Original Article

Fish, long chain omega-3 polyunsaturated fatty acids consumption, and risk of all-cause mortality: a systematic review and dose-response meta-analysis from 23 independent prospective cohort studies

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Background and Objectives: The consumption of fish and long chain omega-3 polyunsaturated fatty acids (n-3 PUFA) may influence the risk of all-cause mortality, but the findings have been inconsistent. The current systematic review and meta-analysis is to clarify the association between fish and long chain n-3 PUFA consumption with risk of all-cause mortality. **Methods and Study Design:** Studies published before March 2017 were identified through electronic searches using PubMed, Scopus and Web of Science database. We included prospective cohort studies that reported relative risks with 95% CI of all-cause mortality for fish and long chain n-3 PUFA consumption. Results were combined using a random effects model. **Results:** Twenty-three prospective cohorts with a total of 1,035,416 participants were included. Twenty-two pooled studies involving 985,126 participants indicated that fish intake was associated with 6% (RR: 0.94; 95% CI: 0.90, 0.98) reduction in risk of all-cause mortality. Six studies with 430,579 participants investigated the association between long chain n-3 PUFA and all-cause mortality risk, the relative risk for highest versus lowest category was 0.86 (95% CI: 0.80, 0.93). Dose-response analysis suggested that the risk of all-cause mortality was reduced by 7% (RR: 0.93; 95% CI: 0.88, 0.99) for every 0.2 g per day increment in long chain n-3 PUFA consumption. **Conclusions:** Current meta-analysis indicates that both fish and long chain n-3 PUFA consumption are inversely associated with risk of all-cause mortality. These findings could have public health implications with regard to lowering risk of all-cause mortality through dietary interventions.

Key Words: fish, long chain n-3 PUFA, all-cause mortality, dose-response, meta-analysis

INTRODUCTION

Since compelling epidemiological studies have demonstrated low coronary heart disease (CHD) mortality may be attributed to high fish consumption, fish has been considered one of the key components of a cardioprotective diet.[1,2] Current AHA (American Heart Association) guidelines for the general population recommends consumption of fish (especially fatty types) at least twice a week.[3] An ecological study, covering 36 countries, found significant inverse associations between fish consumption and all-cause mortality, ischemic heart disease, and stroke.[4] Fish and fish oils are the most common dietary sources of long chain omega-3 polyunsaturated fatty acids (n-3 PUFA), primarily including eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (DPA, 22:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). Evidence shows that regular consumption of EPA and DHA as supplements may reduce arrhythmias, endothelial dysfunction, circulating triglyceride levels, and inflammation.[5] It is likely that long chain n-3 PUFA in fish are the key components responsible for cardiovascular disease (CVD) prevention, the leading cause of morbidity and mortality.[6]

While fish contains long chain n-3 PUFA and other nutrients, it may also contain contaminants.[7] Some studies have reported no beneficial association between fish consumption and risk of all-cause mortality.[8,9] It has been speculated that the hypothesized adverse effects of contaminants or inadequate adjustment for confounding factors may account for the discordant results from epidemiological studies. A meta-analysis including 12 cohorts briefly reported the inverse association between fish consumption and risk of all-cause mortality by quantitatively summarizing part of the existing literature on this topic.[10] However, a recently published meta-analysis of 19 clinical trials suggested that n-3 PUFA supplementation does

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Manuscript received 17 February 2017. Initial review completed and revision accepted 26 June 2017.
doi: 10.6133/apjcn.072017.01

not have a positive effect on lowering all-cause mortality risk.[11] Whether, or to what extent, consumption of fish and long chain n-3 PUFA could specifically reduce the risk of all-cause mortality remains unclear.

Therefore, to provide a comprehensive assessment of the overall association between consumption of fish and long chain n-3 PUFA and all-cause mortality risk, we performed a systematic review and dose-response meta-analysis by summarizing and evaluating all the relevant prospective cohort studies in the existing literature.

METHODS

Search strategy and selection criteria

We identified relevant prospective cohort studies published in English language journals that reported the association between fish consumption or long chain n-3 PUFA with all-cause mortality risk before March 2017 by primarily searching PubMed supplemented by Web of Science and Scopus using the terms "fat", "fatty acid", "docosahexaenoic acid", "eicosapentaenoic acid", "docosapentaenoic acid", "fish", "fish oil" or "seafood" in combination with "mortality" or "death". Full details of the search strategy are shown in Supplementary table 1. Furthermore, the references of retrieved relevant articles were reviewed for more information.

Two investigators (YW and ZJ) independently conducted the literature search, identified potential studies, and extracted relevant information using a predesigned data abstraction form. Discrepancies were resolved through group discussion with a third investigator (DL). We considered prospective cohort studies to be eligible for inclusion if they were based on general healthy populations; the exposure of interest was consumption of any type of fish or dietary long chain n-3 PUFA; the endpoint of interest was total death or all-cause mortality; the risk estimate with corresponding 95% CI of all-cause mortality was reported for n-3 PUFA exposure or fish intake or such information could be recalculated based on the available information in the primary studies; the follow-up years was more than 5 years; and the reference group was the lowest fish intake group.

Data extraction and quality assessment

From each identified article, we extracted the first author's name, country, follow-up years, gender, age of participants, number of cases and participants, exposure assessment and categories, adjusted relative risk with corresponding 95% CI for each category of fish or long chain n-3 PUFA intake, and covariates. We extracted the risk estimate with the most adjustment.

The amount of fish consumption (g/day) was estimated by multiplying the frequency of consumption (serving/day) by the corresponding portion size (g/serving). If there was no portion size description, we deemed it to be 105 g/serving according to He et al.[12] The median or mean amount of fish consumption in each category was used for the dose-response analysis. The midpoint of upper and lower boundaries was considered as the dose of each category if the study reported only the range of fish consumption. If the highest category was open-ended, we assigned the lower end value of the category multiplied by 1.5, and 2 servings/day was considered to be the max upper limit for fish intake. If the lowest boundary was open, we assigned the higher end value of the category multiplied by 0.5. We defined "<1 serving/week", "1-3 servings/week", ">3 servings/week" as low, moderate and high amounts of fish consumption, respectively.

Quality assessment was performed based on the Newcastle-Ottawa criteria for non-randomized studies. A maximum of 9 points was assigned to each study (9 representing the highest quality): 4 for selection, 2 for comparability, and 3 for assessment of outcomes.

Statistical analysis

Relative risk was used for risk estimate, and hazard ratios in cohort studies were treated as relative risks directly. Log transformed relative risk and its corresponding 95% CI from each included study was used for the present meta-analysis. As different studies might report different exposure categories (dichotomous, thirds, quarters, or fifths), we used the study specific relative risk for the highest versus lowest category of fish or long chain n-3 PUFA consumption for the meta-analysis. We then combined the relative risk from each study, weighted by the inverse of their variance, with the DerSimonian and Laird random effects model, which takes variation both within and between studies into consideration.[13] One study used the data from Shanghai Women Health Study (SWHS) and the Shanghai Men Health Study (SMHS),[14] while the SWHS was updated by Lee et al.[15] Thus, we only abstracted the data of male subjects from this article for highest versus lowest category. For studies that reported a relative risk for men and women or different races separately,[8,16,17] we pooled these relative risks to represent the relative risk of fish consumption in these studies. For studies that did not report a relative risk for long chain n-3 PUFA but reported risks for EPA, DHA or DPA separately,[18] we pooled these relative risks for long chain n-3 PUFA exposure.

