitivity analysis

Amongst studies reporting fish intake and risk of HF, sensitivity analysis omitting one study at a time and calculating the pooled relative risk for the remainder of the studies showed that the study by Dijkstra et al.[46] substantially influenced the pooled relative risk. The Pooled RR after excluding Dijkstra et al. [46] was 0.78 (95% CI: 0.64–0.95). Similar exploration done for studies reporting EPA/DHA and the risk of HF revealed that Levitan et al.[34] substantially influenced the pooled RR; the pooled RR after exclusion of this study was 0.82 (95% CI: 0.68–0.99). Result for sensitivity analysis based on geographical location showed that studies conducted in the US had a pooled RR for fish intake and the risk of HF of 0.69 (95% CI: 0.54 – 0.89) and that for EPA/DHA intake and the risk of HF was 0.76 (95% CI:

0.50–1.14). Similar but weaker results obtained for studies performed in Europe, was 0.95 (95% CI: 0.80 – 1.13) and 0.87 (95% CI: 0. 74 – 1.03) respectively.

Exposure modeled as a continuous variable

We observed an inverse and linear relation between fish consumption as well as marine omega-3 fatty acids and the risk of HF (Figure 4). For fish consumption, each 15 g/d higher intake of fish (equivalent to one additional 3.5 oz serving of fish per week) was associated with a 5% lower risk of HF [RR: 0.95 (95% CI: 0.93–0.98)]. Spline analyses were suggestive of non-linearity with no further reductions in risk at doses >300 mg/d (p for spline at 300 mg/d = 0.06) (Supplemental Figure 1). Each 125 mg/d increase in marine omega-3 fatty acids (equivalent of about one serving of 3.5 oz of fatty fish per week) was associated with a 3% lower risk of HF [RR: 0.97 (95% CI: 0.94–0.99)] when all studies were pooled.

Discussion

In this meta-analysis of prospective cohorts, we found that a higher consumption of fish and a higher dietary or plasma concentration of EPA/DHA were each associated with about 15% lower risk of HF compared with the respective lower exposure category. We also found evidence in support of a linear and inverse association between fish consumption and the risk of HF. There was minimal evidence for heterogeneity across studies or geographic location. These findings extend the observed reduction in mortality rate with EPA/DHA among HF patients in the GISSI-heart failure trial[48], where an intervention with 1g of EPA/DHA was associated with a 9% reduction in total mortality compared with placebo after a median follow up of 3.5 years [HR: 0·91 (95% CI: 0·833–0·998}], to include potential decrease in the incidence of HF. What biological mechanisms could support beneficial effects of EPA and DHA on the risk of HF?

Major risk factors of HF include coronary heart disease, hypertension, and diabetes[14,49]. Of these three major risk factors for HF, the literature supports a beneficial effects of EPA/DHA fatal[19,50,51] but not on non-fatal[19,51,52] coronary heart disease. Data on the effects of EPA/DHA on hypertension[23,24,53] or diabetes[54–57] have been inconsistent. Other investigations suggest beneficial effects of EPA/DHA on hemodynamics[24], left ventricular indices[25,27,28], and inflammation[29,58]. Fish oil also inhibits natriuretic peptide production[59] and alters the diacylglycerol composition in the heart and prevents activation of protein kinase C[60,61]; chronic activation of protein kinase C has been related to left ventricular hypertrophy and HF[62].

Despite the absence of consistent results on the relation between fish and EPA/DHA on non-fatal CHD, hypertension, and diabetes, reported studies have been consistent on the role of EPA/DHA on lipids. In particular, fish oil or EPA/DHA has been consistently associated with a lower concentration of triglycerides and these findings have been confirmed with interventional studies. A favorable effect of EPA/DHA on dyslipidemia could favorably influence the risk of HF via reduction of coronary artery disease events. In addition, EPA/DHA have been shown to favorably influence left ventricular function[26–28], heart rate[63], and inflammation[29–31]; suggesting alternative pathways by which EPA/DHA could lower the risk of HF.

