REVIEW

Fish Consumption and the Risk of Chronic Disease: An Umbrella Review of Meta-Analyses of Prospective Cohort Studies

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ABSTRACT

We aimed to present a comprehensive review of published meta-analyses of prospective cohort studies on the association of fish consumption and the risk of chronic disease. A systematic search was undertaken in Pubmed and Scopus to October 2019 to find meta-analyses of observational studies evaluating the association of fish consumption and the risk of chronic disease. Retrospective and cross-sectional studies and studies with unadjusted risk estimates were excluded. The summary relative risk (SRR) for each meta-analysis was recalculated by using a random-effects model. The methodological quality of included meta-analyses and the quality of the evidence were assessed by the AMSTAR and NutriGrade tools, respectively. A total of 34 meta-analyses of prospective observational studies, reporting SRRs for 40 different outcomes obtained from 298 primary prospective cohort studies, were included. Moderate-quality evidence suggested that each 100-g/d increment in fish consumption was associated with a lower risk of all-cause mortality (SRR: 0.92; 95% CI: 0.87, 0.97), cardiovascular mortality (SRR: 0.75; 95% CI: 0.65, 0.87), coronary heart disease (SRR: 0.88; 95% CI: 0.79, 0.99), myocardial infarction (SRR: 0.75; 95% CI: 0.65, 0.93), stroke (SRR: 0.86; 95% CI: 0.75, 0.99), heart failure (SRR: 0.80; 95% CI: 0.67, 0.95), depression (SRR: 0.88; 95% CI: 0.79, 0.98), and liver cancer (SRR: 0.65; 95% CI: 0.48, 0.87). For cancers of most sites, there was no significant association and the quality of the evidence was rated low and very low. In conclusion, evidence of moderate quality suggests that fish consumption is associated with a lower risk of cardiovascular disease, depression, and mortality and, therefore, can be considered as a healthy animal-based dietary source of protein. Further research is needed for outcomes for which the quality of the evidence was rated low and very low, considering types of fish consumed, different methods of cooking fish, and all potential confounding variables. *Adv Nutr* 2020;11:1123–1133.

Keywords: cardiovascular disease, chronic disease, cohort studies, fish, fish protein, meta-analysis, mortality, omega-3 fatty acids

Introduction

The association of fish consumption with the risk of cardiovascular disease (CVD) has been well investigated. Fish are the main dietary sources of the long-chain omega-3 PUFAs (1) EPA (20:5n–3) and DHA (22:6n–3), and thereby have been recognized as one of the best cardioprotective food groups. Results from interventional studies have indicated that dietary interventions to increase fish consumption (2), or supplementation with ω-3 fatty acids (3–5), can result in favorable effects on cardiometabolic risk factors including high blood pressure, inflammation, oxidative stress, and endothelial dysfunction. In addition, ω-3 fatty acids have anti-inflammatory (6) and immune-modulatory properties (7) and, as a result, may have anticarcinogenic effects (8).

Considering the aforementioned evidence, several meta-analyses of observational studies have been performed to investigate the association of fish consumption and the risk of chronic diseases including coronary heart disease (CHD) (9), heart failure (10), hypertension (11), stroke (12), type 2 diabetes (T2D) (13), and cancers at different sites (14–16). However, the strength of the evidence presented by the published meta-analyses has been less addressed. In addition, the interpretation of the results, especially for site-specific cancers, may have been limited by the inclusion of retrospective observational studies and studies with high risk of bias, such as studies with unadjusted effect sizes.

Umbrella reviews have increasingly been used to summarize the evidence presented by published meta-analyses

The authors reported no funding received for this study.
Author disclosures: The authors report no conflicts of interest.
Supplemental Tables 1–4 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
Address correspondence to SS-B (e-mail: s_shabbidar@tums.ac.ir).
Abbreviations used: AMSTAR, assessment of multiple systematic reviews; CHD, coronary heart disease; CVD, cardiovascular disease; SRR, summary relative risk; T2D, type 2 diabetes.

on a specific topic (17, 18). With the use of this approach, investigators can assess the methodological quality of published meta-analyses, evaluate the quality of the evidence and the accuracy of the estimates, and thereby present a balanced and comprehensive overview of a specific topic. Thus, we aimed to perform an umbrella review of published meta-analyses of prospective cohort studies evaluating the association of fish consumption with the risk of any chronic disease including cardiometabolic disease, site-specific cancers, neurological disorders, all-cause and cause-specific mortality, and any other outcome, for which ≥1 published meta-analysis of prospective cohort studies was available.

