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# Fish Consumption and Acute Coronary Syndrome: A Meta-Analysis

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## ABSTRACT

**BACKGROUND:** Findings on the association between fish consumption and acute coronary syndrome are inconsistent. We assessed the role of fish consumption in acute coronary syndrome by conducting a dose-response meta-analysis.

**METHODS:** We conducted a literature search of MEDLINE and Embase databases from 1966 to June 2013 for prospective cohort and case-control studies that evaluated the association between fish consumption and acute coronary syndrome among general populations without cardiovascular disease history. Additional studies were identified via hand search of references of relevant articles. Estimates of relative risk (RR) were pooled using random-effects model. Sex and age effects were also evaluated.

**RESULTS:** Our search retrieved 11 prospective cohort and 8 case-control studies, totaling 408,305 participants. Among prospective cohort studies, the highest category of fish consumption (ie, ≥4 times per week) was associated with the greatest risk reduction in acute coronary syndrome (RR 0.79; 95% confidence interval [CI], 0.70-0.89). In dose-response analysis, each additional 100-g serving of fish per week was associated with a 5% reduced risk (RR per serving 0.95; 95% CI, 0.92-0.97). Subgroup analysis and meta-regression suggested that the risk reduction did not differ across sex or age groups. No heterogeneity was observed among prospective cohort ($P = .73$) and case-control ($P = .29$) studies. There was no evidence of publication bias.

**CONCLUSION:** Our meta-analysis demonstrated that there is an inverse association between fish consumption and the risk of acute coronary syndrome. Fish consumption appears beneficial in the primary prevention of acute coronary syndrome, and higher consumption is associated with greater protection.
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**KEYWORDS:** Cardiovascular diseases; Fatty acids; Meta-analysis; Myocardial infarction; Nutrition

Fish, especially fatty fish, are a rich source of omega-3 fatty acids. Omega-3 fatty acids are polyunsaturated fatty acids, consisting of eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6), which have been shown to have anti-inflammatory, antithrombotic, and antiarrhythmic effects; improve blood lipid profile, and help in vascular relaxation and plaque stability.[1] Yet, controversy exists as to the efficacy of omega-3 fatty acids in preventing cardiovascular diseases, and recent meta-analyses have indicated that omega-3 fatty acid supplements are not associated with cardiovascular disease risk reduction.[2,3] Conversely, it appears that fish, as opposed to omega-3 fatty acid supplements, may be beneficial to cardiovascular health, and the distinction between fish versus omega-3 fatty acid intake requires further exploration.

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Evidence from meta-analyses indicate the cardioprotective effects of fish consumption in relation to different end points such as cerebrovascular diseases, heart failure, and overall cardiovascular mortality,[4-8] but none of these reviews have assessed the role of fish consumption in the primary prevention of acute coronary syndrome. Findings from observational studies, including long-term prospective cohort and case-control studies, have not been consistent, with some studies, but not all, reporting an association between fish consumption and acute coronary syndrome. A systematic review and quantitative analysis of these studies is therefore needed to clarify the association between fish consumption and acute coronary syndrome.

The aim of this study was to investigate the association between fish consumption and acute coronary syndrome by conducting a dose-response meta-analysis. As a secondary objective, we evaluated whether this association varied according to sex and age.

**CLINICAL SIGNIFICANCE**

- Fish consumption is beneficial for the primary prevention of acute coronary syndrome.
- Each additional 100-g serving of fish per week is associated with a 5% reduced risk of acute coronary syndrome.
- Age and sex do not appear to influence the association between fish consumption and acute coronary syndrome.

## METHODS

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) protocol[9] was followed throughout the design, implementation, analysis, and reporting of this systematic review and meta-analysis study.

### Study Selection

We conducted a literature search of MEDLINE and Embase databases from 1966 to June 2013 for studies that evaluated the association between fish consumption and acute coronary syndrome, using search terms for fish ("fish" OR "fish meat" OR "seafood") in combination with those for acute coronary syndrome ("acute coronary syndrome" OR "myocardial infarction" OR "heart infarction" OR "heart infarct") (see **Supplementary Figure 1**, available online for details of search strategy). References of relevant articles were hand searched to identify additional studies. Studies were included if they met the following criteria:

- Prospective cohort or case-control study design.
- Fish consumption as exposure of interest.
- Acute coronary syndrome as outcome of interest.
- The most adjusted relative risk (RR) and 95% confidence interval (CI) were reported.
- The study population consisted of general adult populations without preexisting disease or without a previous acute coronary syndrome event.
- For dose-response analysis, the number of cases and participants or person-years for each category of fish consumption were reported (or data were available to calculate them).