Our findings have some limitations that merit additional comments. First, our inference is based on observational studies. Hence, we cannot exclude chance, residual or unmeasured confounding as alternative explanation for our results. This makes it imperative to confirm our findings in a large randomized trial. Second, the limited number of studies available for current analyses precluded detailed analyses stratified by potential modifiers [i.e., diabetics

vs. non-diabetics, type of omega-3 assessed (phospholipid, cholesteryl ester, red blood cell membrane, etc)]. Furthermore, we did not have sex-specific estimates of relative risk in studies that consisted of men and women to permit stratified analyses by sex. Third, we did not have data on individual studies to assess HF etiology, types (preserved vs. depressed left ventricular systolic function). At this point, it remains unclear whether omega-3 fatty acids exhibit differential effects on systolic vs. diastolic HF. Fourth, we did not have adequate data from individual studies to assess biologic mechanisms underlying the observed effects. Fifth, each cohort used slightly different criteria for HF ascertainment (Table 1). Hence, it might have been difficult to capture mild cases of HF in some studies or HF treated in ambulatory settings. Such incomplete ascertainment of HF might have biased our results. Nonetheless, our study has numerous strengths including the lack of meaningful heterogeneity, the consistency between relative risk obtained from fish intake and estimated dietary or blood EPA/DHA, the relatively high quality of studies included (quality score ranging from 7 to 8), a large pooled sample size, and robustness of the results in a sensitivity analysis.

If confirmed in a large double blind, placebo controlled randomized clinical trial, EPA/DHA could be added to the list of lifestyle factors and pharmacological agents that can be used for the primary prevention of HF.