Methods

Systematic search

Eligible meta-analyses were identified by both authors (AJ and SS-B) who performed independent searches in PubMed and Scopus up to October 2019. The following set of keywords was used to find potential eligible meta-analyses: [Fish AND (review OR "systematic review" OR meta-analysis)]. The literature search was supplemented by screening the reference lists of all relevant reviews and meta-analyses.

Selection of meta-analyses

For the purpose of the present umbrella review, meta-analyses with the following criteria were considered eligible: *1*) meta-analyses of prospective cohort studies that were conducted in the general population aged 18 y or older; *2*) assessed dietary intakes by standard dietary assessment tools (e.g., FFQs, diet history, 24-h dietary recalls, and dietary records); *3*) reported fish consumption as an exposure; *4*) considered the incidence of any chronic disease including CVD, T2D, site-specific cancers, neurological disorders, all-cause and cause-specific mortality, and any other disease as an outcome; and *5*) reported multivariable summary risk estimates and their corresponding 95% CIs.

Meta-analyses of observational studies that combined prospective, retrospective, and cross-sectional studies in their analyses were also eligible. Primary studies and studies with no summary risk estimate (e.g., narrative reviews and systematic reviews without meta-analysis) were excluded. If >1 published meta-analysis was found for a given outcome, the study with the largest number of primary prospective cohort studies was selected. For published meta-analyses that investigated the association of fish intake with the same outcome and included equal numbers of primary prospective cohort studies, the one with more information (e.g., dose-response meta-analysis) was selected. In general, the meta-analysis with the largest number of primary prospective cohort studies included the same primary studies as meta-analyses including fewer studies, with ≥1 additional recent primary cohort study. Therefore, we selected the one with the largest number of primary prospective cohort studies to include more evidence in this review.

Data extraction

One author (AJ) extracted the following information from each included meta-analysis: first author's name, publication year, outcome of interest, number of primary prospective cohort studies, number of participants/cases, and type of comparison (high compared with low meta-analysis or dose-response meta-analysis). We also extracted the following data from the primary studies included in each meta-analysis: first author's name, year of publication, number of participants/cases, maximally adjusted RRs and their 95% CIs, and confounding variables that were included in that model. If confounding variables were not presented in the eligible meta-analyses, we read the full texts of primary studies to extract confounding variables. Data extraction was checked by the second author (SS-B).

Assessment of methodological quality

Both authors (AJ and SS-B) independently performed quality assessments. Disagreements were resolved by consensus. The methodical quality of each published meta-analysis was assessed by a measurement tool for the *assessment of multiple systematic reviews* (AMSTAR) (19, 20). This scale ranges from 0 to 11 and demonstrates the methodological quality of each published meta-analysis. Accordingly, meta-analyses with ≥8 points were considered high quality, and studies with 4–7 points and ≤3 points were considered moderate and low quality, respectively (21).

Statistical analysis

For each included meta-analysis, we extracted maximally adjusted RRs and their 95% CIs from each primary prospective cohort study that was included in that review. Then, we performed our own meta-analyses. For this purpose, we recalculated the summary relative risk (SRR) and its corresponding 95% CI by using the DerSimonian and Laird random-effects model (22). Because some of the included meta-analyses used a fixed-effects model to combine primary effect sizes, we used this approach to present comparable SRRs across all meta-analyses (23). In addition, this approach provided sufficient information for the evaluation of the quality of the evidence (including τ^2, I^2, and publication bias).

For published meta-analyses that included separate risk estimates based on sex or other subgroups from a given primary study, we combined subgroup-specific estimates using a fixed-effects model and used the combined effect size for our analyses. For the published meta-analyses that combined prospective cohorts, retrospective observational studies (e.g., case-control or retrospective cohort studies), and cross-sectional studies in their analyses, we excluded the cross-sectional and retrospective studies and recalculated SRRs using the results from prospective cohort studies only. Primary studies with unadjusted risk estimates were also excluded. We excluded the aforementioned primary studies from the analyses and then recalculated the risk estimates with the use of a random-effects model. In addition, for dose-response meta-analyses that reported SRRs for a specific

measure (e.g., for a 1-serving/wk, 1-serving/d, 15-g/d, or 20-g/d increment in fish consumption), we converted all SRRs to SRR for a 100-g/d increment in fish consumption. For this purpose, we extracted the RR for each primary prospective cohort study that was included in the eligible meta-analyses (from the forest plots). Then, we converted all measures to grams per day, by using the serving sizes reported in those primary studies. Then, we translated all RRs in primary studies into RR for a 100-g/d increment in fish consumption. For this purpose, we calculated the log RR and its 95% CI, then multiplied them by 100/X (X g/d is the specific amount of increase in fish consumption in each primary study, for which the RR was reported). Then, we exponentiated the log RR and its 95% CI to get the RR for an increment of 100 g/d in fish consumption. Finally, we combined study-specific RRs by using a random-effects model. With the use of this approach, we were able to present comparable SRRs across different outcomes. In each meta-analysis, we evaluated between-study heterogeneity by using the I^2 statistic and its 95% CI (24). Because I^2 is dependent on the study size, we also calculated τ^2, which is independent of study size (25). We evaluated potential publication bias using Egger's test (26). Because chronic disease includes 40 different outcomes, we applied a Bonferroni correction ($\alpha = 0.05/40$; $P = 0.00125$) to avoid inflating the rate of false-positive findings due to multiple testing. So, significance was considered as $P < 0.00125$. All analyses were conducted with Stata software version 13 (StataCorp).