We restricted studies to those published in English or French. If a study reported a measure of association and 95% CI for men and women, the results were treated as 2 separate studies in the meta-analysis. For studies that reported results only by different types of acute coronary syndrome (eg, fatal and nonfatal myocardial infarction) or by different types of fish (eg, low- and high-fat fish), the RRs were pooled. Finally, if data were shared or duplicated in more than one study, the first published or most detailed one was included in the analysis.

### Data Extraction

Relevant data were independently extracted by 2 reviewers using a predesigned data collection form. Disagreements were resolved by consensus through discussion, or upon consultation of a third reviewer. The collected data included first author's last name, year of publication, country where the study was conducted, duration and person-years of follow-up, sample size and proportion of men and women, mean and range of age, type and number of acute coronary syndrome events, method used to assess fish consumption, categories of fish consumption, most adjusted RR and corresponding 95% CI for each category of fish consumption, and the variables included in the multivariable model.

### Quality Assessment

Quality assessment was performed using the Newcastle Ottawa Scale, which is one of the most comprehensive tools available for assessing the quality of nonrandomized studies (cohort and case-control studies) in meta-analyses.[10] Scores range from 0 to 9, with a higher score indicating better methodological quality. Studies with a score $\geq$7 were considered as being of higher quality.

### Statistical Analysis

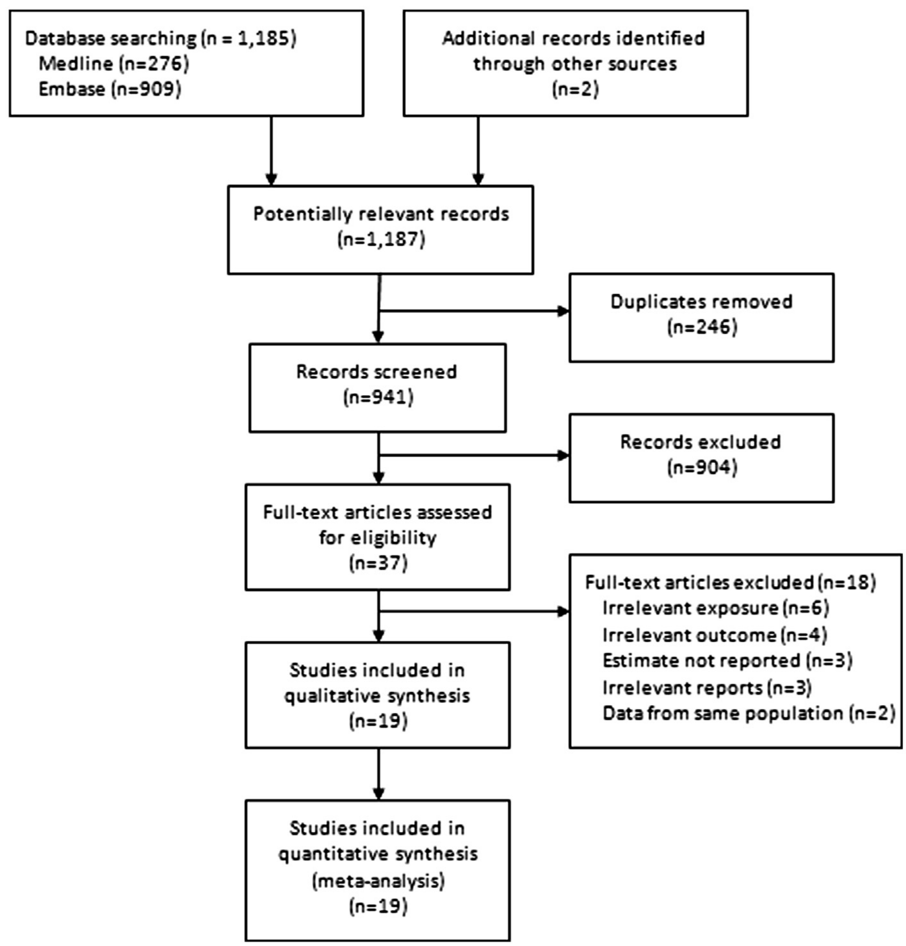
As some studies reported category of consumption in frequency, we first standardized these intake levels by converting frequency into grams per day, using 100 g as a standard portion size for fish, as per dietary guidelines. The mean or median fish intake per category of each study was then used to categorize the levels of intake into 5 standardized intervals, namely "less than once per month" (the reference category), "1 to <4 times per month," "1 to <2 times per week," "2 to <4 times per week," and "$\geq$4 times per week." We assumed that the reported reference exposure category from all studies represented a level of intake that was similar to the standardized reference category. When a range of intake was reported rather than the mean or median, the midpoint value of the upper and lower boundaries of the category was used as the average intake. If the highest level of intake was open ended (eg, ≥5 times per week), we assumed that that boundary had the same magnitude as the closest category. If a study did not report the lower boundary of the lowest category of fish consumption, it was considered to be zero. Additionally, if the mean or median or average amount of fish consumption from 2 or more categories of a single study fell into the same standardized category of fish intake, the estimates were pooled. Dose-response meta-analysis was conducted using generalized least-squares method for trend estimation of summarized dose-response data.[11] Restricted cubic splines with 3 knots at fixed percentiles were used to examine potential nonlinear relationship between fish consumption and acute coronary syndrome. Potential departure from a linear relationship was assessed by testing the null hypothesis that the coefficient of the second spline is equal to 0. Furthermore, we conducted subgroup analysis and meta-regression to investigate the effect of sex and age on the potential association between fish consumption and acute coronary syndrome.