In conclusion, our data are consistent with a lower risk of HF among people consuming higher amounts of EPA/DHA or fish.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Djousse has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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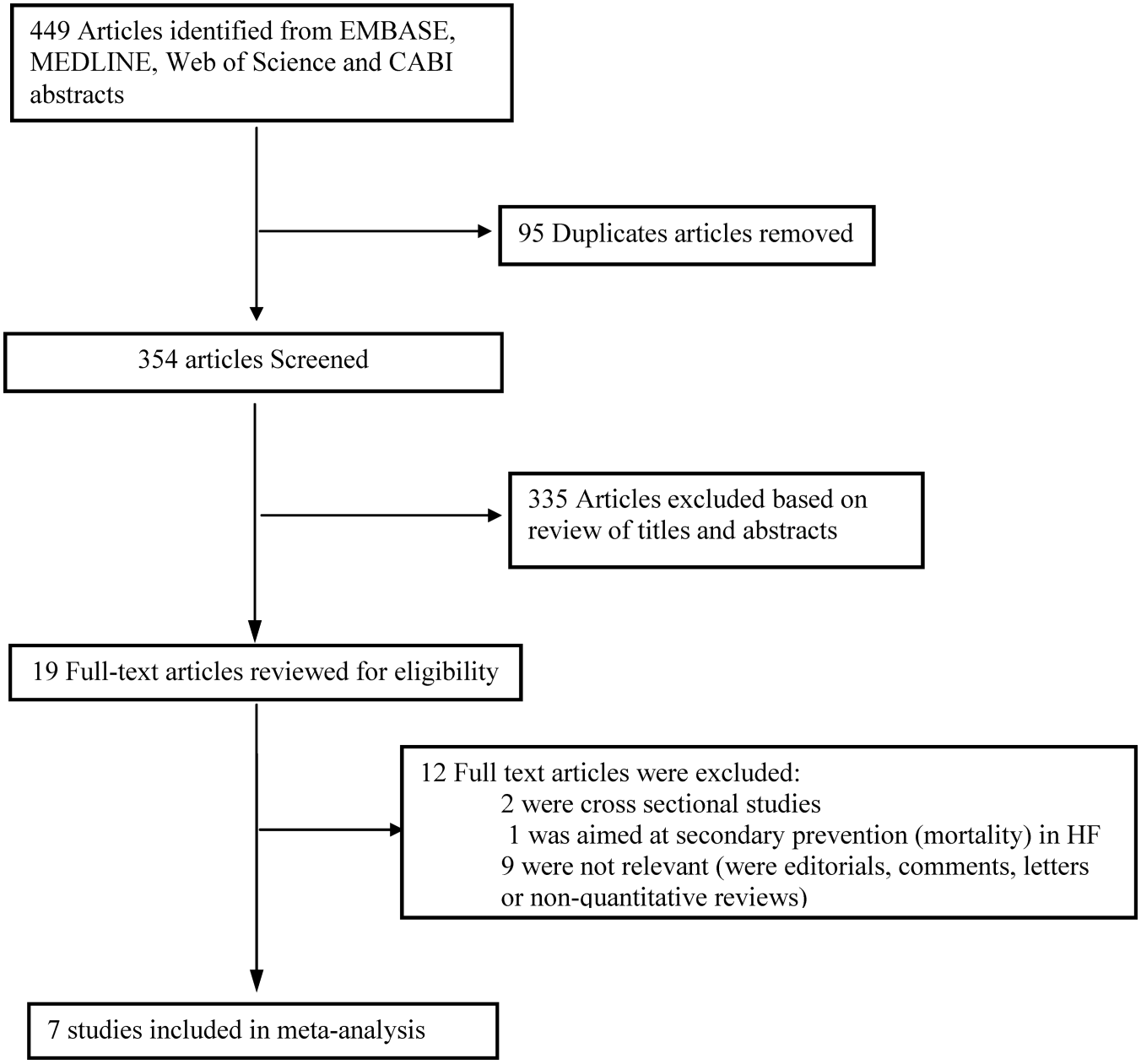
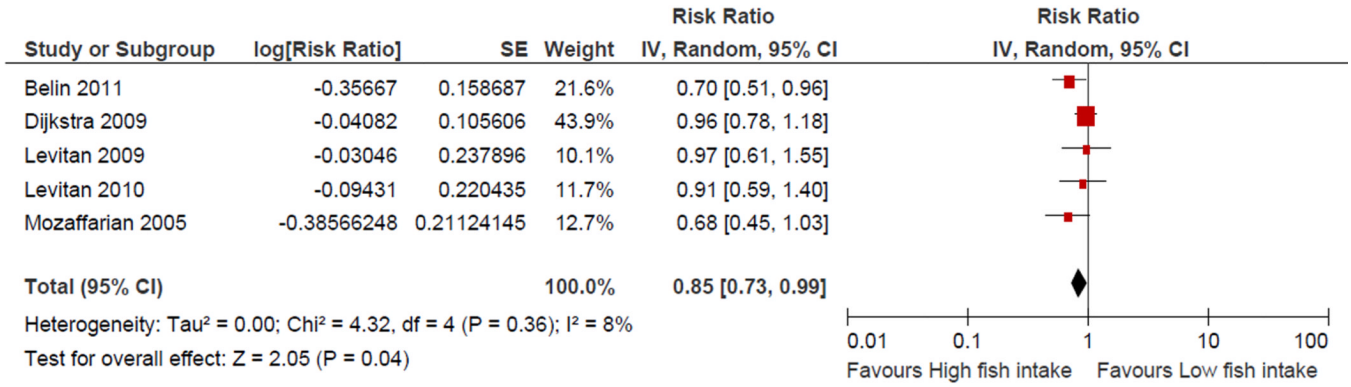