Quality of the evidence

We recalculated the SRR in each included meta-analysis and then assessed the quality of the evidence by using the NutriGrade score (27). This score is a useful tool to judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research (23, 28, 29) and considers nutrition-specific aspects such as dietary assessment methods and diet-associated biomarkers (30). This score includes 8 components including *1*) risk of bias, study quality, or study limitations; *2*) precision of the estimate; *3*) heterogeneity; *4*) directness; *5*) publication bias; *6*) funding bias; *7*) effect size; and *8*) dose–response association. The score ranges from 0 to 10. According to this method, the strength of the evidence obtained from the included meta-analyses was categorized as follows:

- Very low (0–3.99): There is very low confidence in the effect estimate; meta-evidence is very limited and uncertain.
- Low (4–5.99): There is low confidence in the effect estimate; further research will provide important evidence on the confidence and likely change the effect estimate.
- Moderate (6–7.99): There is moderate confidence in the effect estimate; further research could add evidence on the confidence and may change the effect estimate.
- High (≥8): There is high confidence in the effect estimate, and further research probably will not change the confidence in the effect estimate.

Results

A total of 3265 articles were identified by searching the PubMed and Scopus databases (**Supplemental Figure 1**). We reviewed the titles and abstracts of all studies and, as a result, 3194 articles were removed. Seventy-one full texts were fully reviewed for eligibility and, of those, 34 published meta-analyses of observational studies were considered eligible for this umbrella review (31–64). **Supplemental Table 1** provides the reasons for excluding studies and a list of the studies excluded by full-text assessment.

Characteristics of included meta-analyses

The initial systematic search identified 7 published meta-analyses of observational studies for T2D; 6 for stroke; 4 for heart failure; 3 for all-cause and CHD mortality, depression, and colorectal, liver, and esophageal cancers; 2 for CHD, hypertension, age-related macular degeneration, metabolic syndrome, dementia, and pancreatic, prostate, gastric, and ovarian cancers; and 1 meta-analysis for other outcomes. Duplicate meta-analyses reported similar results in terms of the degree and direction of the associations (after exclusion of primary studies that did not meet our inclusion criteria). Of those, the meta-analyses with the largest numbers of primary prospective cohort studies were selected for this review. We also found 1 published meta-analysis with only 1 prospective cohort study for brain tumors (65) and another 1 meta-analysis with only case-control studies for myeloma (66) that were not included in this review.

We identified 34 published meta-analyses of observational studies, reporting 48 SRRs for 40 different outcomes (some of the published meta-analyses reported SRRs for total and different types of fish), obtained from 298 primary prospective cohort studies (**Supplemental Table 2**). Included meta-analyses investigated the following outcomes in their analyses: all-cause mortality (53), CVD mortality (39), CHD (32), CHD mortality (62), myocardial infarction (40), stroke and heart failure (32), heart failure (fried and nonfried fish) (35), T2D (50), T2D (fatty and lean fish) (47), atrial fibrillation (44), hypertension (51), abdominal adiposity (49), metabolic syndrome (43), depression (58), dementia and Alzheimer disease (60), hip fracture (48), rheumatoid arthritis (33), inflammatory bowel disease (46), asthma (57), age-related macular degeneration (64), total cancer mortality (61), breast cancer (63), and colorectal (52), prostate (56), hematological (54), lung (55), oral (37), gastric (59), ovarian (41), bladder (45), pancreatic (42), renal (31), endometrial (36), liver (38), and esophageal cancers (34).

