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ORIGINAL ARTICLE

Fish consumption and all-cause mortality: a meta-analysis of cohort studies

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BACKGROUND/OBJECTIVES: Although fish consumption may have an influence on specific mortality of major chronic diseases, the relationship between fish consumption and all-cause mortality remains inconsistent.
SUBJECTS/METHODS: We performed a systematic search of publications using PubMed and Web of science up to 31 December 2014. Summary relative risk (RR) for the highest versus lowest category of fish consumption on risk of all-cause mortality was calculated by using a random effects model. Potential nonlinear relation was tested by modeling fish intake using restricted cubic splines with three knots at fixed percentiles of the distribution.
RESULTS: Twelve prospective cohort studies with 672 389 participants and 57 641 deaths were included in this meta-analysis. Compared with the lowest category, the highest category of fish intake was associated with about a 6% significantly lower risk of all-cause mortality (RR = 0.94, 95% confidence interval (CI): 0.90, 0.98; $I^2 = 39.1\%$, $P = 0.06$). The dose–response analysis indicated a nonlinear relationship between fish consumption and all-cause mortality. Compared with never consumers, consumption of 60 g of fish per day was associated with a 12% reduction (RR = 0.88, 95% CI: 0.83, 0.93) in risk of total death.
CONCLUSIONS: These results imply that fish consumption was associated with a reduced risk of all-cause mortality.

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INTRODUCTION

Noncommunicable diseases, such as cancers, cardiovascular diseases and type 2 diabetes, are responsible for about two-thirds of deaths worldwide.[1] Therefore, it is urgent to develop efficient strategies that can prevent noncommunicable diseases by reducing their major risk factors and recommending healthy lifestyles, including a well-balanced diet. Fish, as a widely consumed food of human diet, has many health benefits.[2] A growing body of evidence indicates that high consumption of fish may decrease the risk of chronic diseases like coronary heart disease (CHD),[3–5] stroke,[6] type 2 diabetes[7] and certain cancers[8–12] and, consequently, also for all-cause mortality.[13] A systematic review of 17 cohort studies showed that fish consumption had significantly beneficial effects on the prevention of CHD mortality.[14] Recently, the Vitamins and Lifestyle Study (VITAL Study) reported that higher intake of fish was significantly associated with a lower risk of all-cause mortality.[15]

Fish is the most common dietary source of long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs), which has been demonstrated to have antiatherosclerotic and antithrombotic effects.[16,17] However, fish types, cooking methods, toxic metals and other environmental contaminants in fish may have different roles on human health.[18] In addition, evidence from published epidemiological studies did not show consistent results between fish consumption and all-cause mortality.[13,15,19–28] Hence, we conducted a meta-analysis to assess this relationship quantitatively.

MATERIALS AND METHODS

Search strategy

We performed a systematic search in PubMed (www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (www.webofknowledge.com/) for studies published before 31 December 2014. We used the search terms as 'fish intake', 'fish consumption' in combination with 'mortality', 'death' or 'fatal'. Furthermore, we manually reviewed the reference lists of identified papers, previous reviews and relevant meta-analyses to identify any studies that were not found from the preliminary literature searches.

Two investigators (L-GZ and J-WS) independently conducted the literature search. The study was eligible for inclusion if it had the following: (1) had a cohort design based on general healthy population and published in English, (2) used fish consumption as the exposure of interest, (3) identified total death or all-cause mortality as the outcome of interest and (4) reported the relative risk (RR) or hazard risk (HR) (highest versus lowest) and the corresponding 95% confidence interval (CI).

Data extraction

From each eligible study, we extracted the first author's name, study population and region, study period, number of participants, gender, exposure measurement, covariates adjusted RR or HR and the corresponding 95% CI, as well as numbers of cases and person-years or persons for each category of fish consumption. We used the risk estimates that derived from the multivariable-adjusted model that did not include the potential intermediates (such as, blood glucose, triglyceride or inflammatory biomarkers) on the causal pathway from exposure to disease in original studies, because control for an intermediate variable would bring overadjustment bias.[29] Data extraction was implemented independently by two authors. Any inconsistency was solved by the third author (YY).