Figure 1.
Search and selection of studies included in the meta-analysis

Panel A



Panel B

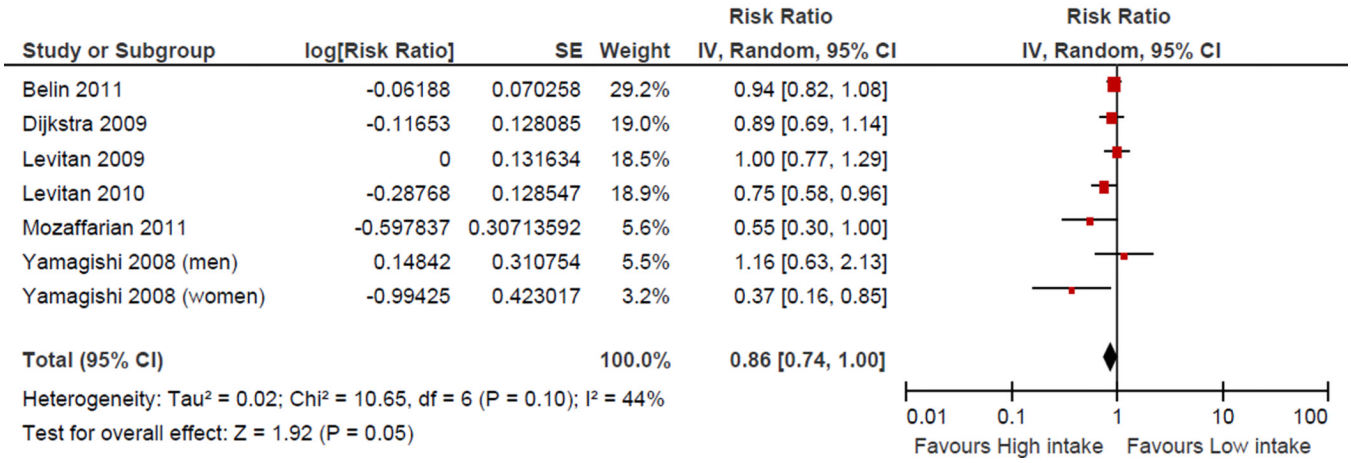


Figure 2.

Adjusted relative risks of heart failure according to the highest vs. lowest category of fish intake (Panel A) and EPA and DHA (Panel B).

CI denotes confidence interval; HF: heart failure; the size of each square is proportional to the study's weight (inverse of variance –IV).