Four eligible meta-analyses (38, 51–53) included 1 primary prospective observational study with an unadjusted risk estimate. We excluded these primary studies from the analyses. Of the 298 primary prospective cohort studies included in the selected meta-analyses, 4 studies reported age-adjusted effect sizes, 1 study reported energy-adjusted effect sizes, and the remainder reported multivariable risk estimates. Two hundred and seventy-one primary prospective

TABLE 1 Summary of the RRs with 95% CIs and quality of the evidence for associations between fish consumption and risks of cardiometabolic diseases and mortality[1]

Outcome	Primary studies, *n*	Cases, *n*	Comparison[2]	Summary RR (95% CI)	*P* value[3]	Quality of the evidence (NutriGrade)
Myocardial infarction	11	8468	Per 100 g/d	0.75 (0.65, 0.93)	0.001	Moderate
Cardiovascular mortality	8	11,720	Per 100 g/d	0.75 (0.65, 0.87)	0.003	Moderate
Heart failure	8	7945	Per 100 g/d	0.80 (0.67, 0.95)	0.01	Moderate
Stroke	20	14,360	Per 100 g/d	0.86 (0.75, 0.99)	0.04	Moderate
CHD	22	16,732	Per 100 g/d	0.88 (0.79, 0.99)	0.03	Moderate
All-cause mortality	38	153,998	Per 100 g/d	0.92 (0.87, 0.97)	0.004	Moderate
Heart failure (fried fish)	2	2813	High vs. low	1.40 (1.22, 1.61)	<0.001	Low
CHD mortality	17	4472	Per 100 g/d	0.65 (0.48, 0.87)	0.004	Low
T2D (fatty fish)	4	2754	High vs. low	0.89 (0.81, 0.97)	0.01	Low
CHD (fatty fish)	4	4501	High vs. low	0.85 (0.72, 1.01)	0.07	Low
Hypertension	7	80,759	Per 100 g/d	1.05 (0.96, 1.15)	0.30	Low
Atrial fibrillation	6	9629	Per 100 g/d	0.60 (0.13, 2.66)	0.82	Low
T2D	16	45,029	Per 100 g/d	1.09 (0.93, 1.28)	0.29	Low
Metabolic syndrome	2	1671	Per 100 g/d	0.60 (0.44, 0.87)	0.003	Very low
Heart failure (nonfried fish)	2	2813	High vs. low	0.69 (0.54, 0.89)	0.004	Very low
T2D (lean fish)	4	2754	High vs. low	0.96 (0.77, 1.25)	0.89	Very low
CHD (lean fish)	2	3253	High vs. low	0.98 (0.85, 1.14)	0.82	Very low

[1] CHD, coronary heart disease; T2D, type 2 diabetes.
[2] For meta-analyses that did not report dose-response estimation, the result of the highest compared with the lowest category was reported.
[3] $P < 0.00125$ was considered significant to avoid inflating the rate of false-positive findings due to multiple testing.

cohort studies (91%) controlled for age in their analyses, 247 studies (83%) considered smoking status, 220 studies (74%) considered BMI, 210 studies (70%) controlled for sex, 191 studies (64%) controlled for energy intake, 185 studies (62%) for alcohol drinking, and 175 studies (59%) for physical activity and other dietary exposures in their analyses. Only 99 primary prospective cohort studies (33%) controlled for family history of the disease assessed as the outcome in that study.

Methodological quality

The methodological quality of the eligible meta-analyses was assessed by a validated AMSTAR tool. The overall and detailed AMSTAR scores for each meta-analysis are provided in Supplemental Tables 2 and **3**, respectively. Of the 34 included meta-analyses in this review, 26 meta-analyses (76%) were conducted with a high-quality approach (AMSTAR score $\geq$8) and 8 (24%) were performed with a moderate-quality method (AMSTAR scores = 6 and 7). The main reasons for which meta-analyses did not receive AMSTAR scores were that included meta-analyses did not determine whether the status of publication was an inclusion criterion, did not provide a list of excluded studies, and did not consider the scientific quality of included studies in preparing their recommendations or conclusions.

Of the 34 included meta-analyses, 24 meta-analyses (71%) evaluated the quality of primary studies using different tools. However, only 16 meta-analyses (47%) considered the scientific quality of primary studies in preparing their recommendations or conclusions, performed subgroup analyses on the basis of study quality, or evaluated the strength of the evidence using a standard tool [Grading of Recommendations Assessment, Development and Evaluation (GRADE) or NutriGrade].

Quality of the evidence

For the purpose of this umbrella review, we used the NutriGrade score to rate the quality of the evidence. Included meta-analyses reported 48 SRRs for 40 different outcomes. Overall, there was no high-quality evidence for the relation of fish consumption and the risk of chronic disease. For the 48 SRRs reported in this review, the quality of the evidence was rated moderate for 8 associations (17%), and was rated low and very low for 46% (n = 22) and 37% (n = 18) of the associations, respectively. The overall and detailed NutriGrade scores for each meta-analysis are provided in Supplemental Tables 2 and **4**, respectively.