In order to perform a dose–response analysis, when fish consumption was measured as 'servings per week', we converted this into '*gram per day*'

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as a standard measure of fish intake according to the information provided by the identified study.[24] For each category, we assigned the median value of each fish category. If the upper bound in the highest category was not available, we assumed that it had the same amplitude as the preceding one. If the distribution of cases or person-years in the study was not reported, we estimated the distribution using the methods described by Aune *et al*.[30]

Statistical analysis

We conducted two types of meta-analyses. First, we combined the RRs for the highest versus lowest category of fish consumption on risk of all-cause mortality by using the DerSimonian and Laird random-effects model, which incorporated both within- and between-study variability.[31,32]

Second, for the dose–response meta-analysis, the method proposed by Greenland and Longnecker[33] and Orsini *et al*.[34] was used to calculate the trend from the correlated log-relative risks across categories of fish consumption. In order to avoid bias estimates, we centered each study to the baseline reference of fish intake.[35] Potential nonlinear relation was tested by modeling fish intake using restricted cubic splines with three knots at fixed percentiles (10, 50 and 90%) of the distribution.[32,34] A *P*-value for nonlinearity of the meta-analysis was evaluated by testing the null hypothesis that the coefficient of the second spline was equal to zero.[36]

Heterogeneity among studies was evaluated by using the *Q* and I^2 statistics. I^2 took values between 0 and 100% and there may be important heterogeneity when $I^2 > 50\%$ or *P* for *Q* statistic < 0.10.[37] In a sensitivity analysis, we sequentially omitted one study at a time from the meta-analysis to examine whether the main results were influenced by a particular study. In order to test the robustness of the combined estimates, separate meta-analysis was performed stratified by gender (men or women), region (USA, Asia or Europe), methods of dietary assessment (validated food frequency questionnaire (FFQ) or others), sample size (using 40 000 participants as the cut point), follow-up duration (using 12 years as the cut point), year of publication (before 2008 or after 2008) and important confounding adjustments (yes or no) for education, body mass index, physical activity, intake of fruit and vegetables, red meat and total energy. Small study bias (for example, publication bias) was assessed through visual inspection of funnel plots and using Egger's[38] and Begg's tests.[39] $P < 0.10$ was deemed to possess publication bias.

All statistical analyses were conducted using STATA software (version 12.0; StataCorp, College Station, TX, USA). *P*-values with two side of < 0.05 were considered statistically significant if not specified.

RESULTS

Literature search and study characteristics

We obtained 2605 articles after removal of duplicates from our preliminary search. After screening the title and abstract, 2564 records were excluded using the general criteria, such as review, animal research and retrospective study. Forty articles were potentially related to our issue for further scrutiny, of which 29 articles were excluded according to the inclusion criteria. With one study[19] obtained from checking reference lists, thus twelve studies[13,15,19–28] were included in the meta-analysis (Figure 1). Takata *et al*.[20] reported the results of Shanghai Women Health Study (SWHS) and the Shanghai Men Health Study (SMHS), whereas the SWHS was updated by a pooled cohort study[13] including eight cohorts in Asia. Then, we only abstracted the data of the SMHS from this study[20] in meta-analysis of highest versus lowest category.

Of the twelve identified studies (Table 1), the median follow-up time was 12 years. Combined, these studies included 672 389 cohort members and 57 641 deaths. Six studies[15,19,24,26–28] were conducted in the United States, four[13,20,22,25] in Asia and two[21,23] in Europe. Most studies[13,15,19–22,24–27] used a structured FFQ to estimate fish intake. All studies adjusted for age and gender as potential confounders (if applicable). Only one study[23] failed to adjust for smoking status and alcohol drinking.