We estimated the pooled relative risk between the highest versus the lowest category of fish, long chain n-3 PUFA intake, separately. Dose-response analysis was carried out for the trend estimation using generalized least squares regression (two stage GLST in Stata).[19] For studies without information on the number of cases, or person years for exposure categories, we used variance weighted least squares regression for the dose-response estimation. Studies with fewer than three exposure categories were excluded from the dose-response analysis. One study had a relatively high reference category of fish consumption when compared with other studies, thus we excluded this article from trend estimation for fish consumption and risk of all-cause mortality.[16] To estimate a potential curve linear association between intake of fish and long chain n-3 PUFA, and risk of all-cause mortality, we used a restricted cubic spline model (three knots).

Study heterogeneity was quantified by I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity. Furthermore, we performed subgroup analysis to examine potential sources of study heterogeneity according to country, gender, follow-up years and the influence of potential residual confounding factors, such as body mass index (BMI), total energy, education, smoking status, and alcohol intake.

Sensitivity analysis was conducted by omitting one study at a time to test if the results were driven by any single study and evaluated the influence of each individual study on the overall relative risk. Publication bias was detected by Begg's rank correlation test and Egger's linear regression test. Stata version 12 (StataCorp LP, College Station, TX, USA) was used for all the statistical analyses.

RESULTS

Study selection and characteristics

The search strategy identified 9448 unique citations after removing duplications. After initial screening based on titles and abstracts, 65 articles remained for further evaluation. In the full-text stage, 42 studies were excluded after applying our exclusion criteria (Supplementary table 2). Overall, we identified 23 eligible publications, which included 79,276 cases of all-cause mortality and 1,035,416 participants (Figure 1).

Characteristics of the 23 eligible articles are shown in Table 1 and covariates adjusted in these studies are shown in Supplementary table 3. Among these studies, 12 were conducted in the United States, 6 in European countries[8,20-24] and 5 in Asia.[14,15,16,25,26] Twenty-two articles[14-17,20-24,26-36] described the association between fish intake and risk of all-cause mortality, and 6 articles[14,16,31,35-37] described the association between long chain n-3 PUFA intake and all-cause mortality risk. Two studies included only women,[31,32] and 1 included only men.[30] One study pooled 8 Asian prospective cohort studies from Bangladesh, China, Japan, Korea, and Taiwan, consisting of 112,310 men and 184,411 women with mean follow-up ranging from 6.6 to 15.6 years.[14] Another study used extremely high reference group of fish and long chain n-3 PUFA intake, and thus this article was excluded from the dose-response analysis.[16] The average score for the quality assessment of included studies was 7.7, and the score for all the studies was 5 or above (Supplementary table 4).

Fish consumption and risk of all-cause mortality

Twenty-two articles from 22 independent cohorts showed an inverse association between fish consumption and risk of all-cause mortality, totaling 75,150 all-cause mortality events and 985,126 participants. For all 22 studies, the relative risk when comparing participants in the highest with the lowest category of fish intake was 0.94 (95% CI: 0.90, 0.98) (Figure 2). There was moderate heterogeneity (I^2=50.2%). No publication bias was observed from the Begg's rank correlation test (p=0.26) or Egger's linear regression test (p=0.14).

Ten articles were included in the dose-response analysis, including 25,871 cases of all-cause mortality and 399,668 participants. We found a curvilinear association between fish intake and all-cause mortality risk (p for non-linearity was 0.005) (Figure 3).

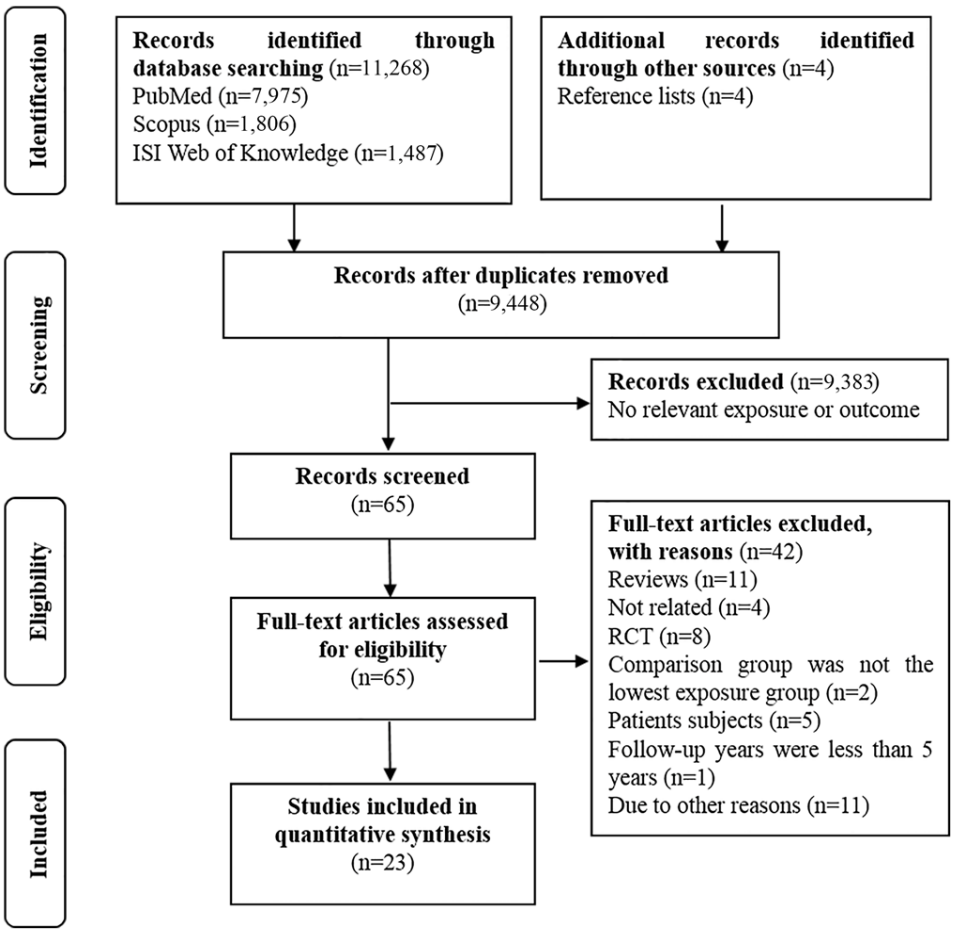

Figure 1. Flow diagram for selection of studies included in the meta-analysis of consumption of fish and long chain n-3 PUFA and all-cause mortality risk.

