



# Fish consumption in multiple health outcomes: an umbrella review of meta-analyses of observational and clinical studies

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**Background:** Omega-3 polyunsaturated fatty acids are known to be associated with numbers of health benefits, and which can be uptake from fish. The aim of this study was to evaluate the current evidence of associations between consumption of fish and diverse health outcomes. Here, we performed an umbrella review to summarize the breadth, strength, and validity of the evidence derived from meta-analyses and systematic reviews of fish consumption on all health outcomes.

**Methods:** The methodological quality of the included meta-analyses and the quality of the evidence were assessed by the Assessment of Multiple Systematic Reviews (AMSTAR) and the grading of recommendations, assessment, development, and evaluation (GRADE) tools, respectively. The umbrella review identified 91 meta-analyses with 66 unique health outcomes, of which 32 outcomes were beneficial, 34 showed nonsignificant associations and only one was harmful (myeloid leukemia).

**Results:** A total of 17 beneficial associations [all-cause mortality, prostate cancer mortality, cardiovascular disease (CVD) mortality, esophageal squamous cell carcinoma (ESCC), glioma, non-Hodgkin lymphoma (NHL), oral cancer, acute coronary syndrome (ACS), cerebrovascular disease, metabolic syndrome, age-related macular degeneration (AMD), inflammatory bowel disease (IBD), Crohn's disease (CD), triglycerides, vitamin D, high-density lipoprotein (HDL)-cholesterol, and multiple sclerosis (MS)], and eight nonsignificant associations [colorectal cancer (CRC) mortality, esophageal adenocarcinoma (EAC), prostate cancer, renal cancer, ovarian cancer, hypertension, ulcerative colitis (UC), and rheumatoid arthritis (RA)] were evaluated as moderate/high quality of evidence. According to dose-response analyses, consumption of fish, especially fatty types, seems generally safe at one-two servings per week and could exert protective effects.

**Conclusions:** Fish consumption is often associated with a variety of health outcomes, both beneficial and harmless, but only about 34% of the associations were graded as based on a moderate/high quality of evidence, and additional multicenter high quality randomized controlled trials (RCTs) with a large sample size are needed to verify these findings in the future.

**Keywords:** Fish consumption; health; umbrella review; meta-analysis; systematic review

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## Introduction

Fish is a rich source of various nutrients, and one of the most commonly consumed sustenance worldwide (1). Per capita fish consumption is steadily increasing, especially in developed countries (2), and even small effects on individual health could be contributing to public health. The nutritional components of fish, especially n-3 polyunsaturated fatty acids (n-3 PUFA), such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA), have been reported to have a protective effect against cardiovascular disease (CVD), cancers, and psychiatric illnesses, to exert immunomodulatory, anti-inflammatory, and anticancer effects, and to affect blood pressure, lipid metabolism, and glucose metabolism in previous experimental studies (3-10). In general, fish types can be divided into two categories; fatty fish and lean fish, among which fatty fish is more popular worldwide (11). Salmon, tuna, sardines, mackerel, and trout, are examples of fatty fish, in which a higher amount of n-3 PUFA is found, which is more beneficial than the saturated fat found in most meats and that in lean species of fish including cod (5,12).

Recently, epidemiological studies have investigated the relevance between fish consumption and a various of outcomes, including mortality, cancers, CVD, metabolic, cognitive disorders, and other health-related outcomes (13). However, there have been inconsistent conclusions

about the overall effect of fish consumption on health problems, and its precise roles vary among different health outcomes (14). Although many of the reported associations could be causal, they could also be flawed due to residual confounding, reporting bias, or other biases, which frequently over-estimate the magnitudes of the observed effects (15,16). To the best of our knowledge, there are no existing umbrella reviews to comprehensively capture the breadth of health outcomes associated with fish consumption. Thus, we performed an umbrella review to summarize the broad, powerful, and efficient evidence derived from meta-analyses and systematic reviews of fish consumption on all health outcomes.

## Methods

### Literature search

Here, PubMed and Web of Science of Systematic Reviews were used for quantitative reviews of fish intake and health outcomes up to May 2021. The search terms were “fish” and “systematic review” OR “meta-analysis”. The references of eligible articles were conducted using manual screen. The search was performed by three independent researchers (M Wang, H Zhao, and X Peng) and consensus was used to resolve any differences in the literature search.

### Eligibility criteria

The inclusion criterion was systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies considering fish intake as the exposure variable of interest and diverse health conditions. Articles with the following characteristics are excluded: (I) review articles without quantitative statistical analysis; (II) studies on genetic polymorphisms related to fish consumption; (III) RCTs including *in vitro* studies or animal trials; (IV) articles not published in English. As we were interested only in the relevance between total fish consumption and health outcomes, articles that evaluated the exposure to a fish ingredient, for example, fish oil or omega-3 fatty acids, were also excluded. If multiple health outcomes were presented in a single article, we included each of these separately. If a single meta-analysis divided into cohort study and case-control study without including the total estimated effect size for both, we lectured the results of cohort study as it was less influenced by recall and selection biases. If more than one published meta-analysis examined the same

### Highlight box

#### Key findings

- Our findings strongly support the important role for fish as part of a healthy diet, which was recommended by the dietary guidelines in various countries, such as the Australian Dietary Guidelines, Dietary Guidelines for Americans, and European Food Safety Authority (EFSA) Dietary Guidelines.

#### What is known and what is new?

- Recent epidemiological studies have investigated the relevance between the consumption of fish and a wide series of outcomes, including mortality, cancers, cardiovascular disease, metabolic, cognitive disorders, and other health-related outcomes;
- We performed an umbrella review to summarize the breadth, strength, and validity of the evidence derived from meta-analyses and systematic reviews of fish consumption on all health outcomes.

#### What is the implication, and what should change now?

- Additional multicenter, high quality RCTs with large sample sizes are needed to verify these findings in the future.

association, we assessed only the largest meta-analysis to avoid duplicate assessment of the same primary studies. In this umbrella review, we did not screen the individual component studies included in each meta-analysis.

### *Data extraction*

Three authors (M Wang, H Zhao, and L Zhong) extracted data separately. From each eligible meta-analysis, the following information was extracted: (I) first author and publication year; (II) study design and outcomes; (III) total population and number of cases; (IV) type of exposure, measure of exposure, and effect sizes [risk ratio, odds ratio (OR), hazard ratio (HR), 95% confidence intervals (CIs), and continuous outcomes]. Finally, the type of effect model, publication bias by Egger's test, and dose-response analyses were abstracted when possible. Discussion was used to resolve the discrepancies in the process of the extracted data.