The DerSimonian and Laird random-effects model,[12] which considers both within- and between-study variation, was used to calculate summary estimates and 95% CIs for each category of fish consumption. Heterogeneity among studies was assessed by using the $I^2$ statistic test.[13] Potential publication bias was assessed by using funnel plots, Egger's regression asymmetry test[14] and Begg's rank correlation test.[15] All statistical analyses were conducted using STATA, version 12.1 (StataCorp, College Station, Tex).

## RESULTS

### Literature Search

The initial search identified 1185 potentially relevant articles (276 from MEDLINE and 909 from Embase). Among them, 246 were duplicates. Two additional articles were identified via hand search. After initial screening, based on titles and abstracts, 37 articles remained. After full-text assessment, 18 articles were excluded for various reasons. Thus, the final set of studies consisted of 19 studies (Figure 1).




*Adapted from PRISMA 2009 flow diagram

**Figure 1** Flow diagram of selection of studies on fish consumption and acute coronary syndrome*.

**Table 1** Characteristics of Included Cohort Studies on Fish Consumption and Acute Coronary Syndrome

| First Author, Year of Publication (Country) | Years & Duration of Follow-Up | Number of Participants | Mean Age (Range), Years | Number of Cases (Outcome) | Dietary Assessment Tool | Categories of Fish Consumption | Covariates |
|---|---|---|---|---|---|---|---|
| Ascherio, 1995 (US)[16] | 1986-1992 6 | 44,895 men | 57.5 (40-75) | 547 (nonfatal MI) | Self-administered FFQ | <1/mo, 1-3/mo, 1/wk, 2-3/wk, 4-5/wk, ≥6/wk | Age, BMI, smoking, alcohol consumption, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of MI before 60 years, profession, intake of n-3 fatty acids |
| Bjerregaard, 2010 (Denmark)[17] | 1993-2003 7.6 | 25,573 men 28,653 women | 56 (50-64) | 854 (nonfatal MI) | Self-administered FFQ | 0-24 g/d, 25-35 g/d, 36-47 g/d, 48-64 g/d, >64 g/d (men); 0-22 g/d, 23-31 g/d, 32-41 g/d, 42-54 g/d, >55 g/d (women) | Education, smoking, alcohol intake, BMI, history of diabetes, systolic blood pressure, serum cholesterol, physical activity, dietary intake of fruits and vegetables, total energy intake, dietary intake of SFA, MUFA and PUFA, menopausal status |
| Daviglus, 1997 (US)[18] | 1957-1959 30 | 1822 men | 47.6 (40-55) | 293 (fatal MI) | Questionnaire-based interview by nutritionists | 0 g/d, 1-17 g/d, 18-34 g/d, ≥35 g/d | Age, education, religion, systolic pressure, serum cholesterol, number of cigarettes smoked, BMI, diabetes, electrocardiographic abnormalities, intake of energy, cholesterol, SFA, MUFA, PUFA, total protein, carbohydrate, alcohol, iron, thiamine, riboflavin, niacin, vitamin C, beta carotene and retinol |
| de Goede, 2010 (Netherlands)[19] | 1993-2007 11.3 | 9604 men 11,738 women | 42.1 (20-65) | 64 (fatal MI) 252 (nonfatal MI) | Self-administered FFQ | <3.3 g/d, 3.3-7.3 g/d, 7.4-14 g/d, >14 g/d | Age, sex, BMI, total energy intake, ethanol intake, smoking, SES, vitamin or mineral supplement use, use of drugs for hypertension or hypercholesterolemia, family history of cardiovascular diseases, SFA intake, fruit and vegetable intake |
| Hu, 2002 (US)[20] | 1980-1994 16 | 84,688 women | 46.5 (34-59) | 1029 (nonfatal MI) | Self-administered FFQ | <1/mo, 1-3/mo, 1/wk, 2-4/wk, ≥5/wk | Age, time periods, smoking, BMI, alcohol intake, menopausal status, postmenopausal hormone use, vigorous to moderate activity, use of aspirin, multivitamin use, vitamin E supplement use, history of hypertension, hypercholesterolemia, diabetes, intake of trans fat, ratio PUFA:SFA, dietary fiber |
| Iso, 2006 (Japan)[21] | 1990-2001 10 | 19,985 men 21,593 women | 49.5 (40-59) | 198 (total MI) | Self-administered FFQ | median 23 g/d, 51 g/d, 78 g/d, 114 g/d, 180 g/d | Age, sex, smoking, alcohol intake, BMI, history of hypertension and diabetes, medication use for hypercholesterolemia, education, sports at leisure time, dietary intake of fruits, vegetables, SFA, MUFA, n-6 PUFA, cholesterol and total energy, public health centers |