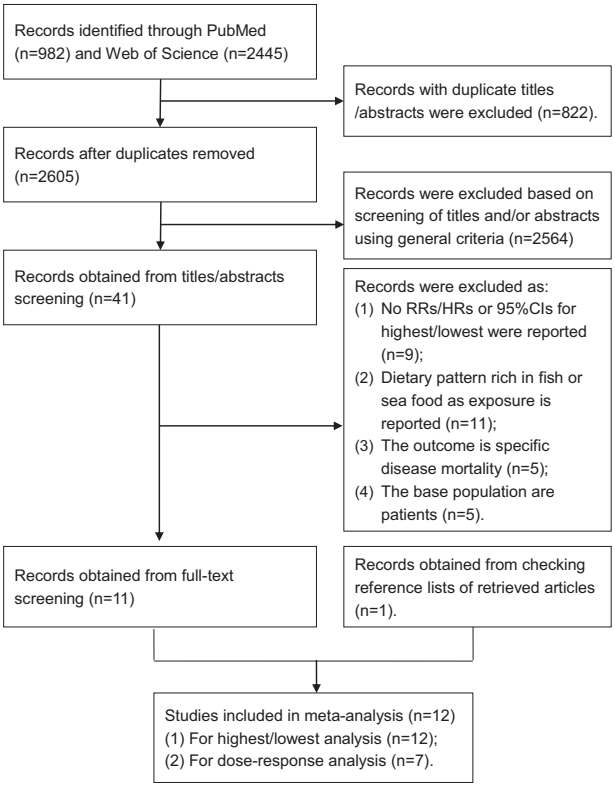

Figure 1. Flow diagram for selection of studies in meta-analysis of fish consumption and all-cause mortality. RR, relative risk; HR, hazard ratio; CI, confidence interval.

Highest versus lowest category

Overall, analysis of 12 prospective studies significantly showed a 6% reduction in risk of all-cause mortality with high intake of fish (RR = 0.94, 95% CI: 0.90, 0.98) with moderate evidence of between-study heterogeneity ($I^2 = 39.1\%$, $P = 0.06$) using a random-effects model (Figure 2). Visual inspection of Begg's test and Egger's test suggested that there was no publication bias (Begg's test: $P = 0.26$; Egger's test: $P = 0.14$).

Sensitivity analysis and subgroup analysis

In sensitivity analysis, we recalculated the combined results by sequentially excluding each study to examine the influence of individual study on the pooled estimate. The risk estimates ranged from 0.92 (95% CI: 0.89, 0.95; $I^2 = 0.0\%$, $P = 0.462$), after excluding Olsen,[21] to 0.95 (95% CI: 0.90, 0.99; $I^2 = 37.4\%$, $P = 0.072$), after excluding Bell.[15] None of the studies considerably affected the summary results.

Subgroup analysis was performed across a number of key study characteristics (Table 2). The pooled RRs did not materially differ between genders. A lower risk was observed in the United States, whereas no association was found in Europe. There was a significantly inverse association in studies published after 2008. Stratifications by other characteristics did not have a substantial impact on the main results.

Dose–response meta-analysis

Although we had contacted with the authors for more detailed information, five studies were excluded from dose–response analysis because only two categories of fish consumption were considered,[21] or no information was provided regarding the amount of fish intake in each category.[13,15,19,26]

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Table 1. General characteristics of prospective studies of fish consumption and all-cause mortality