### *Assessment of methodological quality*

The evaluation of reporting and methodological quality of all included systematic reviews and meta-analyses were analyzed according to the 11 items of the Assessment of Multiple Systematic Reviews (AMSTAR) checklist (17). Each question could be answered with "yes", "no", "can't answer", and "not applicable". A "yes" scored 1 point, whereas the other answers, including "no", "can't answer", and "not applicable", scored 0 points. An overall score of 3 points or less was defined as the cutoff value for low quality, 4–7 points as moderate quality, and 8 points or more as high quality.

### *Evaluation of the grading of evidence*

The grading of recommendations, assessment, development, and evaluation (GRADE) tool was used to assess the quality of evidence for each outcome in each meta-analysis (18). Included observational studies that started with low deterministic evidence by default and were then downgraded or upgraded according to pre-specified criteria. The downgrade criteria included study boundedness [the weight of studies showed risk of bias by the Newcastle-Ottawa Scale (NOS)], inconformity (large amounts of agnogenic cross-study heterogeneity,  $I^2$  was equal or greater than 50% and P value was less than 0.10), indirectness (presence of factors relating to the exposures, population quantity, and

denouements that limit pervasiveness), inexactitude [95% CIs were broad or decussated a minimally momentous discrepancy of 5% relative risk (RR): 0.95–1.05 for all denouements], and publication bias (prominent evidence of minitype-study effects). Upgrading criteria included a large size effect (RR >2 or RR <0.5 in defect of possible confounding factors), a dose-reactiongradient, and falloff by paradoxical confounding effects.

### *Statistical analysis*

The estimated summary effect with its corresponding 95% CI was abstracted from each eligible meta-analysis. The Cochran's Q test and the  $I^2$  statistic were performed to evaluate the heterogeneity between studies. Publication bias was calculated with Egger's test, in which a P value less than 0.1 was considered significant. Dose-response analyses were not reanalyzed since we did not examine the primary articles.

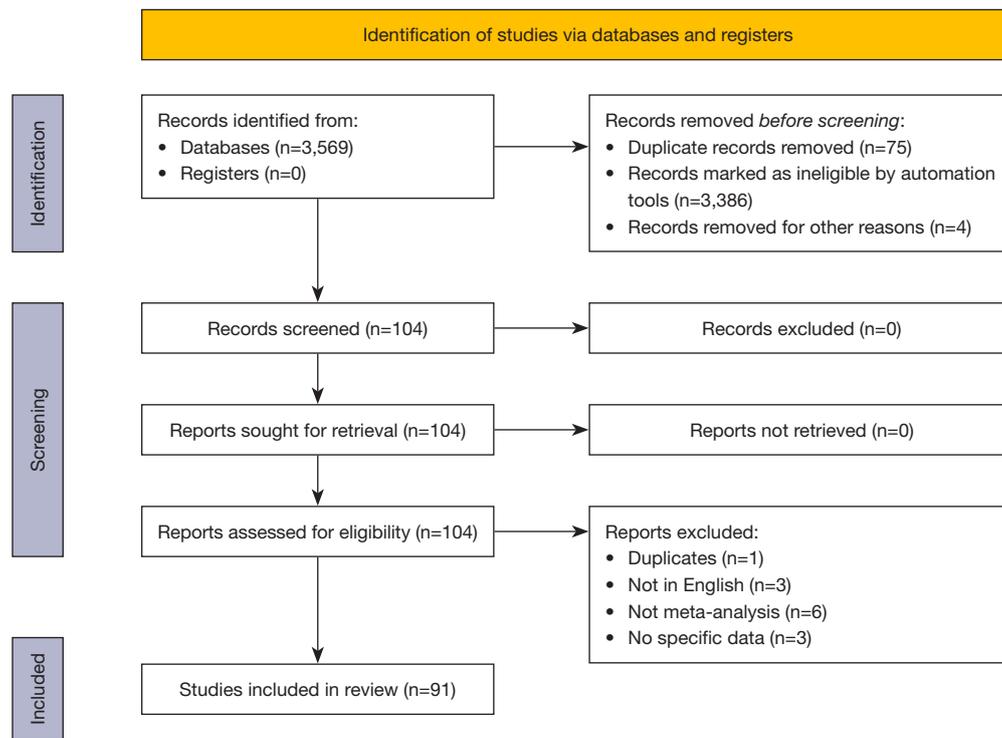
## **Results**

### *Characteristics of meta-analyses*

The search strategy is shown in *Figure 1*. After following the selection process, 91 meta-analyses and systematic reviews of RCTs and observational studies with 66 unique health outcomes were identified, with most outcomes having more than one meta-analysis. The association between fish consumption and mortality is presented in *Table 1* (19-27). *Table 2* (14,22,27-45) presents the associations between consumption of fish and cancer outcomes (46-64), while those between fish consumption and CVD are presented *Table 3* (13,65-77). *Table 4* presents the associations between fish consumption and metabolic outcomes (78-87), and those between fish consumption and cognitive outcomes are presented in *Table 5* (88-97). *Table 6* presents the associations between fish consumption and allergic outcomes (98-100), and those between fish consumption and other outcomes are presented in *Table 7* (101-106).

### *Quality assessment of meta-analyses*

The AMSTAR rating for all studies was determined to be high for approximate 70% or moderate for approximate 30%. The most common reasons for quality downgrades were lack of a registration scheme, unsatisfactory reporting/assessment of the risk of bias in pilot studies, and inappropriate metanalytic methodology.