Table 1. Characteristic of cohort studies included in the meta-analysis of consumption of fish and long chain n-3 PUFA and all-cause mortality risk

Study	Country	Follow-up years	Sex	Age, year	Cases/Participants	Exposure assessment	Exposure type	Exposure categories	Adjusted relative risk
Kahn et al, 1984[27]	US	21	Both	≥30	247/27530	Diet, Semi-FFQ (times/week)	Fish	Highest: ≥1; Reference: never	1.14 (1.00, 1.28)
Daviglus et al, 1997[29]	US	30	Men	40-55	1042/1822	Validated-FFQ (g/day)	Fish	Highest: ≥34 Reference: 0	0.85 (0.64, 1.10)
Mann et al, 1997[20]	UK	13.3	Both	16-79	392/10802	Validated-FFQ (times/week)	Fish	Highest: ≥1; Reference: never	0.96 (0.76, 1.21)
Fraser et al, 1997[28]	US	12	Both	≥84	1387/34198	Validated-FFQ (times/week)	Fish	Highest: <1 Reference: ≥1	0.98 (0.76, 1.24)
Albert et al, 1998[30]	US	11	Men	40-84	1652/20551	Interview (times/week)	Fish	Highest: ≥5 Reference: <0.25	0.73 (0.55, 0.96)
Gillum et al, 2000[17]	US	18.8	Both	25-74	2901/8825	Interview (times/week)	Fish	• Highest: >1 Reference: never • Highest: >1 Reference: never	• Men: 0.89 (0.73, 1.09) • Women: 0.89 (0.71, 1.11)
Yuan et al, 2001[25]	China	12	Men	45-64	2134/18244	Validated-FFQ (times/week)	Fish	Highest: ≥200 Reference: 50	0.79 (0.69, 0.91)
Nagata et al, 2002[16]	Japan	7	Both	≥35	2062/29079	Semi-FFQ (g/day)	• Fish • Long chain n-3 PUFA	• Highest: 157.8 Reference: 46.2 • Highest: 122.4 Reference: 36.6 • Highest: 1.582 Reference: 0.41 • Highest: 1.253 Reference: 0.332	• Men: 0.94 (0.78, 1.12) • Women: 0.86 (0.70, 1.05) • Men: 0.87 (0.73, 1.05) • Women: 0.77 (0.62, 0.94)
Folsom et al, 2004[31]	US	15	Women	55-69	4653/41936	Validated-FFQ (times/week) (g/day)	• Fish • Long chain n-3 PUFA	• Highest: ≥2.5 Reference: <0.5 • Highest: 0.47 Reference: 0.02	• 0.93 (0.83, 1.05) • 0.96 (0.86, 1.06)
Ness et al, 2005[21]	UK	37	Both	7.5	1010/4028	Dietary history (g/day)	Fish	Highest: 44.5 Reference: 1.8	0.98 (0.79, 1.20)
Kelemen et al, 2005[32]	US	15	Women	55-69	3978/ 99826	Semi-FFQ	Fish	Highest vs lowest	0.97 (0.86, 1.09)
Knoops et al, 2006[22]	Europe	10	Both	79-90	1382/ 3117	Dietary history	Fish	Highest: <median Reference: ≥median	0.89 (0.82, 0.97)
Yamagishi et al, 2008[26]	Japan	12.7	Both	40-79	7008/57972	Semi-FFQ (g/day)	Fish	Highest: 72-229 Reference: 27-39	0.92 (0.85, 1.00)

FFQ: food frequency questionnaire; Semi-FFQ: semi-quantitative-food frequency questionnaire.

Table 1. Characteristic of cohort studies included in the meta-analysis of consumption of fish and long chain n-3 PUFA and all-cause mortality risk (cont.)

Study	Country	Follow-up years	Sex	Age, year	Cases/ Participants	Exposure assessment	Exposure type	Exposure categories	Adjusted relative risk
Trichopoulou et al, 2009[9]	Greece	8.5	Both	20-86	652/23349	Validated-FFQ	Fish	Highest: <median Reference: ≥median	1.08 (0.95, 1.22)
Tomasallo et al, 2010[33]	US	12	Both	32-63	342/3847	Interview (times/week)	Fish	Captains: • Highest: ≥1 Reference: 0-0.25 Referents: • Highest: ≥1 Reference: 0-0.25	• 1 (0.63, 1.58) • 0.6 (0.38, 0.95)
Pocobelli et al, 2010[37]	US	10	Both	50-76	3577/77673	Semi-FFQ (times/week)	Long chain n-3 PUFA	Highest: ≥3 Reference: none	0.83 (0.70, 1.00)
Tognon et al, 2011[24]	Gotherburg	8.5	Both	≥70	630/ 1037	Dietary history	Fish	Highest vs lowest	0.96 (0.82, 1.13)
Olsen et al, 2011[8]	Denmark	12	Both	50-64	4126/50290	Validated-FFQ	Fish	• Highest: <median Reference: ≥median • Highest: <median Reference: ≥median	• Men: 1.05 (0.97, 1.15) • Women: 1.04 (0.94, 1.15)
Takata et al, 2013[14]	China	• Women: 11.2 • Men: 5.6	Both	40-74	5836/134296	Validated-FFQ (g/day)	• Fish • DHA • EPA	• Highest: 106.2 Reference: 10.60 • Highest: 0.15 Reference: 0.0085 • Highest: 0.065 Reference: 0.005	• 0.84 (0.76, 0.92) • 0.78 (0.71, 0.86) • 0.79 (0.72, 0.87)
Kappeler et al, 2013[34]	US	22	Both	32-46	3683/17611	Semi-FFQ (times/week)	Fish	Highest: ≥9 Reference: 0	0.93 (0.78, 1.11)
Lee et al, 2013[15]	Asia	6.6-15.6	Both		24283/296721	Validated-FFQ (g/day)	Fish	Highest: quintiles 4 Reference: quintiles 1	0.97 (0.85, 1.12)
Bell et al, 2014[35]	US	6	Both	50-76	3051/70495	Semi-FFQ (times/y) (g/day) (g/day)	• Fish • DHA • EPA	• Highest: >42 Reference: 0 • Highest: >0.207 Reference: 0-0.054 • Highest: >0.112 Reference: 0-0.027	• 0.86 (0.76, 0.98) • 0.86 (0.77, 0.97) • 0.88 (0.79, 0.99)
Villegas et al, 2015[36]	US	5.5	Both	40-79	6914/77100	Validated-FFQ (g/day)	• Fish • Long chain n-3 PUFA	• Highest: 108.66 Reference:4.98 • Highest: 0.36 Reference: 0.02	• 0.92 (0.84, 1.00) • 0.94 (0.86, 1.03)

FFQ, food frequency questionnaire; Semi-FFQ, semi-quantitative-food frequency questionnaire