ID	First author (reference no.)	Country	Follow-up years	Populations	Cohort size	No. of deaths	Dietary assessment method	Quantity	Sex	Adjustment
1	Bell[15]	USA	5	Mixed: main white (93.3%)	70 495	3051	FFQ with 120 items	>42 versus 0 times per year	Both	Age, sex, race/ethnicity, marital status, education, total energy intake, BMI at age 45 years, average alcohol intake at age 45 years, average physical activity in the 10 years before baseline, self-rated health, mammogram in the last 2 years, prostate-specific antigen test in the last 2 years, sigmoidoscopy in the last 10 years, current use of cholesterol-lowering medication, aspirin use in the past 10 years, use of nonaspirin nonsteroidal anti-inflammatory drugs in the past 10 years, smoking, morbidity score, percentage of calories derived from trans fat, percentage of calories derived from saturated fat, number of servings per day of fruits, number of servings per day of vegetables, years of estrogen therapy, years of estrogen+progestin therapy, age at menopause, age at death of father, and age at death of mother.
2	Kappeler[19]	USA	22	Mixed: main non-hispanic white (76.5%)	17 611	3683 (1908 men and 1775 women)	FFQ with 81 items	>9 versus 0 times per month	Both	Age, race, sex, cigarette smoking, alcohol consumption, physical activity, socioeconomic status, BMI, marital status, fruit and vegetables intake, history of hypertension, diabetes, hypercholesterolemia, use of aspirin and ibuprofen, use of mineral and vitamin supplements, family history of diabetes or hypercholesterolemia; hormone replacement therapy and oral contraceptive use (in women).
3	Lee[13]	Asia	6.6–15.6	NA	296 721 (112 310 men and 184 411 women)	24 283 (14 326 men and 9957 women)	FFQ	Q4 versus Q1: mean = 36.6 6 ± 37.2 g per day	Both	Age, BMI, education, smoking habit, rural/urban residence, alcohol intake, fruit and vegetable intake and total energy intake.
4	Takata[20]	China	5.6	Chinese	73 159	2170	FFQ	121.9 versus 11.1 g per day	Men	Age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history and alcohol consumption.
5	Olsen[21]	Denmark	12	Danes	50 290 (23 274 men and 27 016 women)	4126 (2383 men and 1743 women)	FFQ with 192 items	Men: ⩾41 versus <41 g per day. Women: ⩾35 versus <35 g per day	Both	Age, time under study, smoking status, smoking duration, current tobacco consumption, time since cessation, alcohol intake, school education, participation in sports, time spent on sports per week, BMI, intake of red meat, intake of processed meat intake, total energy intake and other dietary components.
6	Yamagishi[22]	Japan	12.7	Japanese	57 972 (22 881 men and 35 091 women	7008	FFQ with 33 items	Men: 86 versus <19 g per day. Women: ⩾84 versus <19 g per day	Both	Age, gender, energy, history of hypertension and diabetes mellitus, smoking status, alcohol consumption, BMI, mental stress, walking, sports, education levels, total energy, and dietary intakes of cholesterol, saturated and n-6 polyunsaturated fatty acids, vegetables and fruit.
7	Ness[23]	UK	37	British	4028 (1995 men and 2033 women)	1010	The food records	44.5 versus 1.8 g per day	Both	Age, sex, energy, childhood family food expenditure, father's social class, district of residence as a child, period of birth, season when studied as a child and Townsend score for current address or place of death.

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Table 1. (Continued)

ID	First author (reference no.)	Country	Follow-up years	Populations	Cohort size	No. of deaths	Dietary assessment method	Quantity	Sex	Adjustment
8	Folsom[24]	USA	10.5	USA post-menopausal women	41 836	4653	FFQ with 127 items	>2.5 versus <0.5 serving per day	Women	Age, energy intake, educational level, physical activity level, alcohol consumption, smoking status, pack-years of cigarette smoking, age at first livebirth, estrogen use, vitamin use, BMI, waist/hip ratio, diabetes, hypertension, intake of whole grains, fruit and vegetables, red meat, cholesterol and saturated fat.
9	Nagata[25]	Japan	6.9	Japanese	29 079 (13 355 men and 15 724 women)	2062 (1163 men and 899 women)	FFQ with 169 items	Men: 157.8 versus 46.2 g per day. Women: 122.4 versus 36.6 g per day	Both	For men: age, total energy, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes mellitus. For women: age, total energy, marital status, years of education, BMI, smoking status, alcohol intake, age at menarche, menopausal status, exercise and history of diabetes mellitus.
10	Gillum[26]	USA	18.8	Mixed: main white (84.1%)	8825	2901 (1513 men and 1388 women)	3-month FFQ	>1 times per week versus never	Both	Baseline age, smoking, history of diabetes, education, high school graduate, systolic blood pressure, serum cholesterol concentration, BMI, alcohol intake and physical activity.
11	Albert[27]	USA	11	US male physicians	20 551	1652	FFQ	⩾5 times per week versus ⩽1 time per month	Men	Age, aspirin and beta carotene treatment assignment, evidence of cardiovascular disease before 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, vigorous exercise, and vitamin E, vitamin C, multivitamin use, other dietary factors (red meat, vegetables, fruits, dairy, chicken or turkey and fried foods).
12	Daviglus[28]	USA	25.8	Chicago men	1822	1042	Standard questionnaires	⩾35 versus 0 g per day	Men	Baseline age, education, religion, systolic pressure, serum cholesterol, number of cigarettes smoked per day, BMI, presence or absence of diabetes, presence or absence of electrocardiographic abnormalities, daily intake of energy, cholesterol, saturated, monounsaturated, fatty acids, total protein, carbohydrate, alcohol, iron, thiamine, riboflavin, niacin, vitamin C, beta carotene and retinol.