**Figure 1** Flowchart of the selection process. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>.

### Mortality

High consumption of fish decreased the risk of all-cause death rate (RR: 0.95; 95% CI: 0.92, 0.98) and prostate cancer death (RR: 0.37; 95% CI: 0.18, 0.74) (21,22). Moreover, compared with the minimum intake of fish (less than one serving per month or one to three servings per month) (one serving =100 g), either low (one serving/week) (RR: 0.84; 95% CI: 0.75, 0.95) or moderate intake of fish (two to four servings per week) (RR: 0.79; 95% CI: 0.67, 0.92), but not high fish consumption (more than five servings per week) (RR: 0.83; 95% CI: 0.68, 1.01), had a significantly beneficial effect on the prevention of coronary heart disease (CHD) mortality (23). An increment intake of fish was also inversely associated with a decreased risk of aortic diseases mortality (including aortic dissection mortality), and the largest benefit was at 1–2 servings a week (RR: 0.52; 95% CI: 0.30, 0.88) (24). Dose-response analysis showed a one serving per day increment in fish consumption was associated with a decreased risk of all-cause mortality (RR: 0.93; 95% CI: 0.88, 0.98) (21). Consistently, the intake of one serving of fish per week was

associated with a decreased risk of CVD mortality (RR: 0.96; 95% CI: 0.94, 0.98) and CHD mortality (RR: 0.94; 95% CI: 0.90, 0.98) (23,25). However, no associations were found between fish consumption and total cancer mortality (RR: 0.99; 95% CI: 0.94, 1.05), aortic aneurysm mortality (HR, 0.84; 95% CI: 0.23, 1.11), as well as colorectal cancer (CRC) mortality (RR: 1.02; 95% CI: 0.90, 1.16) (24,26,27).

### Cancer outcomes

High intake of fish was associated with a reduced risk of oral cancer (OR, 0.74; 95% CI: 0.64, 0.85), brain cancer (RR: 0.83; 95% CI: 0.70, 0.99), hepatocellular carcinoma (HCC) (RR: 0.82; 95% CI: 0.71, 0.94), CRC (RR: 0.88; 95% CI: 0.80, 0.95), lung cancer (RR: 0.79; 95% CI: 0.69, 0.92), esophageal cancer (EC) (RR: 0.69; 95% CI: 0.57, 0.85) and its subtype esophageal squamous cell carcinoma (ESCC) (RR: 0.81; 95% CI: 0.66, 0.99), non-Hodgkin lymphoma (NHL) (RR: 0.80; 95% CI: 0.68, 0.94), and glioma (RR: 0.82; 95% CI: 0.70, 0.97) (28,30,32,38,39,42,43,45). Conversely, a positive association between fish intake and

**Table 1** Associations between fish consumption and mortality

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I <sup>2</sup>	Egger test P value
<b>Significant associations</b>													
All-cause mortality	Fish	Schwingshackl 2017	157,688/NA	RR <sup>a)</sup>	0.95	0.92–0.98	39	39	0	0	Random	51	NA
All-cause mortality	Fish	Schwingshackl 2017	157,688/NA	RR <sup>b2)</sup>	0.93	0.88–0.98	19	19	0	0	Random	53	NA
Prostate cancer-specific mortality	Fish	Szymanski 2010	740/49,661	RR <sup>a)</sup>	0.37	0.18–0.74	4	4	0	0	Random	83	0.22
CHD mortality	Fish	Zheng 2012	NA/315,812	RR <sup>b1)</sup>	0.84	0.75–0.95	16	16	0	0	Random	20.1	0.265
CHD mortality	Fish	Zheng 2012	NA/315,812	RR <sup>d)</sup>	0.79	0.67–0.92	13	13	0	0	Random	56.7	0.018
CVD mortality	Fish	Jayedi 2018	11,720/331,239	RR <sup>e)</sup>	0.96	0.94–0.98	8	8	0	0	Random	0	NA
Mortality of total aortic diseases	Fish	Yamagishi 2019	NA	HR <sup>e)</sup>	0.52	0.30–0.88	7	7	0	0	Random	NA	NA
Aortic dissection mortality	Fish	Yamagishi 2019	NA	HR <sup>e)</sup>	0.40	0.18–0.89	3	3	0	0	Random	NA	NA
<b>Non-significant associations</b>													
Total cancer mortality	Fish	Zhang 2018	NA	RR <sup>a)</sup>	0.99	0.94–1.05	10	10	0	0	Random	39.3	>0.4
Total cancer mortality	Fish	Zhang 2018	NA	RR <sup>b2)</sup>	0.98	0.92–1.05	10	10	0	0	Random	21.3	NA
CHD mortality	Fish	Zheng 2012	NA/315,812	RR <sup>e)</sup>	0.83	0.68–1.01	5	5	0	0	Random	0	NA
CRC mortality	Fish	Geelen 2007	NA	RR <sup>a)</sup>	1.02	0.90–1.16	4	4	0	0	Random	0	0.66
Aortic aneurysm mortality	Fish	Yamagishi 2019	NA	HR <sup>e)</sup>	0.84	0.23–1.11	5	5	0	0	Random	NA	NA

<sup>a)</sup>, highest versus lowest/mone; <sup>b1)</sup>, one serving/week; <sup>b2)</sup>, one serving/day; <sup>c)</sup>, 1–2 servings/week; <sup>d)</sup>, 2–4 servings/week; <sup>e)</sup>, >5 servings/week. CHD, coronary heart disease; CI, confidence interval; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; MA, meta-analysis; NA, not available; RCT, randomized controlled trial; RR, relative risk.