**Table 1** Continued

| First Author, Year of Publication (Country) | Years & Duration of Follow-Up | Number of Participants | Mean Age (Range), Years | Number of Cases (Outcome) | Dietary Assessment Tool | Categories of Fish Consumption | Covariates |
|---|---|---|---|---|---|---|---|
| Kuhn, 2013 (Germany)[22] | 1994-1998<br>8.1 | 20,292 men<br>28,023 women | 50.5 (35-65) | 605 (total MI) | Self-administered FFQ | $<$7.5 g/d, 7.5-14.5 g/d, 14.5-21.5 g/d, 21.5-31.1 g/d, $>$31.1 g/d | Age, sex, study centers, energy intake, alcohol intake, BMI, waist circumference, physical activity, education, smoking, diabetes |
| Morris, 1995 (US)[23] | 1982-1988<br>4 | 21,185 men | 62 (40-84) | 281 (total MI) | Self-administered FFQ | $<$1/wk, 1/wk, 2-4/wk, $\geq$5/wk | Age, level of fish consumption, aspirin and beta-carotene assignment, smoking, alcohol consumption, obesity, diabetes, vigorous exercise, parental history of MI before 60, history of hypertension, history of hypercholesterolemia, vitamin supplement use, SFA intake |
| Mozaffarian, 2003 (US)[24] | 1989-2000<br>9.3 | 1526 men<br>2384 women | 72.7 ($\geq$65) | 363 (nonfatal MI) | Self-administered FFQ picture-sort version | 1/mo, 1-3/mo, 1/wk, 2/wk, $\geq$3/wk | Age, sex, education, diabetes, smoking, pack-years of smoking, tuna/other fish and fried fish/fish sandwich consumption, BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein, intake of SFA, alcohol, beef/pork, fruits and vegetables |
| Yamagishi, 2008 (Japan)[25] | 1988-2003<br>12.7 | 22,881 men<br>35,091 women | 56.1 (40-79) | 329 (fatal MI) | Self-administered FFQ | Median 20 g/d, 33 g/d, 45g/d, 62 g/d, 86 g/d (men); 21 g/d, 33 g/day, 46g/d, 62 g/d, 85 g/d (women) | Age, sex, history of hypertension and diabetes, smoking, alcohol consumption, BMI, mental stress, walking, sports, education, total energy, dietary intake of cholesterol, SFA, n-6 PUFA, vegetables and fruits |
| Yuan, 2001 (China)[26] | 1986-1989<br>12 | 18,244 men | 55.8 (45-64) | 113 (fatal MI) | Questionnaire-based interview | $<$30 g/wk, 30-$<$60 g/wk, 60-$<$100 g/wk, 100-$<$150 g/wk, $\geq$150 g/wk | Age, total energy intake, level of education, BMI, smoking, number of cigarettes smoked, number of alcoholic drinks consumed, history of diabetes, history of hypertension |

BMI = body mass index; FFQ = food frequency questionnaire; MI = myocardial infarction; MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid; SES = socioeconomic status; SFA = saturated fatty acid.