Abbreviations: BMI, body mass index; FFQ, food frequency questionnaire.

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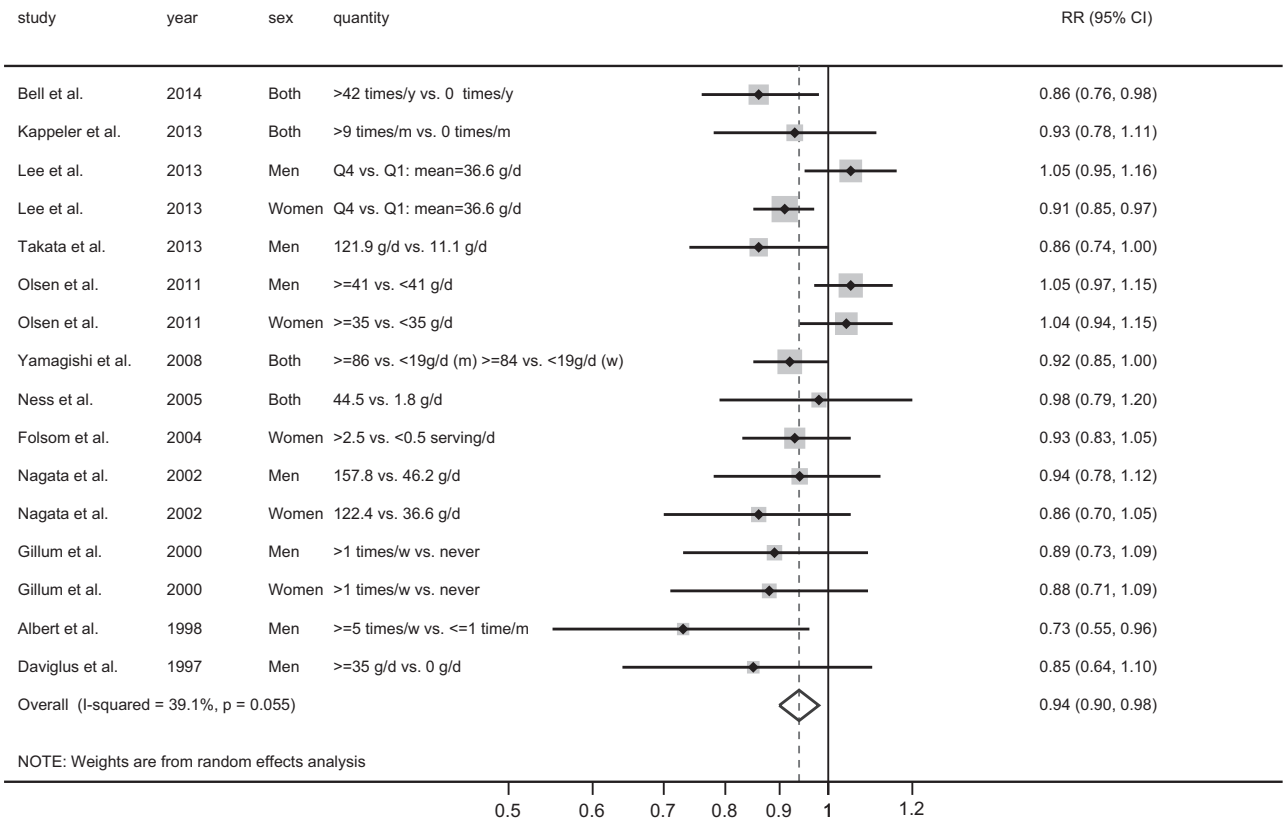

Figure 2. Relative risk of all-cause mortality for highest versus lowest category of fish intake. Overall relative risk calculated with random effects model.