**Table 2** Associations between fish consumption and cancer outcomes

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	Cross-sectional	Effects model	I <sup>2</sup>	Egger test P value
<b>Significant associations</b>													
Brain tumor	Fish	Lian 2017	NA	RR <sup>a)</sup>	0.83	0.70–0.99	9	1	8	0	Random	37.5	0.02
Brain tumor	Fish	Lian 2017	NA	RR <sup>b)</sup>	0.95	0.91–0.98	9	1	8	0	Random	51.7	NA
EC	Fish	Jiang 2016	NA	RR <sup>a)</sup>	0.69	0.57–0.85	18	2	16	0	Random	63.6	NA
ESCC	Fish	Han 2013	4,508/NA	RR <sup>a)</sup>	0.81	0.66–0.99	17	3	14	0	Random	51.9	NA
Glioma	Fish	Zhang 2019	NA	RR <sup>a)</sup>	0.82	0.70–0.97	8	0	8	0	Random	43.6	0.088
CRC	Fish	Wu 2012	NA	RR <sup>a)</sup>	0.88	0.80–0.95	41	22	19	0	Random	56.8	0.45
Liver cancer	Fish	Huang 2015	NA/3,624	RR <sup>a)</sup>	0.82	0.71–0.94	10	5	5	0	Random	12.8	0.07
Liver cancer	Fish	Huang 2015	NA/3,624	RR <sup>c)</sup>	0.94	0.91–0.98	10	5	5	0	Random	0	NA
Lung cancer	Fish	Song 2014	8,799/17,072	RR <sup>a)</sup>	0.79	0.69–0.92	20	3	17	0	Random	73	0.098
Myeloid leukemia	Fish	Sergentanis 2019	416/NA	RR <sup>a)</sup>	1.74	1.22–2.47	3	3	0	0	Random	0.8	NA
NHL	Fish	Yang 2020	7,696/NA	RR <sup>a)</sup>	0.80	0.68–0.94	9	2	7	0	Random	66.3	0.002
Oral cancer	Fish	Hu 2019	5,211/7,005	OR <sup>a)</sup>	0.74	0.64–0.85	15	2	13	0	Random	25.2	0.487
<b>Non-significant associations</b>													
Colon cancer	Fish	Vieira 2017	10,512/NA	RR <sup>b)</sup>	0.91	0.80–1.03	11	11	0	0	Random	0	NA
Rectal cancer	Fish	Vieira 2017	3,944/NA	RR <sup>b)</sup>	0.84	0.69–1.02	10	10	0	0	Random	15	NA
EAC	Fish	Han 2013	1,610/NA	RR <sup>a)</sup>	0.86	0.61–1.22	6	1	5	0	Random	58.4	NA
Gastric cancer	Fish	Wu 2011	5,323/NA	RR <sup>a)</sup>	0.87	0.71–1.07	17	2	15	0	Random	73.3	0.59
Leukemia	Fish	Sergentanis 2019	2,536/NA	RR <sup>a)</sup>	1.02	0.89–1.17	3	3	0	0	Random	0	NA
CLL/SLL	Fish	Sergentanis 2019	1,370/NA	RR <sup>a)</sup>	0.99	0.83–1.19	3	3	0	0	Random	0	NA
MM	Fish	Sergentanis 2019	986/NA	RR <sup>a)</sup>	0.94	0.67–1.33	3	3	0	0	Random	30.2	NA
Prostate cancer	Fish	Szymanski 2010	NA/445,820	RR <sup>a)</sup>	1.01	0.90–1.14	12	12	0	0	Random	NA	0.84
Thyroid cancer	Fish	Cho 2015	NA	RR <sup>a)</sup>	1.01	0.83–1.23	16	0	16	0	Random	58	NA
Renal cancer	Fish	Bai 2013	9,324/608,753	RR <sup>a)</sup>	0.99	0.92–1.07	15	3	12	0	Fixed	23.8	0.38
Ovarian cancer	Fish	Jiang 2014	NA	RR <sup>a)</sup>	1.04	0.89–1.22	5	5	0	0	Fixed	0	0.29
Breast cancer	Fish	Wu 2016	20,810/914,451	RR <sup>a)</sup>	1.04	0.97–1.12	18	18	0	0	Random	47.9	0.613

**Table 2** (continued)

Table 2 (continued)

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	Cross-sectional	Effects model	I <sup>2</sup>	Egger test P value
Breast cancer	Fatty fish	Wu 2016*	NA	RR <sup>a)</sup>	0.81	0.58–1.12	5	2	3	0	Random	87	NA
Breast cancer	Lean fish	Wu 2016*	NA	RR <sup>a)</sup>	1.09	1.00–1.19	4	2	2	0	Random	0	NA
Pancreatic cancer	Fish	Jiang 2019	4,994/1,794,601	RR <sup>a)</sup>	1.04	0.95–1.13	13	13	0	0	Random	0	0.77
Endometrial cancer	Fish	Hou 2017	NA	RR <sup>a)</sup>	1.04	0.84–1.30	12	4	8	0	Random	80.4	NA
Endometrial cancer	Fish	Hou 2017	NA	RR <sup>c)</sup>	1.00	0.94–1.07	10	2	8	0	Random	81.7	NA
Bladder cancer	Fish	Li 2011	NA	RR <sup>a)</sup>	0.86	0.61–1.12	14	5	9	0	Random	85.4	NA

a) highest versus lowest/none; b) one serving = 100 g/day; c) one serving/week; \*, Zhi-Hui Wu. CI, confidence interval; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CRC, colorectal cancer; EAC, esophageal adenocarcinoma; EC, endometrial cancer; ESCC, esophageal squamous cell carcinoma; MA, meta-analysis; MM, multiple myeloma; NA, not available; NHL, non-Hodgkin lymphoma; OR, odds ratio; RR, relative risk.

Table 3 Associations between fish consumption and cardiovascular disease

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I <sup>2</sup>	Egger test P value
Significant associations													
Stroke	Fish	Zhao 2019	NA	HR <sup>a)</sup>	0.90	0.85–0.96	33	33	0	0	Random	39.2	0.084
Stroke	Lean fish	Qin 2018	NA	RR <sup>a)</sup>	0.81	0.67–0.99	4	4	0	0	Random	0	0.324
Hemorrhagic stroke	Fish	Zhao 2019	NA	HR <sup>a)</sup>	0.88	0.80–0.96	13	13	0	0	Random	0	0.084
ACS	Fish	Leung Yinko 2014	8,517/408,305	RR <sup>a)</sup>	0.78	0.70–0.88	19	11	8	0	Random	0	0.6
MI	Fish	Jayed 2019	NA/398,221	RR <sup>a)</sup>	0.73	0.59–0.87	11	11	0	0	Random	72	NA
CHD	Fish	Bechthold 2019	NA	RR <sup>b)</sup>	0.88	0.79–0.99	15	15	0	0	Random	40	NA
HF	Fish	Bechthold 2019	7,945/NA	RR <sup>a)</sup>	0.89	0.80–0.99	8	8	0	0	Random	18	NA
HF	Fish	Bechthold 2019	NA	RR <sup>b)</sup>	0.80	0.67–0.95	7	7	0	0	Random	20	NA
Cerebrovascular disease	Fish	Chowdhury 2012	25,320/675,048	RR <sup>a)</sup>	0.88	0.84–0.93	21	21	0	0	Random	18.5	>0.05
Cerebrovascular disease	Fish	Chowdhury 2012	24,612/650,210	RR <sup>d)</sup>	0.94	0.90–0.98	18	18	0	0	Random	22	>0.05

Table 3 (continued)

Table 3 (continued)