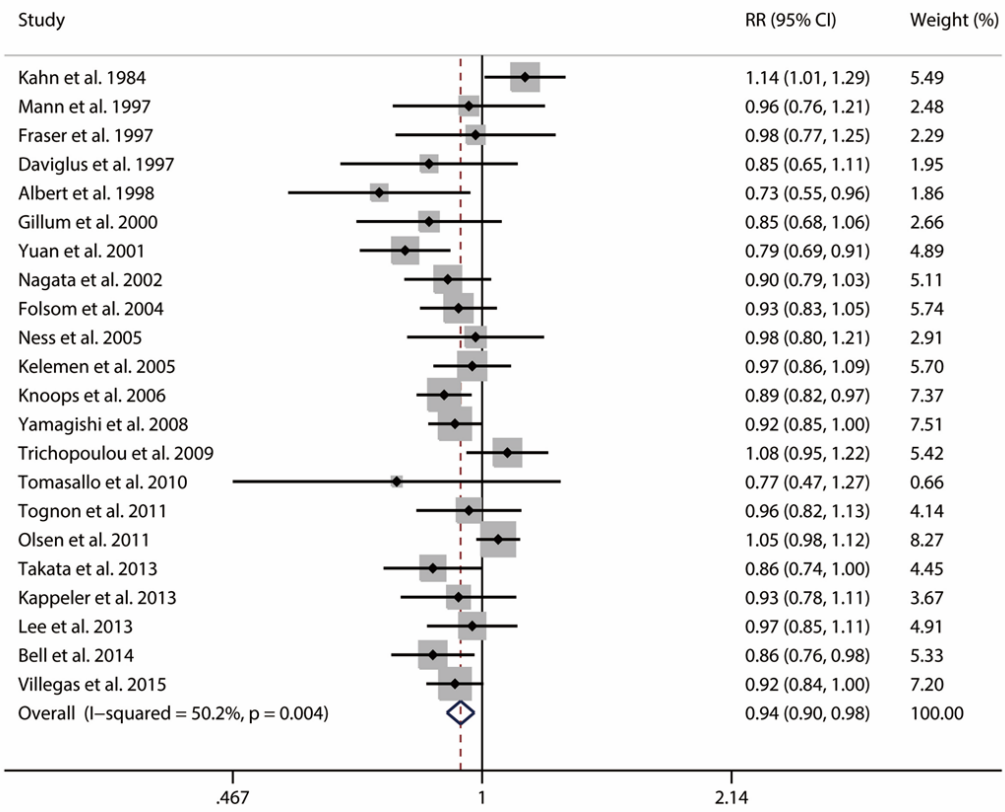

Figure 2. Relative risk of all-cause mortality for highest versus lowest category of fish consumption from 22 prospective cohort studies. Overall relative risk calculated with random effects model. Dots indicate the adjusted RR of individual studies by comparing participants in the highest with those in the lowest fish consumption group. Sizes of the shaded squares are proportional to the percentage weight of each study. The diamond data markers indicate the pooled RR and 95% CI

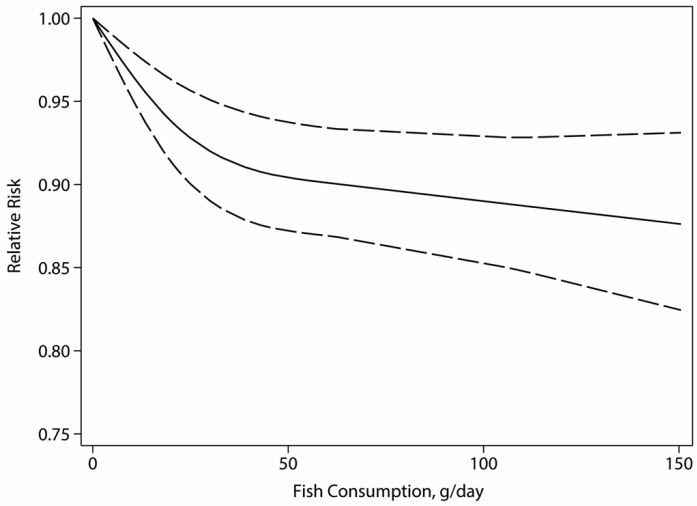

Figure 3. Dose-response analysis for curvilinear association between fish consumption (g/day) and risk of all-cause mortality. Fish consumption was modeled with restricted cubic splines in a fixed-effects dose-response model. The *p* value for non-linearity was 0.005 for fish consumption.

Long chain n-3 PUFA intake and risk of all-cause mortality

Six articles from 6 independent cohort studies reported on dietary long chain n-3 PUFA intake in relation to risk of all-cause mortality, involving 26,093 all-cause mortality events and 430,579 participants. Dietary long chain n-3 PUFA was inversely associated with all-cause mortality risk (RR: 0.86; 95% CI: 0.80, 0.93) (Supplementary figure 1). There was moderate heterogeneity (I^2=57.8%). No publication bias was observed from the Begg's rank correlation test (p=0.34) or Egger's linear regression test (p=0.12).

Four articles were eligible for the dose-response analysis, including 20,454 all-cause mortality events and 323,827 participants. We found no evidence of statistically significant departure from linearity (p for non-linearity was 0.20) (Supplementary figure 2), and for every 0.2 g per day increment in long chain n-3 PUFA consumption

the risk of all-cause mortality decreased by 7% (RR: 0.93; 95% CI: 0.88, 0.99) (Supplementary figure 3).

Subgroup and sensitive analysis

For fish consumption, the inverse association was present in USA and Asian populations, however, it was not significant in European populations (RR: 0.99; 95% CI: 0.92, 1.07). Stratified by different follow-up years and gender, no effect modifications were observed, and moderate heterogeneity still existed (Supplementary table 5). Exclusion of any individual study did not substantially change the summary relative risk (Supplementary figure 4)

For long chain n-3 PUFA, subgroup analysis indicated that the inverse association was present in both USA and Asian populations. No study heterogeneity was observed in studies from European countries (I^2=0). The inverse association was more evident in studies without adjustment for BMI, total energy, smoking status and alcohol intake compared with studies with such adjustment (Supplementary table 5). Exclusion of any individual study did not substantially change the summary relative risk (Supplementary figure 5).

DISCUSSION

In the present meta-analysis, which included 79,276 cases of all-cause mortality and 1,035,416 participants from 23 independent cohort studies, we found that both fish and long chain n-3 PUFA consumption were inversely associated with risk of all-cause mortality. For fish consumption, there was a curvilinear association between fish intake and all-cause mortality risk. For long chain n-3 PUFA, we found no significant curvilinear association between long chain n-3 PUFA intake and risk, and the dose-response analysis indicated that a 0.2 g/day increment in dietary long chain n-3 PUFA was associated with 7% lower risk of all-cause mortality.

Our findings for fish consumption and risk of all-cause mortality were similar to the results of a previous meta-analysis, which combined data from 12 prospective cohort studies, indicating that fish consumption was inversely associated with all-cause mortality risk (RR: 0.94; 95% CI: 0.90, 0.98).[10] Another meta-analysis of randomized controlled trials indicated that long chain n-3 PUFA reduced all-cause mortality by 17% (RR: 0.83; 95% CI: 0.70, 1.04), which was consistent with our results for long chain n-3 PUFA and risk of all-cause mortality.[38] Findings of the present meta-analysis, which generally concur and further extend the findings of the previous one, support a protective role of fish and long chain n-3 PUFA consumption on the risk of all-cause mortality.[10] To the best of our knowledge, results of this study reflect the most comprehensive and updated findings from existing cohort studies.

The findings observed in the current meta-analysis for fish consumption and risk of all-cause mortality may have several alternative explanations. Firstly, fish is not only the most common dietary source of long chain n-3 PUFA, but also a general protein food rich in a variety of nutrients. It is possible that the potential benefits of fish consumption could be due to long chain n-3 PUFA in addition to a wider array of nutrients as well as their interaction. For example, fish is a good source of trace elements, especially selenium, which may have synergistic antioxidant effects against all-cause mortality from CVD or preventing methyl mercury toxicity. Methyl mercury can be easily bio-accumulated in the aquatic food chain and food webs, particularly larger and longer-living fishes such as shark and swordfish.[39,40] Strain et al have argued that methyl mercury may have potentially detrimental effects on neurodevelopment in infants if consumed in sufficient amount, but there may be an interaction between methyl mercury and other nutrients abundant in fish.[41] Such nutritional factors might modify the neurotoxic action of methyl mercury in high fish-eating populations. For example, findings from Seychelles Child Development Study revealed no association between pre-natal methyl mercury exposure from fish consumption and abnormal development in subsequent children.[42] Secondly, the quality of fish protein is higher than that of some other animal proteins such as pork, beef, chicken and milk proteins in terms of either the protein efficiency ratio or the biological value or the indices of the amino acid profile.[43] For example, taurine, which serves as a biomarker for seafood intake, has been observed to have beneficial effects on lowering all-cause mortality risk from CVD.[44,45] Thirdly, fish tends to have higher levels of long chain n-3 PUFA and lower levels of saturated fatty acids than other animal sources of protein.[43] Consumption of fish may displace that of other animal protein, such as red meat. A recent meta-analysis indicated that higher consumption of total red meat and processed meat was associated with an increased risk of all-cause mortality.[46] The concomitant decline in consumption of other food such as red meat may be, at least in part, responsible for the positive impact of fish intake.