We observed a significantly nonlinear relationship ($P = 0.020$) between fish consumption and all-cause mortality in seven studies (Figure 3). With the increase in fish consumption, risk estimates showed a sharp decline and then leveled off. Compared with the reference group (0 g per day), the RR reached a lowest point at ~60–80 g per day. The selection of different numbers and positions of knots did not significantly change these results.

DISCUSSIONS

To our knowledge, this is the first meta-analysis to quantitatively assess the association between fish consumption and all-cause mortality from prospective cohort studies, which indicated that a higher intake of fish was associated with about a 6% significantly lower risk of all-cause mortality. Results from the dose–response meta-analysis suggested that fish consumption was associated with all-cause mortality in a nonlinear manner with a steeper decrease in all-cause mortality at intakes below ~60 g per day. No publication bias was detected in our study.

Findings from the present meta-analysis are consistent with previous meta-analysis on fish consumption associated with the mortality of major chronic diseases, including cardiovascular disease and cancer. A meta-analysis of 17 prospective cohort studies indicated that every 15 g per day increment of fish intake decreased the risk of CHD mortality by 6% (RR = 0.94, 95% CI: 0.90, 0.98).[14] Numbers of studies found that fish consumption decreased the mortality of specific cancers, such as colorectal,[40] lung[41] and prostate cancers.[42]

It is biologically plausible that fish consumption is associated with all-cause mortality. First, n-3 PUFAs are particularly rich in fish. Mozaffarian and Rimm[43] conducted a meta-analysis of 15 randomized controlled trials and found that marine n-3 PUFAs reduced total mortality by 17% (pooled RR = 0.83, 95% CI: 0.68, 1.00; $P = 0.046$). Multiple mechanisms of n-3 PUFAs are involved in this chemopreventive activity, including cell growth inhibition and enhanced apoptosis, suppression of neoplastic transformation and antiangiogenicity.[16,44] In addition, it could be attributed to a wider array of nutrients that are abundant in fish, such as vitamins,[45,46] essential amino acids[47,48] and trace elements.[49,50] Third, higher fish consumption may simply be an indicator of a healthier dietary pattern or higher socioeconomic status, which is associated with a better medical care and a lower mortality.[51,52]

Three studies were excluded because they provided risk estimates using moderate fish consumption (third or fourth quintile) as reference. However, we could not calculate risk estimates using the information available. In two European studies,[53,54] no association was seen for higher fish consumption and all-cause mortality when compared with moderate fish intake. However, there seemed to be a U-shaped trend for fatty fish consumption on risk of total mortality.[53] Another study[55] was conducted in Japan and reported that a RR of 0.99 (95% CI: 0.77, 1.27) for all-cause mortality for subjects who ate fish more than twice a day compared with those who ate it only one or two times per week.

With moderate significant heterogeneity found, there are some reasons to explain the inconsistency between studies. First, in sensitivity analysis, we found that the risk estimates were different between locations, which may reflect racial disparities. Second, even though the consumption of fish for almost all studies was measured by a structured FFQ, various kinds of fish and cooking methods may have different effects. Different fish have different nutritional profiles and biological effects, one obvious example

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Table 2. Pooled relative risks for the highest compared with the lowest fish consumption and all-cause mortality