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I <sup>2</sup>	Egger test P value
Cerebrovascular disease	Fish	Chowdhury 2012	16,890/394,958	RR <sup>a)</sup>	0.88	0.81–0.96	8	8	0	0	Random	20	>0.05
Cerebrovascular disease	Fatty fish	Chowdhury 2012	2,695/62,799	RR <sup>a)</sup>	0.84	0.72–0.98	4	4	0	0	Random	10.1	>0.05
Triglycerides	Fish	Alhassan 2017	596/1,128	MD	-0.11 mmol/L	-0.18 to -0.04	14	0	0	14	Random	0	NA
Triglycerides	Fatty fish	Alhassan 2017	438/831	MD	-0.11 mmol/L	-0.19 to -0.03	12	0	0	12	Random	7	NA
HDL-cholesterol	Fish	Alhassan 2017	584/1,104	MD	0.06 mmol/L	0.02–0.11	13	0	0	13	Random	28	NA
HDL-cholesterol	Fatty fish	Alhassan 2017	438/831	MD	0.08 mmol/L	0.04–0.13	12	0	0	12	Random	0	NA
Non-significant associations													
Stroke	Fatty fish	Qin 2018	NA	RR <sup>a)</sup>	0.88	0.74–1.04	5	5	0	0	Random	26.2	0.891
CHD	Fish	Bechthold 2019	16,732/NA	RR <sup>a)</sup>	0.94	0.88–1.02	22	22	0	0	Random	52	NA
Ischemic stroke	Fish	Zhao 2019	NA	HR <sup>a)</sup>	0.96	0.89–1.03	15	15	0	0	Random	27.9	0.084
Cerebrovascular disease	Lean fish	Chowdhury 2012	2,695/62,799	RR <sup>a)</sup>	1.03	0.90–1.19	4	4	0	0	Random	0	>0.05
Triglycerides	Lean fish	Alhassan 2017	158/297	MD	-0.09 mmol/L	-0.26 to 0.04	2	0	0	2	Random	0	NA
HDL-cholesterol	Lean fish	Alhassan 2017	146/273	MD	-0.02 mmol/L	-0.10 to 0.06	1	0	0	1	Random	NA	NA
AF	Fish	Li 2017	NA	RR <sup>a)</sup>	1.01	0.94–1.09	6	6	0	0	Random	0	NA
AF	Fish	Li 2017	NA	RR <sup>c)</sup>	0.99	0.96–1.02	6	6	0	0	Random	23	NA
Hypertension	Fish	Schwingshackl 2017	NA/83,612	RR <sup>a)</sup>	1.01	0.92–1.10	8	8	0	0	Random	57	NA
Hypertension	Fish	Schwingshackl 2017	NA	RR <sup>b)</sup>	1.07	0.98–1.16	7	7	0	0	Random	74	NA
VTE	Fish	Zhang 2020	NA	RR <sup>a)</sup>	1.02	0.93–1.11	6	6	0	0	Random	33	0.176

a) highest versus lowest/none; b) one serving = 100 g/day; c) one serving/week; d) 2–4 versus ≤1 serving a week; e) ≥5 versus ≤1 serving a week. MA, meta-analysis; CI, confidence interval; RCT, randomized controlled trial; NA, not available; HR, hazard ratio; RR, relative risk; MD, mean difference; ACS, acute coronary syndrome; MI, myocardial infarction; CHD, coronary heart disease; HF, heart failure; HDL, high-density lipoprotein; AF, atrial fibrillation; VTE, venous thromboembolism.

**Table 4** Associations between fish consumption and metabolic disease

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I <sup>2</sup>	Egger test P value
Significant associations													
Metabolic Syndrome	Fish	Kim 2015	NA	RR <sup>a)</sup>	0.71	0.58–0.87	2	2	0	0	fixed	60.7	NA
Metabolic Syndrome	Fish	Kim 2015	NA	RR <sup>c)</sup>	0.94	0.90–0.98	2	2	0	0	Fixed	66.3	NA
T2DM	Fatty fish	Namazi 2019	NA	RR <sup>b)</sup>	0.89	0.82–0.98	5	5	0	0	Random	0	0.42
Vitamin D	Fish	Lehmann 2015	NA	MD <sup>a)</sup>	4.4 nmol/L	1.7–7.1	9	0	0	9	Random	25	NA
Vitamin D	Fish	Lehmann 2015	NA	MD <sup>d)</sup>	3.8 nmol/L	0.6–6.9	10	0	0	10	Random	38	NA
Vitamin D	Fish	Lehmann 2015	NA	MD <sup>a)</sup>	8.3 nmol/L	2.1–14.5	4	0	0	4	Random	0	NA
Vitamin D	Fatty fish	Lehmann 2015	NA	MD <sup>a)</sup>	6.8 nmol/L	3.7–9.9	7	0	0	7	Random	0	NA
Non-significant associations													
T2DM	Fish	Schwingshackl 2017	NA/45,029	RR <sup>a)</sup>	1.04	0.95–1.13	16	16	0	0	Random	76	NA
T2DM	Fish	Schwingshackl 2017	NA	RR <sup>b)</sup>	1.09	0.93–1.28	15	15	0	0	Random	84	NA
T2DM	Lean fish	Namazi 2019	NA	RR <sup>a)</sup>	1.03	0.87–1.22	5	5	0	0	Random	51	0.36
Vitamin D	Lean fish	Lehmann 2015	NA	MD <sup>a)</sup>	1.9 nmol/L	-2.3 to 6.0	7	0	0	7	Random	37	NA

<sup>a)</sup>, highest versus lowest/none; <sup>b)</sup>, one serving = 100g/day; <sup>c)</sup>, one serving/week; <sup>d)</sup>, short-term studies (4–8 weeks); <sup>e)</sup>, long-term studies (6 months or 23 weeks). CI, confidence interval; MA, meta-analysis; MD, mean difference; NA, not available; RCT, randomized controlled trial; RR, relative risk; T2DM, type 2 diabetes.