Dose-response analysis indicated a curvilinear association between fish intake and all-cause mortality risk. Compared with little or no intake, modest fish consumption (40 g/day) lowers relative risk by 9% or more, which is consistent with the recommendation made by the AHA Dietary Guidelines for at least two servings of fish per week. A higher intake of fish did not substantially lower the all-cause mortality risk further, suggesting a threshold effect. This threshold effect may be explained by findings among high fish consumption populations, for example, Japanese people, who are known for their high level of fish intake, additional fish intake predicts little further reduction in risk of all-cause mortality. This is because most of the population ate fish more than the threshold for maximum mortality benefits.[47] Another explanation could be the potential risks from toxic compounds accumulated in fish such as mercury, dioxins, and polychlorinated biphenyls (PCBs). Virtanen et al found that high mercury content was significantly associated with an increased risk of all-cause mortality and attenuated the beneficial effects of fish oils on the risk of all-cause mortality from CVD.[12]

Subgroup analysis showed the inverse association did not exist in studies from European countries. The discordant results observed for European populations may be explained by the distinct way in which fish is typically prepared and cooked in Europe. For instance, in Sweden, where fatty fish are commonly eaten salted, a high salt intake may be related to increased blood pressure, which

is associated with increased risk of CVD outcome.[48,49] Likewise, in the UK, where fish is often eaten battered and deep-fried in oil, these cooking methods may lead to unfavorable balance of benefit versus harm, because potentially harmful fats, such as trans-fatty acids, might be introduced during the frying process.[50,51] Another possible explanation could be that different populations may respond differently to dietary fish based on varied genetic backgrounds. In our meta-analysis, one study conducted by Gillum performed separate analyses on different races.[18] It was found that the white population seemed to be more sensitive to the protective effect from dietary fish in relation to risk of all-cause mortality than that of the black population in their study.

The concordant results observed for long chain n-3 PUFA compared with overall fish intake may also have several mechanisms. Long chain n-3-PUFA could strongly affect CHD death through lowering triglyceride levels, reducing blood pressure, decreasing platelet aggregation (thereby affecting hemostasis), and contributing to a reduction in arrhythmia.[52-54] In addition, long chain n-3 PUFA may have other favorable effects, such as, anti-inflammatory activity, improving endothelial function and increasing arterial compliance, all of which are related to a decreased risk of all-cause mortality.[5] As long chain n-3 PUFA are almost exclusively found in fish, the effect of the reduction in all-cause mortality associated with fish consumption could be also, at least in part, explained by the effect of long chain n-3 PUFA.

Compared with the previous meta-analysis, the current meta-analysis has several strengths.[10] Firstly, our meta-analysis reinforces earlier results by including an additional 10 large scale prospective cohorts. For fish consumption and all-cause mortality risk, our meta-analysis involved a total of 75,150 all-cause mortality events and 985,126 participants, almost 1.5 times as many as the previous one, and the large sample size allowed us to quantitatively assess the association more accurately than the previous meta-analysis. Secondly, we assessed the relation of all-cause mortality with consumption of long chain n-3 PUFA. Because long chain n-3 PUFA is almost exclusively found in marine food, dietary long chain n-3 PUFA intake can be viewed as a surrogate marker for fish intake. The consistent results for fish and long chain n-3 PUFA intake with risk of all-cause mortality strengthened our findings. Thirdly, for dose-response analysis, we excluded the article conducted by Nataga et al which had a very high reference group of fish intake (41.4 g/day).[16] Such high reference might lead to a plausible "U-shape" trend.

However, the current meta-analysis also has several limitations. Firstly, heterogeneity was present for both fish and long chain n-3 PUFA and all-cause mortality risk, and this was only partly explained by our subgroup analyses. These are likely related to misclassification of fish types, because dietary questionnaires typically seek information on fish group rather than on specific fish types. Considering the substantial differences in quantity of long chain n-3 PUFA intake between marine species, for instance, fatty fish versus lean fish, these inaccuracies may lead to potential poor allocation of nutrient content, which may have weakened the associations. Secondly, available data on the individual long chain n-3 PUFA was rather limited, therefore further prospective studies are needed for a more detailed analysis of association between individual n-3 PUFA and risk of all-cause mortality. Thirdly, we could not exclude the possibility that the inverse association between fish, long chain n-3 PUFA and risk of all-cause mortality is partially explained by other underlying diet or healthy lifestyle factors not measured in the studies, even though most of the studies included were well-designed and adjusted for major confounding factors in the analyses.

In conclusion, our findings found inverse associations of fish and long chain n-3 PUFA consumption with risk of all-cause mortality. It is preferable to promote fish consumption at least twice per week and increase long chain n-3 PUFA intake through dietary approaches for the general population.

ACKNOWLEDGEMENTS

We thank Prof. Andrew J. Sinclair at the School of Medicine, Deakin University, Victoria, Australia for helping to revise this manuscript.

AUTHOR DISCLOSURES

The authors declare that they have no conflicts of interest. This study was supported by the National Basic Research Program of China (973 Program: 2015CB553604).

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Supplementary table 1. Electronic search strategy

PubMed and Scopus search	
1	Fat (title/abstract)
2	Fatty acid (title/abstract)
3	Docosahexaenoic acid (title/abstract)
4	Eicosapentaenoic acid (title/abstract)
5	Docosapentaenoic acid (title/abstract)
6	Fish (title/abstract)
7	Fish oil (title/abstract)
8	Seafood (title/abstract)
9	Death (title/abstract)
10	Mortality (title/abstract)
11	OR/1-8
12	OR/9-10
13	11 AND 12
14	Limit 13 to (English language)

Supplementary table 2. Reasons for full-text excluded studies

Reasons for exclusion	References
Follow-up years were less than 5 years	Lee et al, 2009[1]
Subjects were patients	Kromhout et al, 1995[2]; Whiteman et al, 1999[3]; Erkkila et al, 1999[4]; Hu et al, 2003[5]; Lindber et al, 2008[6]
Reference groups were not the lowest exposure group	Osler et al, 2003[7]; Nakamura et al, 2004[8]
Reviews	Fraser et al, 1999[9]; Sellmayer et al, 2002[10]; Hooper et al, 2004[11]; Mori et al, 2006[12]; Shimazu et al, 2007[13]; Albert et al, 2007[14]; Scorza et al, 2009[15]; He et al, 2009[16]; Mozaffarian et al, 2010[17]; Ford et al, 2013[18]; Engell et al, 2013[19]
RCT	Burr et al, 1989[20]; Feskens et al, 1993[21]; Jones et al, 2002[22]; Flores et al, 2009[23]; Itakura et al, 2011[24]; Masson et al, 2013[25]; Li et al, 2014[26]; Colin-Ramirez et al, 2014[27]
Due to other reasons	Gordon et al, 1981[28]; Daviglus et al, 1995[29]; Yamori et al, 2006[30]; Turunen et al, 2008[31]; Anderson et al, 2009[32]; Chen et al, 2013[33]; Harris et al, 2013[34]; Hisamatsu et al, 2013[35]; Wakai et al, 2014[36]; Yu et al, 2015[37]; Mozaffarian et al, 2013[38]
Not related	Di Giuseppe et al, 2009[39]; Chiuve et al, 2009[40]; Farrell et al, 2014[41]; Greisenegger et al, 2015[42]