Fish consumption and the risk of cardiometabolic disease and mortality

Table 1 presents the associations of fish consumption with the risks of cardiometabolic disease and mortality. There was moderate quality of evidence for an inverse association of fish consumption with the risks of all-cause and CVD mortality, CHD, myocardial infarction, stroke, and heart failure. There was also a strong inverse association for CHD mortality, but the quality of the evidence was rated low. Fish consumption was not associated with the risks of T2D, atrial fibrillation, and hypertension.

Table 1 also presents the associations of different types of fish with the risks of heart failure, CHD, and T2D. There was an inverse association between fatty fish consumption and the risk of T2D and a positive association between fried fish

TABLE 2 Summary of the RRs with 95% CIs and quality of the evidence for associations between fish consumption and risks of site-specific cancers[1]

Outcome	Primary studies, *n*	Cases, *n*	Comparison[2]	Summary RR (95% CI)	*P* value[3]	Quality of the evidence (NutriGrade)
Liver cancer	5	1572	Per 100 g/d	0.65 (0.48, 0.87)	0.007	Moderate
Myeloid leukemia	2	416	High vs. low	1.60 (1.10, 2.35)	0.01	Low
Gastric cancer	5	2813	Per 100 g/d	1.16 (1.00, 1.28)	0.05	Low
Prostate cancer mortality	4	740	High vs. low	0.37 (0.18, 0.74)	0.005	Low
Bladder cancer	5	1141	High vs. low	0.86 (0.53, 1.39)	0.53	Low
Colorectal cancer	20	19,787	Per 100 g/d	0.93 (0.85, 1.01)	0.07	Low
Total cancer mortality	10	49,952	Per 100 g/d	0.98 (0.91, 1.07)	0.69	Low
Breast cancer	11	13,323	Per 100 g/d	1.00 (0.81, 1.23)	0.84	Low
Prostate cancer incidence	12	13,924	High vs. low	1.02 (0.91, 1.15)	0.69	Low
Ovarian cancer	5	1288	High vs. low	1.04 (0.89, 1.22)	0.60	Low
Pancreatic cancer	13	4994	Per 100 g/d	1.06 (0.90, 1.25)	0.42	Low
Esophageal squamous cell carcinoma	3	726	High vs. low	0.87 (0.60, 1.27)	0.47	Very low
Multiple myeloma	3	986	High vs. low	0.94 (0.67, 1.33)	0.87	Very low
Lung cancer	3	11,624	High vs. low	0.95 (0.73, 1.24)	0.69	Very low
CLL/SLL	3	1370	High vs. low	0.99 (0.83, 1.19)	0.74	Very low
Endometrial cancer	4	2245	Per 100 g/d	1.00 (0.65, 1.61)	0.56	Very low
Leukemia	3	2536	High vs. low	1.02 (0.89, 1.17)	0.43	Very low
Oral cancer	2	226	High vs. low	1.03 (0.66, 1.61)	0.90	Very low
Renal cancer	3	2443	High vs. low	1.07 (0.81, 1.39)	0.65	Very low
Non-Hodgkin's lymphoma	4	3865	High vs. low	1.08 (0.94, 1.24)	0.62	Very low

[1] CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
[2] For meta-analyses that did not report dose-response estimation, the result of the highest compared with the lowest category was reported.
[3] $P < 0.00125$ was considered significant to avoid inflating the rate of false-positive findings due to multiple testing.

and the risk of heart failure. The quality of the evidence was rated low for these associations.

Fish consumption and site-specific cancer risk

Table 2 shows the association of fish consumption and site-specific cancer risk. We found moderate quality of evidence for the relation of fish consumption with the risk of liver cancer (SRR for each 100-g/d increment: 0.65; 95% CI: 0.48, 0.87). There was also low-quality evidence for the inverse association of fish consumption and the risk of prostate cancer mortality, as well as for the positive association of fish consumption and the risk of myeloid leukemia and gastric cancer. Fish consumption was not associated with the risk of cancers at other sites.

Fish consumption and other outcomes

Table 3 presents the associations of fish consumption with the risks of other diseases. The quality of the evidence was rated moderate for depression (SRR for the highest compared with the lowest category: 0.88; 95% CI: 0.79, 0.98). We also found low-quality evidence for inverse associations of fish consumption with the risks of Alzheimer disease, hip fracture, and age-related macular degeneration. Fish consumption was not associated with the risk of rheumatoid arthritis, dementia, asthma, or inflammatory bowel disease.

Nonlinear dose-response meta-analysis

Nonlinear dose-response analysis was performed for 16 associations. Of those, there were inverse linear associations for all-cause and CVD mortality, CHD, myocardial infarction, stroke, and heart failure. The results suggested nonlinear dose-response relations for CHD mortality, hypertension, Alzheimer disease, and age-related macular degeneration. There was no evidence of a U- or J-shaped association between fish consumption and the risk of chronic disease.