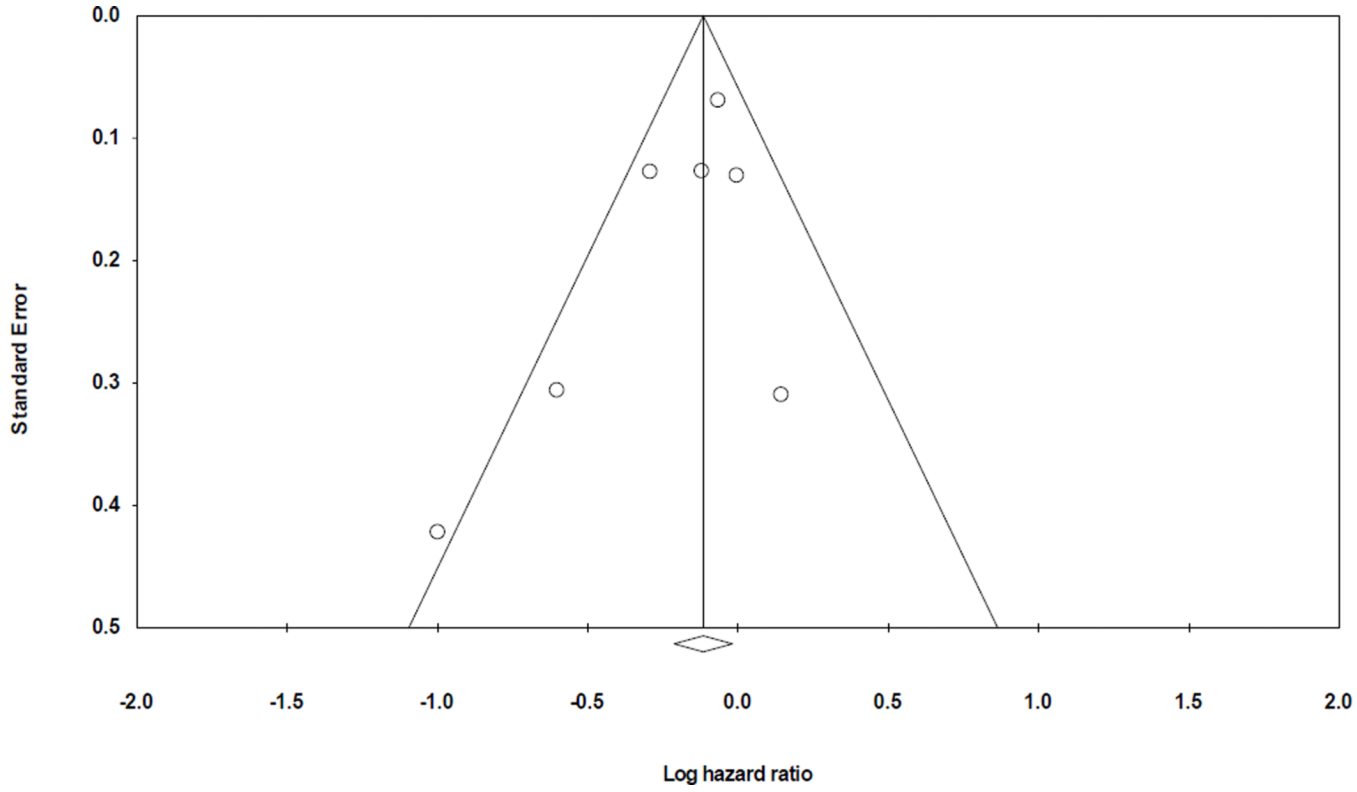


Figure 3.
Funnel plot assessing publication bias

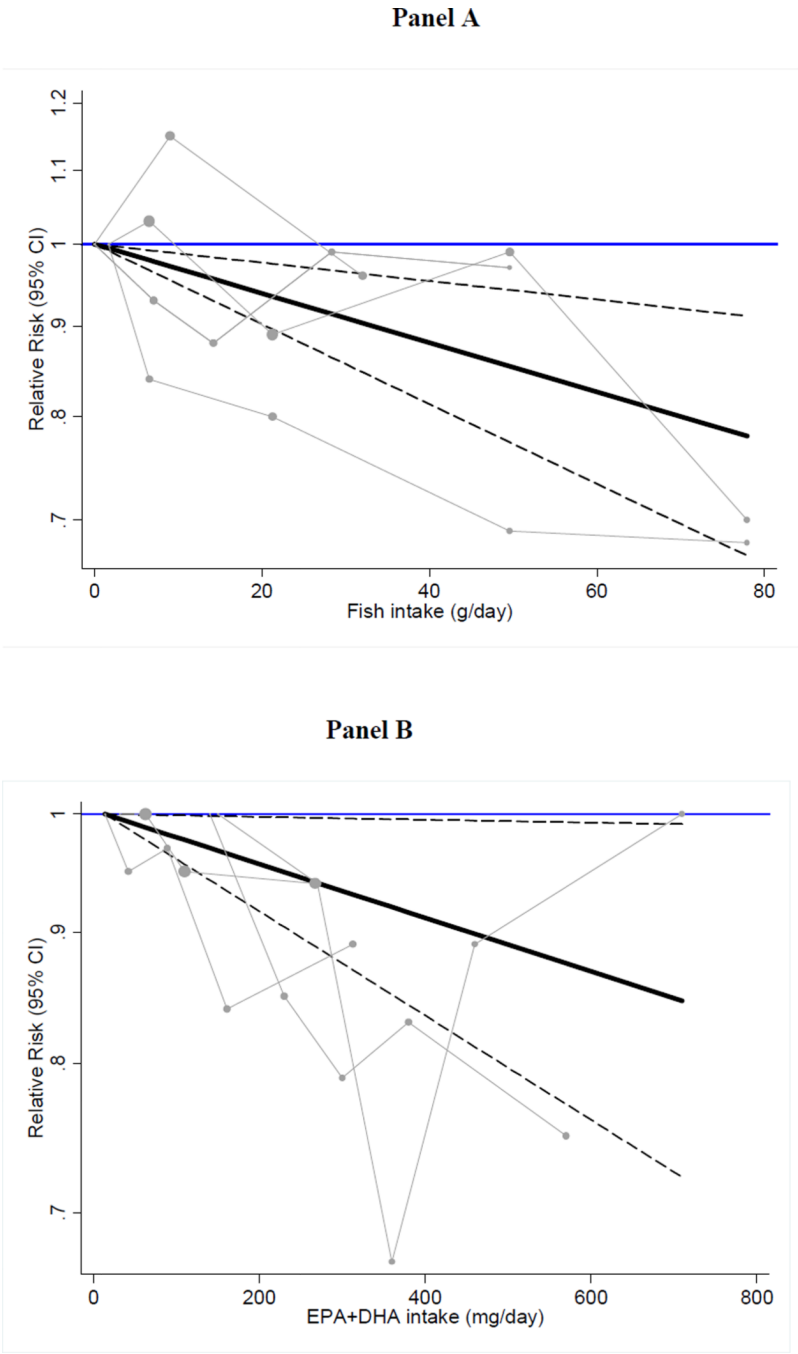


Figure 4.