Supplementary table 3. Adjusted covariates for the included studies in the meta-analysis

Study	Adjusted covariates in each included study
Kahn et al, 1984[43]	Age, sex, smoking, history of disease, and age at initial exposure to the Seventh-Day Adventist Church
Daviglus et al, 1997[44]	Base-line age and education; religion; systolic pressure; serum cholesterol; number of cigarettes smoked per day; body-mass index; presence or absence of diabetes; presence or absence of electrocardiographic abnormalities; and daily intake of energy, cholesterol, saturated, monounsaturated, and polyunsaturated fatty acids, total protein, carbohydrate, alcohol, iron, thiamine, riboflavin, niacin, vitamin C, beta carotene, and retinol.
Mann et al, 1997[45]	Age, sex, smoking habit, and social class
Fraser et al, 1997[46]	NA
Albert et al, 1998[47]	Age (continuous), aspirin and beta carotene treatment assignment, evidence of cardiovascular disease (angina, myocardial infarction, stroke, transient ischemic attack, percutaneous transluminal angioplasty, or coronary artery bypass grafting) prior to 12-month questionnaire, body mass index (quartiles), smoking status (current [<20 cigarettes per day, ≥20 cigarettes per day], past, never), history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption (≤monthly, weekly, daily), vigorous exercise (<weekly, ≥weekly), and vitamin E, vitamin C, and multivitamin use.
Gillum et al, 2000[48]	Age, smoking, history of diabetes, education, high school graduate, systolic blood pressure, serum cholesterol concentration, body mass index, alcohol intake, and physical activity.
Yuan et al, 2001[49]	Age (years) and total energy intake (calories/day), level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, ≥26 kg/m2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, ≥29), history of diabetes (no, yes), and history of hypertension (no, yes).
Nagata et al, 2002[50]	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 (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).
Folsom et al, 2004[51]	Age, energy intake, educational level (<high school, high school, or >high school), physical activity level (low, medium, or high), alcohol consumption (0, <4, or ≥4 g/day), smoking status (current, former, or never), pack-years of cigarette smoking (continuous), age at first live birth (nullipara, <30 years, or ≥30 years), estrogen use (current, former, or never), vitamin use (yes, no, or unknown), body mass index (quintiles), waist/hip ratio (quintiles), diabetes (yes or no), hypertension (yes, no, or unknown), intake of whole grains, fruit and vegetables, red meat, cholesterol, and saturated fat (all in quintiles).
Ness et al, 2005[52]	Age, energy, sex, 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
Kelemen et al, 2005[53]	Age, total energy, saturated fat, polyunsaturated fat, monounsaturated fat, and trans-fat (expressed as percentage of energy and categorized into quintiles), total fiber, dietary cholesterol, dietary methionine (all quintiles are based on energy-adjusted values), alcohol (≤14 g/day vs. >14 g/day), smoking (never, former, current), activity level (active vs. not active), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–28.9, ≥29.0), history of hypertension, postmenopausal hormone use, multivitamin use, vitamin E supplement use, education (high school education or less vs. post-high school), and family history of cancer, animal protein model is also adjusted for vegetable protein and vice versa.
Knoops et al, 2006[54]	Age, gender, physical activity, smoking, alcohol use, number of years of education, BMI, chronic disease at baseline and study center. The median of the items was used as cutoff point. For the healthy items, the subjects who scored zero were used as reference group, while for the detrimental items; subjects with a high consumption were used as reference group.
Yamagishi et al, 2008[55]	History of hypertension and diabetes mellitus, smoking status, alcohol consumption, body mass index, mental stress, walking, sports, education levels, total energy, and dietary intakes of cholesterol, saturated and n-6 polyunsaturated fatty acids, vegetables, and fruit.
Trichopoulou et al, 2009[56]	Sex, age (<45, 45-54, 55-64, ≥65, categorically), education (none/elementary school degree, secondary or technical school degree, university degree or higher, categorically), smoking status (never, former, and current at enrolment with cigarettes per day 1-10, 11-20, 21-30, 31-40, ≥41 ordered), waist/hip ratio (sex specific fifths, ordered), body mass index (sex specific fifths, ordered), MET score (fifths, ordered), and total energy intake (fifths, ordered).
Tomasallo et al, 2010[57]	Sex, age, body mass index, and income at study baseline.

Supplementary table 3. Adjusted covariates for the included studies in the meta-analysis (cont.)

Study	Adjusted covariates in each included study
Pocobelli et al, 2010[58]	Sex, age, current use of medication for depression or anxiety; current use of blood pressure medication; a history of lung cancer, colon cancer, bladder cancer, leukemia, pancreatic cancer, non-Hodgkin lymphoma, melanoma, prostate cancer, breast cancer, cervical cancer, uterine cancer, ovarian cancer, and all other cancers combined; ischemic heart disease (defined as a previous heart attack), coronary bypass surgery, angioplasty, or diagnosis of angina; stroke; congestive heart disease; rheumatoid arthritis; diabetes; viral hepatitis; cirrhosis of the liver; other chronic liver disease; emphysema, chronic bronchitis, or chronic obstructive pulmonary disease; kidney disease; ulcerative colitis or Crohn disease; Parkinson disease; and osteoporosis in women
Tognon et al, 2011[59]	Sex, baseline body mass index (BMI), waist circumference, smoking status, physical activity level, marital status, education, and birth cohort.
Olsen et al, 2011[60]	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, red meat intake, and processed meat intake, total energy intake.
Takata et al, 2013[61]	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 (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only).
Kappeler et al, 2013[62]	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).
Lee et al, 2013[63]	Age, BMI, education, smoking habit, rural/urban residence, alcohol intake, fruit and vegetable intake, and total energy intake
Bell et al, 2014[64]	Age (as the time scale), sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed, or missing), education (high school graduate or less, some college, or college/advanced degree), total energy intake (kcal/day; continuous), body mass index (weight (kg)/height (m)2) at age 45 years (<18.5, 18.5–<25.0, 25.0–29.9, ≥30.0, or missing), average alcohol intake at age 45 years (none, <1 drink/day, 1–2 drinks/day, >2 drinks/day, or missing), average physical activity in the 10 years before baseline (MET-hours/week; tertiles), self-rated health (excellent, very good, good, fair, or poor), mammogram in the last 2 years (yes/no), prostate-specific antigen test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use in the past 10 years (none, low, high, or missing), use of nonaspirin, nonsteroidal anti-inflammatory drugs in the past 10 years (none, low, high, or missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, or >35.0 pack-years), morbidity score, percentage of calories derived from trans-fat (quartiles), percentage of calories derived from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–9, ≥10, or missing), years of estrogen + progestin therapy (none, <5, 5–9, ≥10, or missing), age at menopause (≤39 years, 40–44 years, 45–49 years, 50–54 years, ≥55 years, or missing), age at death of father (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years), and age at death of mother (≤59 years, 60–69 years, 70–79 years, 80–89 years, or ≥90 years).
Villegas et al, 2015[65]	Age, kcal/day, BMI, smoking, alcohol consumption, physical activity level, income level, education level, presence of chronic disease, insurance coverage, race, gender, and total meat intake per day.