**Table 5** Associations between fish consumption and cognitive disease

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	Cross-sectional	Effects model	I <sup>2</sup>	Egger test P value
Significant associations													
Depression	Fish	Li 2016	NA/102,785	RR <sup>a)</sup>	0.83	0.74–0.93	26	10	0	16	Random	64.5	0.419
Dementia	Fish	Bakre 2018	3,139/40,668	RR <sup>b)</sup>	0.80	0.74–0.87	8	6	2	0	Fixed	0	0.597
AD	Fish	Zeng 2017	NA	RR <sup>a)</sup>	0.80	0.65–0.97	7	7	0	0	Fixed	48.2	NA
AD	Fish	Zeng 2017	NA	RR <sup>b)</sup>	0.88	0.79–0.99	7	7	0	0	Random	55.3	NA
MS	Fish	Rezaeizadeh 2022	2,370/7,170	RR <sup>a)</sup>	0.77	0.64–0.92	6	6	0	0	Random	54.7	0.051
Non-significant associations													
Mild cognitive impairment	Fish	Zeng 2017	NA	RR <sup>a)</sup>	1.03	0.78–1.37	2	2	0	0	Fixed	0	NA

<sup>a)</sup>, highest versus lowest/none; <sup>b)</sup>, one serving/week. AD, Alzheimer's disease; CI, confidence interval; MA, meta-analysis; MS, multiple sclerosis; NA, not available; RR, relative risk.

**Table 6** Associations between fish consumption and allergic disease

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I <sup>2</sup>	Egger test P value
<b>Significant associations</b>													
Current asthma	Fish	Papamichael2018	NA	OR <sup>a)</sup>	0.75	0.60–0.95	3	3	0	0	Random	11.5	NA
Current wheeze	Fish	Papamichael2018	NA	OR <sup>b)</sup>	0.62	0.48–0.80	2	2	0	0	Random	0	NA
Current asthma	Fatty fish	Papamichael2018	NA	OR <sup>c)</sup>	0.35	0.18–0.67	2	2	0	0	Random	0	NA
Eczema	Fish	Zhang 2017	NA/13,823	RR <sup>d)</sup>	0.61	0.47–0.80	4	4	0	0	Random	68	NA
Allergic rhinitis	Fish	Zhang 2017	NA/9,987	RR <sup>e)</sup>	0.54	0.36–0.81	3	3	0	0	Random	74	NA
<b>Non-significant associations</b>													
Current wheeze	Fish	Papamichael2018	NA	OR <sup>d)</sup>	0.81	0.64–1.02	9	9	0	0	Random	82.4	NA
Asthma	Fish	Yang 2013	NA	RR <sup>e)</sup>	0.90	0.69–1.18	2	2	0	0	Fixed	0	NA
Sensitization	Fish	Zhang 2017	NA/3,099	RR <sup>f)</sup>	0.88	0.65–1.21	2	2	0	0	Random	33	NA
Eczema	Fish	Zhang 2017	NA/15,945	RR <sup>f)</sup>	0.88	0.75–1.04	10	10	0	0	Random	53	NA
Allergic rhinitis	Fish	Zhang 2017	NA/32,589	RR <sup>f)</sup>	0.95	0.62–1.45	3	3	0	0	Random	44	NA
Wheeze	Fish	Zhang 2017	NA/42,096	RR <sup>f)</sup>	0.94	0.83–1.07	8	8	0	0	Random	26	NA
Asthma	Fish	Zhang 2017	NA/37,295	RR <sup>f)</sup>	0.94	0.75–1.18	4	4	0	0	Random	52	NA
Wheeze	Fish	Zhang 2017	NA/8,597	RR <sup>g)</sup>	0.94	0.77–1.14	2	2	0	0	Random	0	NA
Asthma	Fish	Zhang 2017	NA/8,902	RR <sup>g)</sup>	0.84	0.69–1.02	3	3	0	0	Random	0	NA

<sup>a)</sup>, children (0–4 years old) for 'all fish' intake versus 'no fish'; <sup>b)</sup>, children (0–4.5 years old) for 'all fish' intake versus 'no fish'; <sup>c)</sup>, 'fatty fish' intake versus 'no fatty fish' in children (8–14 years); <sup>d)</sup>, children (0–13 years old) for 'all fish' intake versus 'no fish'; <sup>e)</sup>, highest versus lowest in adults; <sup>f)</sup>, maternal fish intake during pregnancy; <sup>g)</sup>, fish intake in infancy. CI, confidence interval; MA, meta-analysis; NA, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

**Table 7** Associations between fish consumption and AMD, IBD, skeletal, and arthritis disease

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I <sup>2</sup>	Egger test P value
Significant associations													
AMD	Fish	Dinu 2019	NA/237,464	RR <sup>a)</sup>	0.82	0.75–0.90	8	8	0	0	Random	33	NA
IBD	Fish	Mozaffari 2020	823/41,601	ES <sup>a)</sup>	0.68	0.46–1.00	6	1	5	0	Random	76.4	NA
CD	Fish	Mozaffari 2020	NA	ES <sup>a)</sup>	0.54	0.31–0.96	5	1	4	0	Random	NA	NA
Hip fracture	Fish	Sadeghi 2019	NA	ES <sup>a)</sup>	0.88	0.79–0.98	6	4	2	0	Fixed	57.9	>0.44
Non-significant associations													
UC	Fish	Mozaffari 2020	NA	ES <sup>a)</sup>	0.82	0.56–1.22	3	2	1	0	Fixed	30.6	NA
RA	Fish	Di Giuseppe 2014	3,346/174,702	RR <sup>a)</sup>	0.96	0.91–1.01	7	3	4	0	Random	0	0.27

<sup>a)</sup>, highest versus lowest/none. AMD, age-related macular degeneration; CD, Crohn's disease; CI, confidence interval; ES, estimated size; IBD, inflammatory bowel disease; MA, meta-analysis; NA, not available; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; UC, ulcerative colitis.

myeloid leukemia risk (RR: 1.74; 95% CI: 1.22, 2.47) was observed in high-compared with low-intake categories (44). The subgroup analysis by sex showed a protective effect of fish consumption on lung cancer was present only in females (39), and when the subgroup analysis was conducted by geographic location, a protective effect was only observed in HCC and lung cancer for Asian populations, as well as oral cancer and ESCC for European populations (28,32,39,43).