## Study Characteristics

The combined studies included 11 prospective cohort[16-26] and 8 case-control[27-34] studies, totaling 408,305 participants (398,177 for prospective cohort and 10,128 for case-control studies), with 47.1% being male. The mean age was 55.8 years (age range 20-84 years). There were 8517 cases of acute coronary syndrome. The majority of the studies were from the US (5 studies) and Japan (3 studies). The remaining were from various European countries, and one study was from China. Among prospective cohort studies, the average follow-up time was 11.2 years, ranging from 4 to 30 years (**Tables 1, 2**).

## Fish Consumption and Acute Coronary Syndrome

Among prospective cohort studies, a significant association was observed between fish consumption and a reduced risk of acute coronary syndrome (**Table 3**, **Figure 2**). The highest category of fish consumption (ie, $\geq$4 times per week) was associated with the greatest risk reduction in acute coronary syndrome (RR 0.79; 95% CI, 0.70-0.89). No evidence of heterogeneity was found ($I^2 = 0.0\%$, $P = .73$). Although most of the studies (9 of 11) were of high quality, we conducted an analysis to exclude the studies of low quality, and obtained similar results. Because all except 2 studies reported hazard ratios as measures of association, we performed a separate analysis for these studies. The results were similar, with the highest category of fish consumption being associated with a 21% reduced risk of acute coronary syndrome (hazard ratio 0.79; 95% CI, 0.69-0.90). In sensitivity analysis excluding the largest study, we also found a significant reduction in the risk of acute coronary syndrome (RR 0.76; 95% CI, 0.66-0.88). Furthermore, the results did not differ according to country.

Among case-control studies, fish consumption also appeared to reduce the risk of acute coronary syndrome (RR 0.76; 95% CI, 0.67-0.87 for 1 to <2 times per week), but the association was nonsignificant for the highest versus lowest category. Similar to prospective cohort studies, little heterogeneity was observed ($I^2 = 20.2\%$, $P = .29$). Generally, the case-control studies were of poorer quality, and only 2 studies were considered as being of high quality, with their score being 7 each. In sensitivity analysis, no substantial change was seen after excluding the largest study.

## Dose-Response Analysis

Eight prospective cohort studies provided sufficient data to conduct a dose-response analysis. It was found that each additional 100-g serving of fish per week was associated with a risk reduction in acute coronary syndrome by 5% (RR 0.95; 95% CI, 0.92-0.97). We did not find evidence for a nonlinear relationship ($P = .92$).

## Effect of Sex and Age

There were 6 studies (5 prospective cohort and 1 case-control studies) that were conducted among men only, and 4 studies (2 prospective cohort and 2 case-control studies) that were among women only. The subgroup analysis of prospective cohort studies of men versus women did not support a sex difference in the association between fish intake and acute coronary syndrome (RR 0.84; 95% CI, 0.70-1.01 and RR 0.80; 95% CI, 0.61-1.06 for men and women, respectively). There was also no evidence that the association differed by sex according to meta-regression (RR 0.95; 95% CI, 0.56-1.64).

In additional meta-regression analyses where we included age as a continuous variable, there was no significant effect of age on the association between fish consumption and acute coronary syndrome. However, there was only modest variation in age across the included studies, with most studies having a mean age in the range of 47 to 62 years.

## Publication Bias

No evidence of publication bias was found among the prospective cohort and case-control studies. This was supported by funnel plots, which did not show presence of asymmetry (**Supplementary Figure 2**, available online), as well as the Egger's test ($P = .60$) and the Begg's test ($P = .44$).

## DISCUSSION

Our meta-analysis demonstrated that there is an inverse association between fish consumption and the risk of acute coronary syndrome. We observed a greater risk reduction with increasing fish intake, and with each additional 100-g serving per week, the risk of acute coronary syndrome was further reduced by 5%.

This study represents an updated investigation of the role of fish consumption in acute coronary syndrome. While several meta-analyses of observational studies have evaluated the effect of fish consumption on different cardiovascular outcomes,[35-39] none of them have specifically examined acute coronary syndrome as an outcome. The landmark DART (Diet and Reinfarction) trial demonstrated that fish consumption was beneficial for the secondary prevention of myocardial infarction, with $\geq$2 servings of fish per week being associated with reduced cardiovascular mortality risk.[40] Yet, the benefits of omega-3 fatty acid supplements in the secondary prevention of cardiovascular diseases remain controversial in light of recent meta-analyses that have combined the evidence from randomized controlled trials and found no association.[2,3] Additionally, there is also a need to distinguish between primary versus secondary prevention. We explored the relationship between fish and acute coronary syndrome among generally healthy populations, as opposed to clinical trials. Our findings from prospective cohort studies confirm that fish