Heterogeneity

Supplemental Table 2 presents the results for heterogeneity. The evidence of heterogeneity was absent (I^2 <25%) for 50% ($n = 24$) of the associations, low ($I^2 = 25\%–50\%$) for 13% ($n = 6$) of the associations, moderate ($I^2 = 50\%–75\%$) for 29% ($n = 14$) of the associations, and high (I^2 >75%) for 8% ($n = 4$) of the associations in the high compared with low analyses. For outcomes for which the quality of the evidence was rated moderate, the evidence of heterogeneity was absent for CVD mortality, depression, liver cancer, and heart failure; moderate for CHD, all-cause mortality, and stroke; and high for myocardial infarction.

The potential sources of heterogeneity were geographical location (T2D, bladder cancer, all-cause mortality, myocardial infarction, and total cancer mortality), sample size (bladder cancer, myocardial infarction, and total cancer mortality), dietary assessment method (prostate and bladder cancers), follow-up duration (T2D and breast cancer), adjustment for energy intake (myocardial infarction and breast cancer), and menopausal status (breast cancer).

Publication bias

Supplemental Table 2 presents the results for publication bias. Overall, there was evidence of publication bias ($P < 0.05$)

TABLE 3 Summary of the RRs with 95% CIs and quality of the evidence for associations between fish consumption and risks of other diseases[1]

Outcome	Primary studies, *n*	Cases, *n*	Comparison[2]	Summary RR (95% CI)	*P* value[3]	Quality of the evidence (NutriGrade)
Depression	8	5732	High vs. low	0.88 (0.79, 0.98)	0.03	Moderate
Alzheimer disease	5	915	Per 100 g/d	0.41 (0.19, 0.98)	0.02	Low
Age-related macular degeneration (total)	8	4202	Per 100 g/d	0.44 (0.27, 0.75)	0.003	Low
Rheumatoid arthritis	3	820	Per 100 g/d	0.75 (0.41, 1.41)	0.40	Low
Abdominal adiposity	2	2364	Per 100 g/d	0.83 (0.71, 0.97)	0.02	Low
Hip fracture	3	1953	High vs. low	0.92 (0.84, 1.00)	0.05	Low
Age-related macular degeneration (late)	4	NA	High vs. low	0.76 (0.59, 0.99)	0.04	Very low
Age-related macular degeneration (early)	3	NA	High vs. low	0.78 (0.62, 0.97)	0.03	Very low
Dementia	4	1182	Per 100 g/d	0.65 (0.38, 1.15)	0.14	Very low
Asthma	2	551	High vs. low	0.90 (0.69, 1.18)	0.45	Very low
Inflammatory bowel disease	2	250	High vs. low	1.12 (0.44, 2.02)	0.82	Very low

[1] NA, not available.
[2] For meta-analyses that did not report dose-response estimation, the result of the highest compared with the lowest category was reported.
[3] $P < 0.00125$ was considered significant to avoid inflating the rate of false-positive findings due to multiple testing.

for CHD mortality, age-related macular degeneration, myocardial infarction, liver cancer, dementia, and rheumatoid arthritis.

Discussion

The present umbrella review gathered current evidence obtained from prospective cohort studies regarding the association of fish consumption and the risk of chronic disease and, as a result, presented a broad overview of health outcomes of fish consumption. On the basis of the NutriGrade score, we found moderate quality of evidence for the inverse association of fish consumption with the risks of all-cause and CVD mortality, CHD, myocardial infarction, stroke, heart failure, depression, and liver cancer. There was also an inverse association for CHD mortality, metabolic syndrome, prostate cancer mortality, hip fracture, Alzheimer disease, and age-related macular degeneration, but the quality of the evidence was rated low. We found low-quality evidence for the positive association of fish intake with the risks of gastric cancer and myeloid leukemia.

With regard to CVD incidence and mortality, our results are completely in line with current understanding regarding the cardioprotective effects of fish consumption. Fish are the main dietary sources of the long chain ω-3 fatty acids EPA and DHA, which have favorable effects against inflammation and endothelial dysfunction (67–69). ω-3 Fatty acids have lipid-lowering (70) and modest blood pressure–lowering properties (71). They have favorable effects against oxidative stress (72, 73) and platelet aggregation (74) and may also decrease blood viscosity and increase arterial compliance (75). It is also proposed that circulating or tissue concentrations of docosapentaenoic acid (22:5n–3), another long-chain ω-3 fatty acid present in seafood, may have cardiovascular benefits (76).