According to dose-response analyses, fish intake of one serving per week was associated with a decreased risk of brain cancer (RR: 0.95; 95% CI: 0.91, 0.98) and HCC (RR: 0.94; 95% CI: 0.91, 0.98) (29,32). There was no relevance between a high intake of fish with the risk of prostate cancer (RR: 1.01; 95% CI: 0.90, 1.14), renal cancer (RR: 0.99; 95% CI: 0.92, 1.07), ovarian cancer (RR: 1.04; 95% CI: 0.89, 1.22), gastric cancer (RR: 0.87; 95% CI: 0.71, 1.07), thyroid cancer (RR: 1.01; 95% CI: 0.83, 1.23), bladder cancer (RR: 0.86; 95% CI: 0.61, 1.12), breast cancer (RR: 1.04; 95% CI: 0.97, 1.12), endometrial cancer (RR: 1.04; 95% CI: 0.84, 1.30), pancreatic cancer (RR: 1.04; 95% CI: 0.95, 1.13), colon cancer (RR: 0.91; 95% CI: 0.80, 1.03), rectal cancer (RR: 0.84; 95% CI: 0.69, 1.02), esophageal adenocarcinoma (EAC) (RR: 0.86; 95% CI: 0.61, 1.22), leukemia (RR: 1.02; 95% CI: 0.89, 1.17), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (RR: 0.99; 95% CI: 0.83, 1.19), and multiple myeloma (MM) (RR: 0.94; 95% CI: 0.67, 1.33) (22,36,38,43,44,47,48,51,53,55,56,62,63). However, for endometrial cancer, although the null association was observed for every one additional serving/week of fish intake, an inverse association was detected in studies conducted in Europe (RR: 0.90; 95% CI: 0.84, 0.97) and studies adjusted for smoking (RR: 0.95; 95% CI: 0.91, 1.00), and a significant positive association was detected in studies conducted in Asia (RR: 1.15; 95% CI: 1.10, 1.21) (62). In addition, studies conducted in Europe (RR: 0.71; 95% CI: 0.61, 0.82) and Australia (RR: 0.76; 95% CI: 0.63, 0.92) have shown that fish consumption is associated with a significantly reduced risk of ovarian cancer, and studies adjusted for the use of oral contraceptives (RR: 0.79; 95% CI: 0.63, 0.99) and parity (RR: 0.79; 95% CI: 0.63, 0.99) (48). In addition, a slightly increased risk of thyroid cancer was observed among those consuming high amounts of fish in iodine nondeficient areas (RR: 1.18; 95% CI: 1.03, 1.35) (53).

### Cardiovascular outcomes and ischemic diseases

Fish consumption was associated with a decreased risk

of acute coronary syndrome (ACS) (RR: 0.78; 95% CI: 0.70, 0.88), cerebrovascular disease (RR: 0.88; 95% CI: 0.84, 0.93), heart failure (HF) (RR: 0.89; 95% CI: 0.80, 0.99), myocardial infarction (MI) (RR: 0.73; 95% CI: 0.59, 0.87), and stroke (HR, 0.90; 95% CI: 0.85, 0.96), multiple sclerosis (MS) (OR: 0.77; 95% CI: 0.64, 0.92), especially hemorrhagic stroke (HR, 0.88; 95% CI: 0.80, 0.96) (65–69). Considering the different types of fish, the consumption of fatty fish (RR: 0.84; 95% CI: 0.72, 0.98) could decrease the risk of cerebrovascular disease, while no significant association was found for lean fish (RR: 1.03; 95% CI: 0.90, 1.19) (66). In contrast, the reduction of stroke risk was associated with the consumption of lean fish (RR: 0.81; 95% CI: 0.67, 0.99), but not fatty fish (RR: 0.88; 95% CI: 0.74, 1.04) (13).

According to dose-response analyses, an increment of two servings per week of fish consumption could decrease the risk of cerebrovascular disease by 4% (RR: 0.96; 95% CI: 0.93, 0.99) (66). A linear dose-responses analyses showed the risk of stroke decreased by 2–12% with increased fish consumption up to one-seven servings/week (69). Also, an increase of one serving of fish per day could decrease the risk of HF (RR: 0.80; 95% CI: 0.67, 0.95) by 20%, and an increase of one serving per week was associated with a 4% decreased risk of MI (RR: 0.96; 95% CI: 0.94, 0.99) in Asia (RR: 0.94; 95% CI: 0.91, 0.97) and a 5% reduced risk of ACS (RR: 0.95; 95% CI: 0.92, 0.97), respectively (65,67,68).

There was a small association between consumption of fish and CHD risk comparing the highest categories and the lowest categories, a small association was seen between fish intake and risk of CHD (RR: 0.94; 95% CI: 0.88, 1.02), atrial fibrillation (AF) (RR: 1.01; 95% CI: 0.94, 1.09) and venous thromboembolism (VTE) (RR: 1.02; 95% CI: 0.93, 1.11), but neither association reached significance (70,73,77). In addition, dose-responses analyses showed the intake of one serving of fish per day was associated with a 12% (RR: 0.88; 95% CI: 0.79, 0.99) decreased risk of CHD, particularly for females (RR: 0.64; 95% CI: 0.50, 0.81) (70).

In addition, a meta-analysis of 14 RCTs showed consumption of fish, especially fatty fish, was associated with a moderately significant reduction in plasma triglycerides levels [mean difference (MD): -0.11 mmol/L; 95% CI: -0.18, 0.04] and an increase in high-density lipoprotein (HDL) levels (MD: 0.06 mmol/L; 95% CI: 0.02, 0.11) (74). Highest compared with the lowest category (RR: 1.01; 95% CI: 0.92, 1.10) and dose-responses analyses (RR: 1.07; 95% CI: 0.98, 1.16) of fish intake were not statistically

significantly associated with the risk of hypertension, respectively (75).

### *Metabolic outcomes*

The consumption of fish increased serum 25-hydroxyvitamin D [25(OH)D] concentrations by a weighted MD of 4.4 nmol/L (MD: 4.4 nmol/L; 95% CI: 1.7, 7.1), and long-term (~6 months) (MD: 8.3 nmol/L; 95% CI: 2.1, 14.5) consumption showed a higher MD than short-term (4–8 weeks) (MD: 3.8 nmol/L; 95% CI: 0.6, 6.9). Considering the type of the fish, the consumption of fatty fish resulted in a MD of 6.8 nmol/L (MD: 6.8 nmol/L; 95% CI: 3.7, 9.9), whereas for lean fish the MD was 1.9 nmol/L (MD: 1.9 nmol/L; 95% CI: -2.3, 6.0) (78). Moreover, consumption of fish was associated with a reduced risk of metabolic syndrome (MetS) (RR: 0.71; 95% CI: 0.58, 0.87), and an increase of one serving/week fish intake could reduce the risk by 6% (RR: 0.94; 95% CI: 0.90, 0.98) (79). In addition, total fish (RR: 1.04; 95% CI: 0.95, 1.13) and lean fish consumption (RR: 1.03; 95% CI: 0.87, 1.22) were not significantly related to the risk of type 2 diabetes mellitus (T2DM), while fatty fish consumption (RR: 0.89; 95% CI: 0.82, 0.98) was inversely associated with the risk of T2DM (80,82).

