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Review

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

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SUMMARY

Background & 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.
Results: A total of 176,441 subjects and 5480 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.

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 may 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.

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1. 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.

1.1. 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.

1.2. 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.

1.3. 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).

1.4. 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 (I^2 >50%), we 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.

1.5. 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).

2. Results

2.1. Search results

The literature search yielded 449 papers of which 7 articles were included in the current analyses after various exclusions (Fig. 1). We retained seven prospective studies conducted in the US ($n = 4$) or Europe ($n = 3$) with 176,441 participants in whom 5480 incident HF occurred. The sample sizes varied across studies from 2735 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

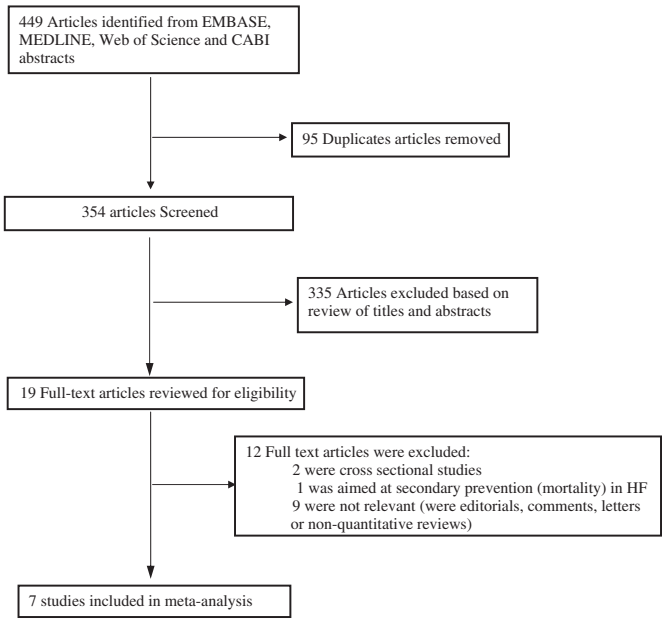

Fig. 1. Search and selection of studies included in the meta-analysis.