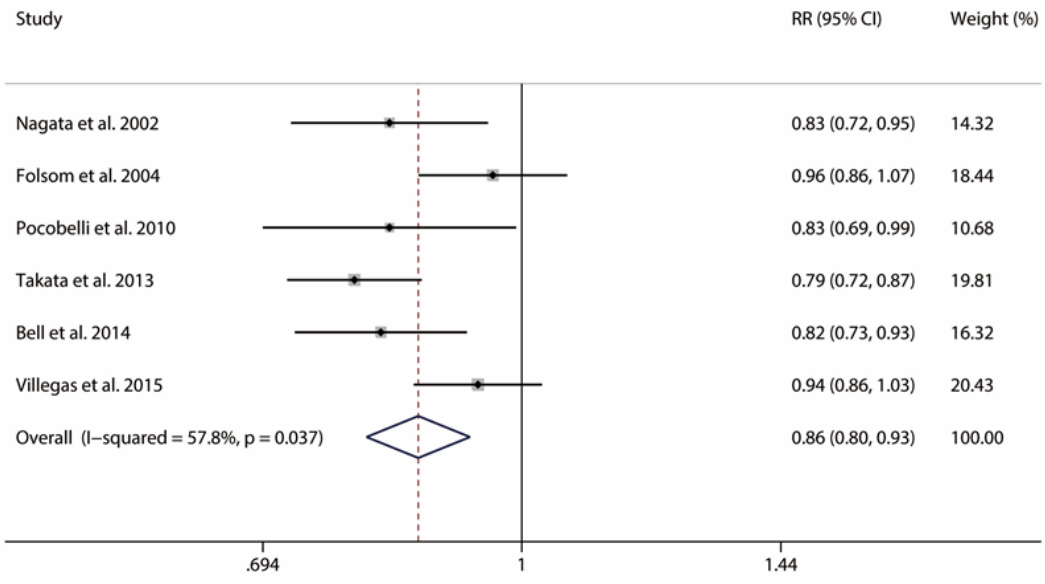
Supplementary table 4. Quality assessment of included studies on fish, long chain n-3 PUFA and risk of all-cause mortality

Study	Selection	Comparability	Outcome/exposure	Overall quality
Kahn et al, 1984[43]	3	2	2	7
Daviglus et al, 1997[44]	3	2	3	8
Mann et al, 1997[45]	2	2	3	7
Fraser et al, 1997[46]	3	0	3	5
Albert et al, 1998[47]	4	2	3	9
Gillum et al, 2000[48]	3	2	3	8
Yuan et al, 2001[49]	3	2	3	8
Nataga et al, 2002[50]	3	2	3	8
Folsom et al, 2004[51]	3	2	2	8
Ness et al, 2005[52]	3	2	3	8
Kelemen et al, 2005[53]	3	2	3	8
Knoops et al, 2006[54]	2	2	3	7
Yamagishi et al, 2008[55]	3	2	3	8
Trichopoulou et al, 2009[56]	3	2	3	8
Tomasallo et al, 2010[57]	2	2	3	7
Pocobelli et al, 2010[58]	3	2	3	8
Tognon et al, 2011[59]	2	2	2	6
Oslen et al, 2011[60]	3	2	3	8
Takata et al, 2013[61]	3	2	3	8
Kappler et al, 2013[62]	3	2	3	8
Lee et al, 2013[63]	3	2	3	8
Bell et al, 2014[64]	3	2	3	8
Villegas et al, 2015[65]	3	2	3	8

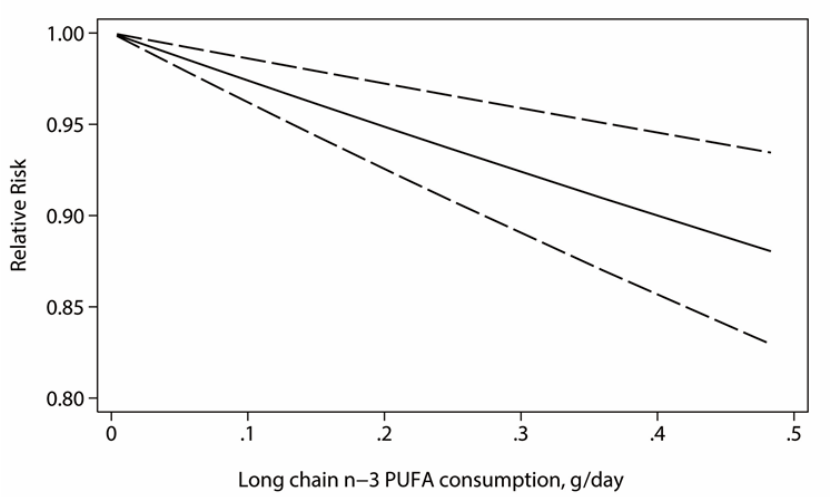
The study quality was assessed according to the Newcastle Ottawa Quality assessment scale for cohort studies and case-control studies. This scale awards a maximum of 9 points to each study: 4 for selection, 2 for comparability, and 3 for assessment of outcomes (for cohort study) or exposures (for case-control study). Comparability was assessed based on the adjustment of age.

Supplementary table 5. Subgroup analysis of consumption of fish and long chain n-3 PUFA and risk of all-cause mortality