**Table 2** Characteristics of Included Case-Control Studies on Fish Consumption and Acute Coronary Syndrome

| First Author, Year of Publication (Country) | Years | Number of Participants | Mean Age (Range), Years | Number of Cases (Outcome) | Dietary Assessment Tool | Categories of Fish Consumption | Covariates |
|---|---|---|---|---|---|---|---|
| Gramenzi, 1990 (Italy)[27] | 1983-1989 | 936 women | 49 (21-69) | 287 (total MI) | Questionnaire-based interview | <1/wk, 1/wk, >1/wk | Age, area of residence, education, smoking, hyperlipidemia, diabetes, hypertension, BMI, intake of carrots, green vegetables, fresh fruit, meat, ham and salami, butter, total fat score, coffee consumption, alcohol consumption |
| Lockheart, 2007 (Norway)[28] | 1995-1997 | 211 men and women | 62.4 (45-75) | 106 (total MI) | Interview using FFQ | Median 32 g/d, 99 g/d (low-fat); 12 g/d, 52 g/d (high-fat) | Age, marital status, education, family history of heart disease, smoking, energy intake |
| Martinez-Gonzalez, 2002 (Spain)[29] | 1999-2001 | 277 men 65 women | 61.6 (<80) | 171 (total MI) | Self-administered FFQ | <60 g/d, >77 g/d | Age, sex, hospital, smoking, BMI, high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity, SES, intake of olive oil, fiber, fruits, vegetables, alcohol, meat/meat products and white bread/rice/pasta |
| Oliveira, 2010 (Portugal)[30] | 1999-2003 | 1460 men 1556 women | 52 (33-69) | 820 (nonfatal MI) | Interview using FFQ | Median <35.5 g/d, ≥35.5 g/d (excluding cod); <13.5 g/d, ≥13.5 g/d (cod) | Sex, age, education, total energy intake, intake of fruit, refined cereals and white meat, smoking, regular physical activity, family history of MI, BMI, menopause, hormone replacement therapy |
| Panagiotakos, 2005 (Greece)[31] | 2000-2001 | 1562 men 364 women | 60.1 (49-75) | 848 (nonfatal ACS) | Questionnaire-based interview | Never, <150 g/wk, 150-300 g/wk, >300 g/wk | Age, sex, smoking, hypertension, hypercholesterolemia, HDL cholesterol, LDL cholesterol, diabetes, physical inactivity, BMI, food items consumed |
| Sasazuki, 2001 (Japan)[32] | 1996-1998 | 1340 men 506 women | 59.5 (40-79) | 458 (nonfatal MI) | Questionnaire-based interview | <2/wk, 2-3/wk, ≥4/wk | Smoking, alcohol use, sedentary job, leisure-time physical activity, hyperlipidemia, hypertension, diabetes, angina pectoris, obesity, tofu consumption, fruit consumption |
| Tavani, 2001 (Italy)[33] | 1995-1999 | 675 men 310 women | 60 (25-79) | 507 (nonfatal MI) | Interview using FFQ | <1/wk, 1-<2/wk, ≥2/wk | Age, sex, education, BMI, cholesterol, smoking, coffee, alcohol, meat, vegetables, fruit, calorie intakes, physical activity, hyperlipidemia, diabetes, hypertension, family history of MI in first-degree relatives |
| Wennberg, 2011 (Sweden)[34] | 1987-1999 | 648 men 218 women | 58.7 (34-77) | 392 (total MI) | Self-administered FFQ | <1/mo, 1/mo-<1/wk, 1-2/wk, >2/wk | Apolipoprotein B/apolipoprotein A-I, smoking, systolic blood pressure, diabetes, education, consumption of fruit and vegetables, consumption of wine, consumption of strong beer, level of physical activity |

ACS = acute coronary syndrome; BMI = body mass index; FFQ = food frequency questionnaire; MI = myocardial infarction; MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid; SES = socioeconomic status; SFA = saturated fatty acid.