Subgroups	n	*RR*	*95% CI*	I^2 *(%)*	P-*value*
All studies	12	0.94	0.90, 0.98	39.1	0.055
Gender					
Male	8	0.93	0.85, 1.01	55.0	0.030
Female	6	0.94	0.89, 1.00	21.5	0.272
Region					
USA	6	0.89	0.83, 0.95	0.0	0.795
Asia	4	0.93	0.88, 0.99	35.7	0.169
Europe	2	1.04	0.98, 1.11	0.0	0.836
Validated FFQ					
Yes	4	0.92	0.86, 0.99	45.1	0.105
No	8	0.95	0.90, 1.01	34.9	0.129
Year of publication					
< 2008	6	0.96	0.90, 1.01	61.9	0.010
2008+	6	0.90	0.84, 0.96	0.0	0.809
Sample size					
< 40 000	6	0.89	0.83, 0.96	0.0	0.829
40 000+	6	0.96	0.90, 1.01	62.2	0.010
Duration of follow-up					
< 12 year	6	0.91	0.86, 0.97	40.9	0.106
12+	6	0.97	0.92, 1.03	25.4	0.226
Major confounders adjusted					
Education					
Yes	8	0.95	0.90, 0.99	50.5	0.027
No	4	0.90	0.83, 0.99	0.0	0.501
Body mass index					
Yes	10	0.94	0.90, 0.99	43.3	0.042
No	2	0.90	0.80, 1.02	0.0	0.320
Physical activity					
Yes	9	0.93	0.88, 0.98	40.2	0.073
No	3	0.96	0.87, 1.05	51.8	0.101
Energy					
Yes	9	0.95	0.91, 0.99	45.8	0.041
No	3	0.88	0.79, 0.97	0.0	0.549
Red meat intake					
Yes	4	0.95	0.86, 1.05	66.0	0.019
No	8	0.93	0.89,0.96	0.0	0.509
Smoking and drinking					
Yes	11	0.94	0.90, 0.98	42.9	0.040
No	1	0.98	0.80, 1.21	—	—
Fruit and vegetables intake					
Yes	8	0.95	0.89, 1.00	59.3	0.008
No	4	0.90	0.83, 0.98	0.0	0.938

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; RR, relative risk. I^2, measure of heterogeneity; *P*, *P*-value for heterogeneity.

being white fish and fatty fish. This inaccurate classification of fish may lead to potential poor allocation of nutrient composition to food, which may attenuate the associations. Furthermore, the mortality of population from different country varied considerably, and these differences between each study may reflect a different constituent ratio of cause from cardiovascular diseases, cancers or other diseases.

The present study has a number of strengths, such as large sample sizes (57 641 deaths among 672 389 individuals), follow-up duration of at least 5 years and prospective cohort design. Furthermore, our findings were stable and robust in subgroups and sensitivity analyses.

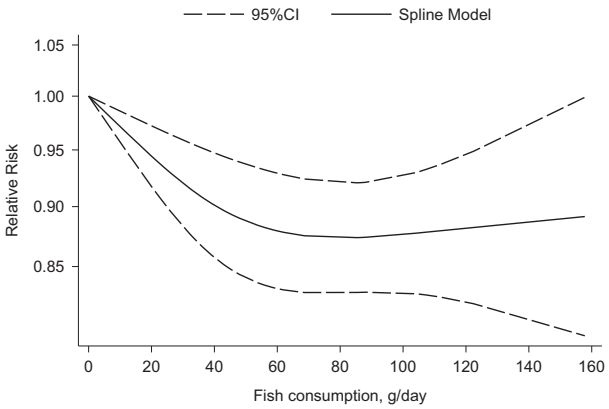

Figure 3. Relative risks of all-cause mortality associated with fish consumption (from seven studies). Fish consumption was modeled with restricted cubic splines in a fixed-effects dose–response model. The *P*-values for nonlinearity were 0.020 for fish consumption. Compared with the reference group (0 g per day), the RR is 0.94 (95% CI: 0.92, 0.97), 0.90 (95% CI: 0.86, 0.95), 0.88 (95% CI: 0.83, 0.93), 0.88 (95% CI: 0.84, 0.92), 0.89 (95% CI: 0.84, 0.94) and 0.89 (95% CI: 0.83, 0.96) for 20, 40, 60, 80, 100 and 120 g per day, respectively. RR, relative risks; CI, confidence interval.

Our study also has several limitations. First, the pooled results may be biased by residual confounding that is inherent in the original studies.[56] Second, although our major interest was all-cause mortality, we ought to further infer which causes of death were responsible for the associations we observed.[57] Effects on total mortality in a population would therefore depend on the proportion of deaths due to CHD. However, data are lacking from the retrieved studies to conduct a subgroup analysis of cause-specific mortality. Third, we have not performed subgroup analysis according to fish type (fresh fish and processed fish, fatty fish and non-fatty fish), because of the lack of information available from original studies. Finally, because of this meta-analysis only including published studies, the conclusion should be made with caution.

In conclusion, there is an inverse association between fish consumption and all-cause mortality. According to the dose–response analysis, intake of at least 60 g per day fish should be recommended. Potential public health benefits may exist based on the observation that increased dietary fish intake was associated with a decreased risk of all-cause mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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