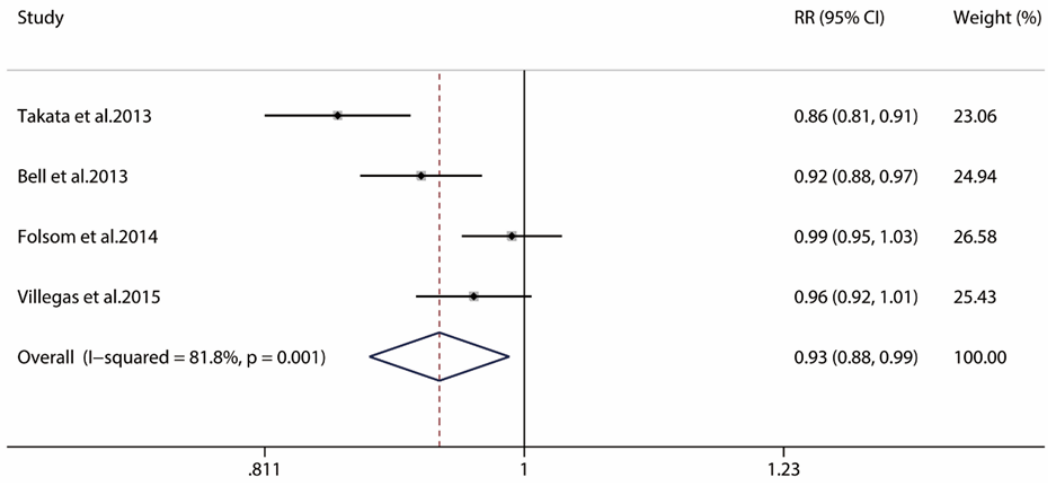
	Fish				Long chain n-3 PUFA			
	n	RR	95% CI	I^2, %	n	RR	95% CI	I^2, %
All studies	22	0.94	(0.90, 0.98)	50.2	6	0.86	(0.80, 0.93)	57.8
Country								
USA	11	0.93	(0.87, 0.99)	41.2	4	0.90	(0.83, 0.97)	43.9
Europe	6	0.99	(0.92, 1.07)	55.4	/	/	/	/
Asia	5	0.89	(0.84, 0.95)	22.3	2	0.80	(0.74, 0.87)	0
Gender								
Men	10	0.89	(0.82, 0.96)	51.8	0	/	/	/
Women	9	0.93	(0.88, 0.99)	26.8	1	0.96	(0.86, 1.07)	/
Both	11	0.97	(0.92, 1.03)	59.3	5	0.84	(0.79,0.91)	47.4
Follow-up years								
≥12	14	0.95	(0.89, 1.01)	53.9	1	0.96	(0.86, 1.07)	/
<12	8	0.92	(0.87, 0.97)	37.4	5	0.84	(0.79, 0.91)	47.4
BMI adjustment								
Yes	16	0.92	(0.88, 0.97)	52.3	3	0.87	(0.79, 0.96)	50.6
No	6	0.97	(0.89, 1.07)	47.1	3	0.86	(0.75, 0.98)	73.3
Energy adjustment								
Yes	15	0.94	(0.90, 0.98)	47.0	5	0.87	(0.80, 0.94)	65.4
No	7	0.93	(0.82, 1.04)	61.8	1	0.83	(0.69, 0.99)	/
Education adjustment								
Yes	17	0.93	(0.89, 0.97)	44.9	5	0.87	(0.80, 0.95)	64.8
No	5	0.95	(0.81, 1.13)	60.4	1	0.83	(0.72, 0.95)	/
Smoking adjustment								
Yes	19	0.93	(0.89, 0.98)	56.5	6	0.86	(0.80, 0.93)	57.8
No	3	0.96	(0.82, 1.12)	0	0	/	/	/
Alcohol adjustment								
Yes	14	0.91	(0.87, 0.96)	50.6	5	0.87	(0.80, 0.94)	65.4
No	8	1.02	(0.95, 1.10)	10.8	1	0.83	(0.69, 0.99)	/



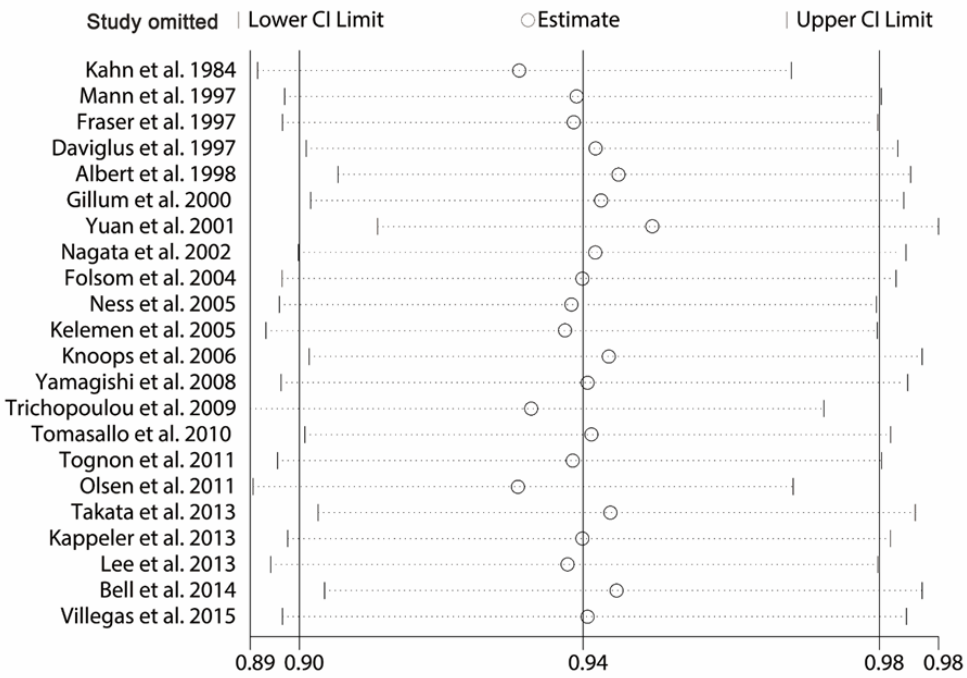
Supplementary figure 1. Relative risk of all-cause mortality for highest versus lowest category of long chain n-3 PUFA from 6 cohort studies. Overall relative risk calculated with random effects model. Dots indicate the adjusted RR of individual studies by comparing participants in the highest with those in the lowest fish consumption group. Sizes of the shaded squares are proportional to the percentage weight of each study. The diamond data markers indicate the pooled RR and 95% CI.



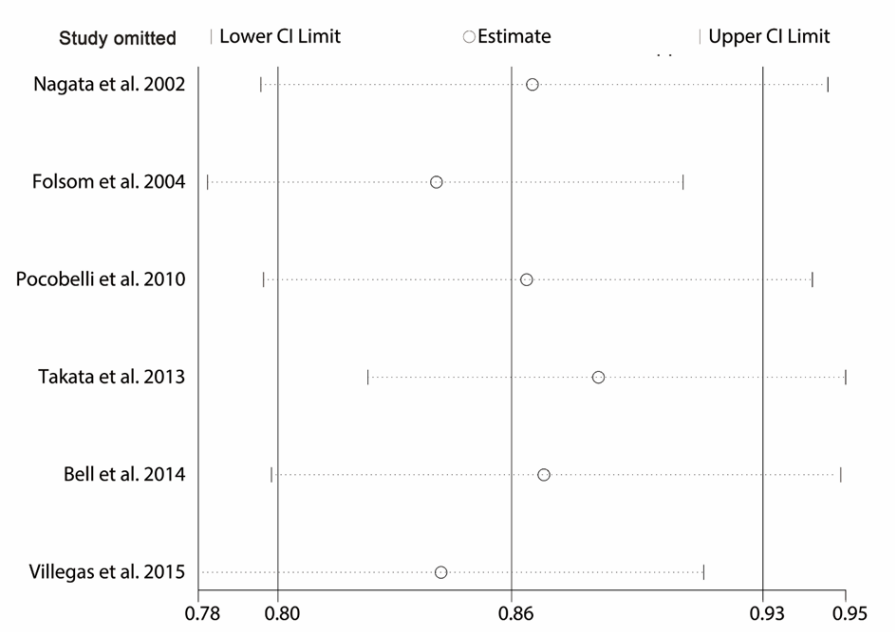
Supplementary figure 2. Dose-response analysis for curvilinear association between long chain n-3 PUFA consumption (g/day) and risk of all-cause mortality. Long chain n-3 PUFA consumption was modeled with restricted cubic splines in a fixed-effects dose-response model. The p value for non-linearity was 0.20 for long chain n-3 PUFA consumption.



Supplementary figure 3. Dose-response meta-analysis for per 0.2 g/day increment of long chain n-3 PUFA intake and risk of all-cause mortality.



Supplementary figure 4. Sensitivity analysis of consumption of fish and risk of all-cause mortality.



Supplementary figure 5. Sensitivity analysis of consumption of long chain n-3 PUFA and risk of all-cause mortality.

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