Dose-response association of fish intake (Panel A) and dietary EPA+DHA with the risk of heart failure using random effects GLST analysis.

Pooled relative risks (solid black lines) and 95% confidence intervals (dashed lines) at each quantity of intake are reported. Gray lines connect study-specific relative risk according to fish or EPA/DHA levels. Vertical axis is on a log scale represents relative risk. The median intake in the lowest category of fish (0 g/d) and EPA+DHA (14 mg/d) were used as reference groups to estimate the pooled relative risks of the higher levels.

Table 1

Characteristics of prospective studies on fish or marine omega-3 fatty acids and heart failure *

Study	Location/Duration (average follow-up)	% female	Age, (Y)	No. of HF cases	Criteria for incident HF ascertainment	No. of participants	Measure of exposure intake	Study Quality *	Adjusted Covariates
Belin et al. 2011	United States/1992–2008 (10.0 Y)	100	50–79	1 858	Adjudication of hospitalized HF events defined by Symptoms and signs consistent with congestive HF, plus: pulmonary edema by chest X-ray; or dilated ventricle or poor ventricular function by imaging studies; or physician diagnosis of HF and receiving medical treatment.	84 493	Dietary fish: <1 serving/mth(C1), ≥5 serving/wk (C5). DHA+ EPA intake: <0.020 (Qt1), ≥0.071 (Qt4).	7	Age, ethnicity, education, physical activity, smoking, alcohol, DM, HTN, AF, MI/CABG/PTCA, BMI, time-dependent MI, fiber, fruit/vegetable servings, fried fish servings, saturated fat intake (%), DHA+EPA (%), ALA (%), linoleic acid (%), fried food servings, and sodium intake (mg)
Dijkstra et al.2009	Netherlands/ 1990–2008(11.4 Y)	59	≥55	669	Definite HF defined in accordance with the HF criteria of the European Society of Cardiology (a combination of HF diagnosed by a medical specialist and the presence of typical symptoms, such as breathlessness at rest or during exertion, ankle oedema, and pulmonary crepitations, confirmed by evidence of cardiac dysfunction e.g. chest X-ray, echocardiography) or Probable HF (defined as at least two typical symptoms suggestive of HF were present, and at least 1 of the following: history of cardiovascular disease (e.g., myocardial infarction, hypertension), response to treatment for HF, or objective evidence of cardiac dysfunction, while	5 299	Dietary fish: none(C1), ≥20g/day(C3). DHA+ EPA intake: <28mg/day(Q1), ≥212mg/day (Q5).	7	Age, sex, total energy intake, smoking, BMI, education, and intake of alcohol, fat, saturated fat, *trans*-fat and meat.