Fish are one of the main components of highly recommended healthy dietary patterns such as the Mediterranean diet (77) and Dietary Approaches to Stop Hypertension dietary pattern (78). Other healthy dietary patterns such as the Nordic diet (79), the Prudent dietary pattern (80, 81), and the Alternate Healthy Eating Index (82) also recommend people to consider fish in their diet. The 2015–2020 Dietary Guidelines for Americans recommend an intake of ~240 g/wk (2 servings/wk) of a variety of seafood, which provide a mean consumption of 250 mg/d of EPA and DHA (83). Meta-analyses of prospective cohort studies have suggested that higher consumption of meat, especially processed meat, may increase the risk of major public health concerns such as T2D (84), CHD (85), and breast and colorectal cancers (86, 87). Thus, fish can be considered as a healthy animal-based dietary source of protein.

The type of fish consumed in the diet may be an important factor. In this review, we did not find an association between total fish consumption and the risk of T2D. However, an additional analysis indicated that higher intake of fatty fish, but not lean fish, was associated with a lower risk of T2D. Oily fish such as salmon, herring, mackerel, and tuna are rich in vitamin D, and have a higher content of EPA and DHA than that of lean fish (88). One fatty fish serving per week (120 g/wk) provides the recommended daily intake of ω-3 (250 mg/d), whereas multiple servings of lean fish such as cod are required to achieve the recommended intake (89).

Different methods of fish preparation should also be taken into consideration. Although higher intake of fish was associated with a lower risk of heart failure, higher intake of fried fish was associated with a higher risk. Deep-frying is an inappropriate method of cooking fish which may diminish the beneficial effects of fish consumption (90). In addition, some types of large predatory fish such as shark, swordfish, and tilefish are one of the main dietary sources of methylmercury (91), which may induce neurotoxicity (92) and may have adverse effects against brain development (93) and cognition (94). With regard to CVD, evidence from prospective cohort studies did not show an association between higher concentrations of mercury in toenail, the best

long-term biological marker for intake of mercury (95, 96), and the risk of CVD (97, 98). However, the 2018 American Heart Association scientific statement suggested that the benefits of 1–2 servings/wk, especially when a variety of seafood is consumed, outweigh the potential risks associated with mercury content of fish (89).

Different types of fish consumed in each region, different methods of preparing fish such as frying, deep-frying, and steaming, and the use of butter for preparing fish may explain, in part, the observed regional differences in the association of fish consumption and the risk of chronic disease. Meta-analyses of prospective cohort studies suggested that higher fish consumption may be associated with a higher risk of T2D in the United States, but not in European and Asian countries (50, 99). Another 2 recent meta-analyses of prospective cohort studies found inverse linear associations of fish consumption with the risk of all-cause and CVD mortality (39) and myocardial infarction (40) in Asian countries, and in contrast, found modest U-shaped associations in Western countries. There was also such a regional difference for inflammatory bowel disease (46) and lung cancer (55), for which higher fish consumption was associated with a lower risk in Asian countries, but not in Western countries.

For site-specific cancers, we found moderate quality of evidence that higher fish consumption was associated with a lower risk of liver cancer. There was also an inverse association for prostate cancer mortality, but the quality of the evidence was rated low. For cancers at other sites, we did not find significant inverse associations and the quality of the evidence was rated low or very low.

Existing evidence regarding the association of fish and ω-3 fatty acids with cancer risk is scarce. A meta-analysis of prospective cohort studies found a modest inverse association between higher intake of marine ω-3 fatty acids and the risk of breast cancer, and in contrast, found no association for fish (63). Another systematic review did not find sufficient evidence to suggest a relation between fish-derived ω-3 fatty acid and the risk of prostate cancer (100). Current evidence regarding the inverse associations of fish and ω-3 fatty acids with cancer risk is mainly from in vitro studies, as well as case-control studies which are subject to recall and selection biases; thus, further well-performed prospective cohort studies are needed to fully investigate this association.

However, there are several plausible biological mechanisms which may create a potential link between ω-3 fatty acids and cancer risk. ω-3 Fatty acids have anti-inflammatory (101) and immune-modulatory properties (7). Results from interventional studies indicated that supplementation with ω-3 fatty acids can reduce the production of inflammation markers (102–104). Thus, ω-3 fatty acids may have protective effects against cancer risk, especially for cancers that are highly related to inflammation such as liver cancer. It is proposed that >90% of liver cancers are attributable to hepatic injury and inflammation (105). In addition, ω-3 fatty acids may regulate several cancer-related biological pathways such as transcription factor activity, gene expression, signal transduction, apoptosis, angiogenesis, and metastasis (101).

We found a significant positive association between fish consumption and the risks of gastric cancer and myeloid leukemia. However, the interpretation of the results is limited by the low number of studies included (5 studies for gastric cancer and 2 for myeloid leukemia) and low quality of the evidence. Nevertheless, further research is needed to investigate the association of intake of different types of fish such as oily, lean, and salted fish, or different methods of cooking fish, with cancer risk.