**Table 3** Pooled Measures of Acute Coronary Syndrome According to Category of Fish Consumption

| | RR (95% CI) per Category of Fish Consumption | | | | |
|---|---|---|---|---|---|
| | <Once per Month | 1 to <4 Times per Month | 1 to <2 Times per Week | 2 to <4 Times per Week | ≥4 Times per Week |
| Prospective cohort | 1.00 | 0.82 (0.72-0.92) | 0.85 (0.72-1.01) | 0.83 (0.71-0.96) | 0.79 (0.70-0.89) |
| Highest quality studies | 1.00 | 0.84 (0.74-0.95) | 0.81 (0.73-0.91) | 0.84 (0.73-0.95) | 0.79 (0.70-0.89) |
| Hazard ratio only | 1.00 | 0.83 (0.73-0.95) | 0.81 (0.72-0.90) | 0.81 (0.70-0.95) | 0.79 (0.69-0.90) |
| Largest study excluded | 1.00 | 0.82 (0.72-0.92) | 0.85 (0.72-1.01) | 0.80 (0.67-0.96) | 0.76 (0.66-0.88) |
| Case-control | 1.00 | — | 0.76 (0.67-0.87) | 0.84 (0.64-1.10) | 0.73 (0.49-1.09) |

CI = confidence interval; RR = relative risk.

consumption is beneficial in the primary prevention of acute coronary syndrome.

The potential differential effect of omega-3 fatty acids from fish versus supplements has previously been highlighted. It has been suggested that the bioavailability and functioning of nutrients obtained from foods compared with supplements may differ.[41] A 6-week experimental study comparing salmon to fish oil capsules found that EPA and DHA from dietary fish were more effectively incorporated into plasma lipids, leading to higher plasma concentrations of omega-3 fatty acids.[42] In another study where participants were randomly assigned to the consumption of oily fish or omega-3 fatty acid capsules providing the same amount of EPA and DHA, EPA content in erythrocytes was found to increase more rapidly in the fish group.[43] Thus, while omega-3 fatty acids have been shown to favorably impact markers of cardiovascular diseases, whether they come from a complex food matrix such as fish, or are in an isolated form, could possibly explain why differences are observed between fish and omega-3 fatty acid supplements.

It has also been indicated that adherence to high omega-3 fatty acid diets in nutritional interventions may be poor.[44] It is plausible that one of the reasons why fish have a cardioprotective effect relative to supplements is that adherence to fish consumption may be higher. Fish can be included in the diet as a high-quality protein food and contain a wide

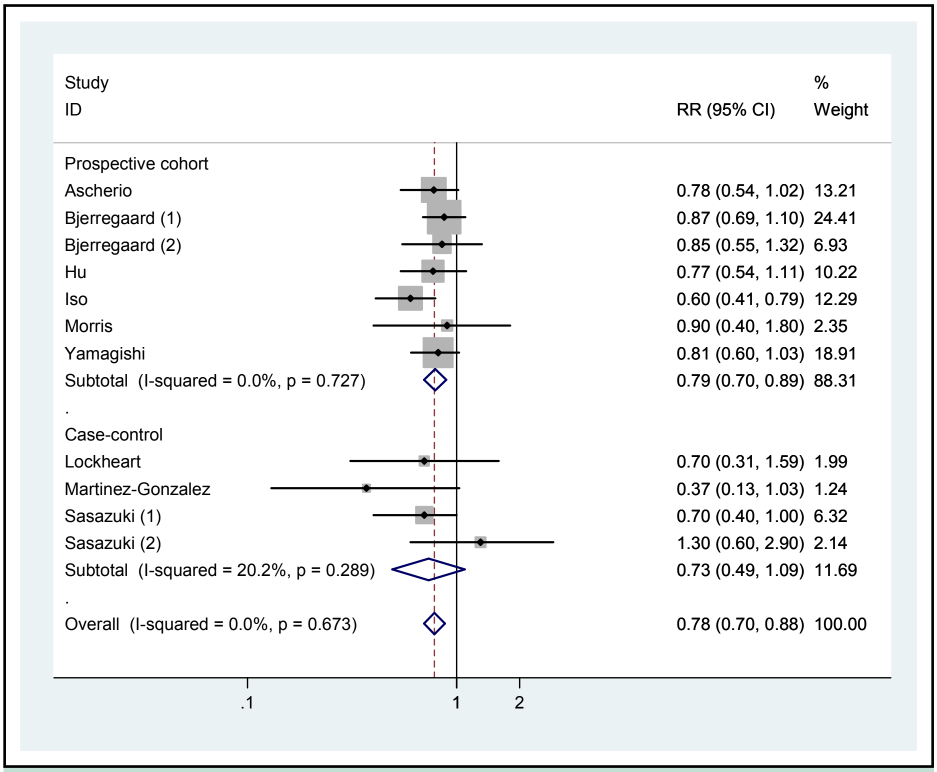



**Figure 2** Meta-analysis of prospective and case-control studies on fish consumption and acute coronary syndrome comparing the highest (≥4 times per week) to lowest (less than once per month) category of intake.

array of other valuable nutrients including vitamins (A, D, $B_3$, $B_6$, $B_{12}$) and minerals (calcium, phosphorus, selenium, iron, magnesium, potassium, iodine). These nutrients have diverse properties that are beneficial to the overall health. Higher vitamin D levels have also been linked to reduced acute coronary syndrome mortality and morbidity.[45] Hence, when considering omega-3 fatty acid intake for cardiovascular benefits, a diet-based approach including fish, rather than supplements, may be warranted.