Study	Location/Duration (average follow-up)	% female	Age, (Y)	No. of HF cases	Criteria for incident HF ascertainment	No. of participants	Measure of exposure intake	Study Quality*	Adjusted Covariates
					symptoms could not be attributed to another underlying disease, such as chronic obstructive pulmonary disease)				
Levitan et al. 2009	Sweden/1998–2004 (7.0^{M} Y)	0	45–79	597	Hospitalization for or death from HF was identified by codes 428 (International Classification of Disease-9), I50, or I11.0 (International Classification of Disease-10) as the primary diagnosis	39 367	Dietary fish: never (C1), ≥3 serving/wk (C5). Marine Omega-3 intake: <0.15g/day(Q1), ≥0.71g/day (Q5).	7	Age, BMI, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of MI at <60 years, cigarette smoking, marital status, self-reported history of HTN, and high cholesterol.
Levitan et al. 2010	Sweden/1998–2006 (NA)	100	48–83	651	Hospitalization for or death from HF was identified by codes 428 (International Classification of Disease-9), I50, or I11.0 (International Classification of Disease-10) as the primary diagnosis	36 234	Dietary fish: <1 serving/wk(C1), ≥3 serving/wk (C4). Marine Omega-3 intake: <0.14g/day(Q1), ≥0.57g/day(Q5).	7	Age, education, BMI, physical activity, cigarette smoking, living alone, postmenopausal hormone use, total energy intake, alcohol intake, fiber intake, sodium intake, intake of red or processed meat, family history of MI before 60 years, self-reported history of HTN, self-reported history of high cholesterol.
Mozaffarian et al. 2005	United States/1990–2002 (NA)	58	≥65	955	Confirmation of CHF required each of the following: 1) a diagnosis of CHF by a treating physician; 2) either CHF symptoms (shortness of breath, fatigue, orthopnea, or paroxysmal nocturnal dyspnea) plus signs (edema, rales, tachycardia, gallop rhythm, or displaced apical impulse) or supportive clinical findings on echocardiography,	4 738	Dietary fish: <1 serving/mth(C1), ≥5 serving/wk (C5).	8	Age, gender, race, enrollment site, education, DM, BMI, prevalent CHD, prevalent stroke/ transient ischemic attack, smoking, leisure-time physical activity, total caloric intake, intake of fried fish, intakes of saturated fat, fruits, and alcohol intake.

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Study	Location/Duration (average follow-up)	% female	Age, (Y)	No. of HF cases	Criteria for incident HF ascertainment	No. of participants	Measure of exposure intake	Study Quality*	Adjusted Covariates
					contrast ventriculography, or chest radiography; and 3) medical therapy for CHF, defined as diuretics plus either digitalis or a (diuretics and either digitalis or a vasodilator [nitroglycerin, hydralazine, angiotensin-converting enzyme inhibitor]).				
Mozaffarian et al. 2011	United States/1992–2006 (9.7 Y)	58	≥65	555	Confirmation of CHF required each of the following: 1) a diagnosis of CHF by a treating physician; 2) either CHF symptoms (shortness of breath, fatigue, orthopnea, or paroxysmal nocturnal dyspnea) plus signs (edema, rales, tachycardia, gallop rhythm, or displaced apical impulse) or supportive clinical findings on echocardiography, contrast ventriculography, or chest radiography; and 3) medical therapy for CHF, defined as diuretics plus either digitalis or a (diuretics and either digitalis or a vasodilator [nitroglycerin, hydralazine, angiotensin-converting enzyme inhibitor]).	2 735	Total Omega-3 intake: (Qt1), (Qt4).	8	Age, sex, race, education, enrollment site, smoking status, DM, AF, physical activity, BMI, WC, alcohol use and omega-3 fatty acid concentration over time.
Yamagishi et al.2008	United States/1997–2003 (14.5 Y)	53	45–64	195	Incident HF was defined by the first HF hospitalization (International Classification of Diseases, Ninth	3 575	Long-chain omega-3 intake: (Q1), (Q5).	7	Age, sex, BMI, systolic blood pressure, antihypertensive medication use, plasma total and HDL cholesterol, DM,

Study	Location/Duration (average follow-up)	% female	Age, (Y)	No. of HF cases	Criteria for incident HF ascertainment	No. of participants	Measure of exposure intake	Study Quality*	Adjusted Covariates
					Revision [ICD-9] code 428 in any position) or any deaths where the death certificate included a HF code (code 428, ICD-9 or I50, ICD-10, in any position).				smoking status, cigarette-years, ethanol and energy intakes, education level and sports index.

*AF, atrial fibrillation; ALA, alpha-linolenic acid; BMI, Body mass index; C, category; CABG, coronary artery by-pass graft; CHD, coronary heart disease; DM, diabetes mellitus; DPA, docosahexaenoic acid;

EPA, eicosapentaenoic acid; F, female; g, grams; HDL, high density lipoprotein; HF, heart failure; HTN, hypertension; MI, myocardial infarction; mth, month; mg, milligrams; NA, not available; No., number;

PTCA, percutaneous transluminal coronary angioplasty; Q, quintile; Qt, quartile; WC, waist circumference; wk, week; y, year.

*Study quality assessed using the Newcastle-Ottawa Scale (range, 1–9 stars); MMedian.