We also found a moderate quality of the evidence for the inverse association of fish intake and the risk of depression. Meta-analyses of interventional studies indicated that supplementation with EPA and DHA may be effective in reducing depressive symptoms (106, 107) and, thus, can be considered as a potential treatment of depressive disorders (108). The anti-inflammatory properties of ω-3 fatty acids are one of the mediatory pathways through which they can improve depressive symptoms (109, 110). They can also regulate depression-related neuronal mechanisms such as neuronal homeostasis (111), phospholipid turnover (112), neuronal inflammatory cascades (113), and dopaminergic and serotonergic neurotransmission (114). The International Society for Nutritional Psychiatry Research practice guidelines for ω-3 fatty acids suggested that either pure EPA (with a recommended daily dosage of 1–2 g) or an EPA/DHA combination with a ratio >2 (EPA/DHA >2) can be considered as an effective treatment of major depressive disorders (115).

This umbrella review presented a broad picture of the association of fish consumption with the risks of different chronic diseases. The associations of fish consumption and the risk of chronic disease, especially CVD, have been investigated in several meta-analyses. However, the strength of the evidence has been less addressed in published meta-analyses. We performed a systemic search to find existing literature, excluded case-control studies and studies with unadjusted risk estimates, and evaluated the methodological quality of the included meta-analyses, as well as the quality of the evidence. In addition, we standardized the results across different outcomes.

However, some potential limitations need to be considered when interpreting the results. First, almost all primary studies included in this review relied on single baseline measurements and did not perform repeated dietary assessment during the follow-up period. Thus, the results may have been affected by misclassification of exposures and, as a result, we may have reached either underestimated or overestimated effect sizes. Second, of the 48 SSRs presented in this umbrella review, the analyses of 77% of the associations ($n = 37$) were conducted with <10 primary prospective cohort studies; thus, the interpretation of the results for these outcomes is limited by the low number of studies included. Third, we did not find high-quality evidence for the relation of fish consumption and the risk of chronic disease. In addition, the quality of the evidence was rated low or

very low for 83% of the associations ($n = 40$). Thus, further research is needed for outcomes for which the certainty of evidence was rated low or very low. Fourth, although evidence of publication bias was found for only 13% of the associations ($n = 6$), there were <10 primary prospective cohort studies available for 77% of the associations. Thus, we do not have reliable evidence of publication bias for these outcomes. Fifth, of the 298 primary prospective cohort studies included in this review, only 99 studies (33%) controlled for family history of the disease assessed as the outcome in that study. In addition, we were able to examine the associations of different types of fish or different methods of cooking fish only for T2D, CHD, and heart failure. Sixth, we did not investigate the degree of the associations and the strength of the evidence across different subgroups. There was evidence of a regional difference for the relation of fish consumption with the risks of CVD and T2D. Thus, future research should consider potential differences across different geographic locations. Finally, for published meta-analyses with the same outcomes, we selected and included those with the largest number of primary prospective studies. However, almost all included meta-analyses stated that they searched the reference lists of all relevant meta-analyses and, therefore, it is unlikely that some primary studies have been missed due to inclusion of those meta-analyses with the largest number of primary studies. Nevertheless, narrative reviews and systematic reviews without meta-analyses were not included in this review and some primary studies may have been published after the publication of each meta-analysis. Therefore, some primary prospective cohort studies may have been missed in this review and, as a result, some of the results could have been influenced by missing studies.

Conclusions

This umbrella review presented a broad overview of the association of fish consumption with the risk of chronic disease and found evidence of moderate quality that higher fish consumption may decrease the risks of all-cause and CVD mortality, CHD, myocardial infarction, heart failure, stroke, and depression. For cancers at most sites, there was no significant association and the quality of the evidence was rated low or very low.

Future research should focus on outcomes for which low numbers of primary prospective cohort studies were available, or the quality of the evidence was rated low or very low, especially cancers at different sites. Future research should also focus on the associations of different types of fish such as oily, lean, or salted fish, or different methods of cooking fish such as frying, deep-frying, or steaming, with the risk of chronic disease. The research should also perform repeated dietary assessments to obtain more reliable data and consider potential differences across geographical locations, as well as confounders such as family history of the disease, in its analyses.

Acknowledgments

The authors' responsibilities were as follows—SS-B: is the guarantor; and both authors: conceived and designed the study, conducted the systematic search, screened the articles, selected the eligible articles, extracted information from the eligible studies, performed the analyses, interpreted the results, wrote the first draft of the manuscript, and read and approved the final manuscript. Both authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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