Most of the studies included in this meta-analysis used food frequency questionnaires to assess fish consumption. Although fish consumption is a recognized proxy for omega-3 fatty acid intake, blood concentrations of omega-3 fatty acids may reflect dietary intake more strongly.[46] Some studies have suggested that low blood levels of omega-3 fatty acids may be associated with an increased risk of acute coronary syndrome.[47-49] The omega-3 index, which is the sum of EPA and DHA in erythrocyte membranes, expressed as a percentage of total erythrocyte fatty acids, is a novel biomarker of blood concentrations of omega-3 fatty acids.[50] The omega-3 index has been indicated as a reliable biomarker for assessing long-term omega-3 fatty acid intake, and fish consumption has been shown to strongly correlate with higher omega-3 index.[51] It has also been shown that men are better able to increase blood levels of omega-3 fatty acids with dietary advice on fish intake, likely because men consume larger portion sizes than women, which may not be captured by dietary assessment with food frequency questionnaires.[44]

This study summarizes the evidence from observational studies but presents with some limitations. Our meta-analysis consisted of studies that adjusted for many important confounders, including socioeconomic status and various lifestyle behaviors such as different dietary factors, physical activity, and smoking. However, residual confounding is still possible, given that fish consumption may be associated with healthier lifestyle behaviors that are difficult to measure. Another limitation is that we had a relatively small sample of studies, which cannot eliminate the possibility of publication bias. Whether the association between fish consumption and acute coronary syndrome differed by sex was inconclusive, possibly due to our small number of studies. We also did not find an age effect, but this could be due to the narrow age range. It would have been equally interesting to evaluate whether the association differed by type of fish or acute coronary syndrome, but we did not have enough studies to conduct these analyses.

In conclusion, fish consumption appears to be beneficial in the primary prevention of acute coronary syndrome. An inverse association between fish consumption and the risk of acute coronary syndrome was observed. A dose-response relationship was found between fish consumption and the reduced risk of acute coronary syndrome. Future studies are needed to further investigate whether sex differences and age effects exist. Moreover, more research is required to elucidate whether this association varies according to the type of fish.

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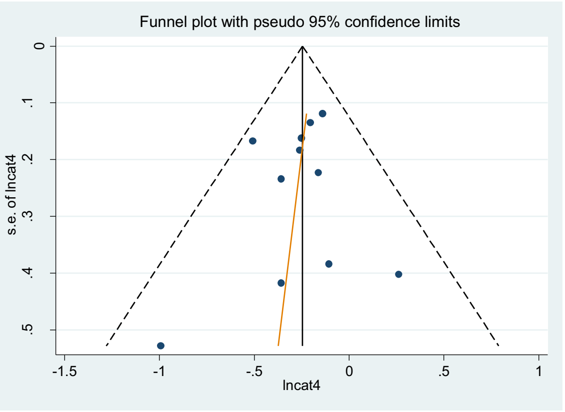
Medline

1. "Fishes"[Mesh]
2. "Seafood"[Mesh]
3. “fish”[tiab]
4. 1 or 2 or 3
5. "Acute Coronary Syndrome"[Mesh]
6. "Myocardial Infarction"[Mesh]
7. “acute coronary syndrome”[tiab]
8. “myocardial infarction”[tiab]
9. “heart infarction”[tiab]
10. “heart infarct”[tiab]
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. limit 12 to (English or French)
14. limit 13 to human

Embase

1. exp fish/ or exp fish meat/
2. exp sea food/
3. fish*.tw.
4. seafood*.tw.
5. 1 or 2 or 3 or 4
6. exp acute coronary syndrome/ or exp heart infarction/
7. myocardial infarction.tw.
8. acute coronary syndrome.tw.
9. 6 or 7 or 8
10. 5 and 9
11. limit 10 to (English or French)
12. limit 11 to yr="1966 - 2013"
13. limit 12 to human

**Supplementary Figure 1** Search strategies for studies on fish consumption and acute coronary syndrome.




**Supplementary Figure 2** Funnel plot of studies on fish consumption and acute coronary syndrome.