### *Cognitive outcomes*

Highest compared with the lowest category of fish intake was associated with a decreased risk of developing depression (RR: 0.83; 95% CI: 0.74, 0.93) in Europe (RR: 0.72; 95% CI: 0.63, 0.82) (88). Analyses of high versus low consumption of fish indicated dementia risk was reduced by 20% (RR: 0.80; 95% CI: 0.74, 0.87) regardless of income level, and dose-response models showed fish consumption could decrease the risk of dementia by 16%, 22%, and 23% for low level consumers (consumed fish once weekly) (RR: 0.84; 95% CI: 0.72, 0.98), middle level consumers ( $\geq$  twice weekly) (RR: 0.78; 95% CI: 0.68, 0.90), and high level consumers ( $\geq$  once daily) (RR: 0.77; 95% CI: 0.61, 0.98), respectively (94). For Alzheimer's disease (AD), an inverse association was observed for the highest compared with the lowest fish intake category (RR: 0.80; 95% CI: 0.65, 0.97), and for each additional one serving per week (RR: 0.88; 95% CI: 0.79, 0.99) (95). However, increasing fish intake had no obvious effect on the risk of mild cognitive impairment (MCI) (RR: 1.03; 95% CI: 0.78, 1.37) (96). Fish consumption was also associated with a decreased risk of

MS (OR, 0.77; 95% CI: 0.64, 0.92) (97).

### *Allergic outcomes*

Comparing the highest group of fish consumption with the lowest group, no significant association was found between fish and asthma among adults (98). Additionally, maternal fish intake during pregnancy did not affect any atopic outcome in children and adults, whereas total fish or fatty fish consumption during the infancy period seemed to have a protective impact on asthma, wheeze, eczema, and allergic rhinitis in children, especially up to 4.5 years old or 8–14 years old, respectively (99,100).

### *Other outcomes*

There was no dose-response association between fish consumption and risk of rheumatoid arthritis (RA) (RR: 0.96; 95% CI: 0.91, 1.01) (101). Fish consumption was inversely associated with risk of hip fracture [estimated size (ES), 0.88; 95% CI: 0.79, 0.98] (102), while it conferred a beneficial effect on the development of age-related macular degeneration (AMD) (RR: 0.82; 95% CI: 0.75, 0.90), regardless of whether early (RR: 0.84; 95% CI: 0.73, 0.97) or late AMD (RR: 0.79; 95% CI: 0.70, 0.90) (103). In addition, using a random-effects model, a marginally negative association was observed between fish consumption and inflammatory bowel disease (IBD) (ES, 0.68; 95% CI: 0.46, 1.00), while a strong inverse association regarding Crohn's disease (CD) (ES, 0.54; 95% CI: 0.31, 0.96) was detected in studies conducted in Asian countries (ES, 0.54; 95% CI: 0.37, 0.78) and in studies adjusted for BMI and smoking (ES, 0.35; 95% CI: 0.19, 0.66) (106).

### *Heterogeneity*

Approximately, 44% of the meta-analyses had low heterogeneity, with  $I^2 < 25\%$ ; 8% had very high heterogeneity, with  $I^2 > 75\%$ ; and 42% had moderate-to-high heterogeneity, with  $I^2$  ranging from 25–75%. The individual studies in each meta-analysis differed for a number of factors, including geography and ethnicity, treatment differences, methods used to determine fish consumption, measurements of fish consumption, duration of follow-up, and evaluation of outcomes. The remaining 6% of the included meta-analyses did not disclose the heterogeneity of the studies that included specific comparisons, nor were

they re-analyzed using randomized or fixed models.

### *Publication bias*

Egger's regression test was performed in the present umbrella review. P value for publication bias were reported in 36 included meta-analyses, three of which reported statistical evidence of publication bias. These included CHD mortality (P=0.018), NHL (P=0.002), and brain tumor (P=0.02) (23,29,45). While not report significant publication bias was reported in the remaining meta-analyses, in all probability that unmeasured publication bias exists in numerous of the conclusive evaluations we have rendered and not assessed.

### *Strength of epidemiologic evidence*

A total of 15 inverse associations (including all-cause mortality, prostate cancer mortality, CVD mortality, ESCC, glioma, oral cancer, NHL, ACS, cerebrovascular disease, triglycerides, MetS, AMD, IBD, CD, and MS), two positive associations (vitamin D and HDL-cholesterol), and nine nonsignificant associations [comprising CRC mortality, EAC, prostate cancer, renal cancer, ovarian cancer, hypertension, VTE, ulcerative colitis (UC), and RA] showed moderate/high epidemiologic evidence.

In total, 15 additional inverse associations (mortality of total aortic diseases, aortic dissection mortality, brain cancer, EC, CRC, liver cancer, lung cancer, stroke, hemorrhagic stroke, MI, HF, depression, dementia, AD, and hip fracture) and one positive association (myeloid leukemia) showed statistically significant risk estimates, and their credibility was weak.

The other 24 outcomes (such as total cancer mortality, aortic aneurysm mortality, CHD mortality, colon cancer, rectal cancer, gastric cancer, leukemia, CLL/SLL, MM, thyroid cancer, breast cancer, pancreatic cancer, endometrial cancer, bladder cancer, ischemic stroke, CHD, AF, T2DM, asthma, sensitization, eczema, allergic rhinitis, wheeze, and MCI) did not show significant associations, and the quality of evidence was low or very low.

## **Discussion**

### *Main findings*

This umbrella review of meta-analyses of RCTs and observational studies provides a comprehensive overview

and critical assessment of the consumption of fish associated with human health. A total of 64 outcomes, including mortality, cancer, CVD, metabolic, cognitive, allergy, and other outcomes, have been studied. The methodologic quality varied considerably across the published meta-analyses. The quality of evidence was graded as moderate or high for all-cause mortality, prostate cancer mortality, CVD mortality, ESCC, oral cancer, ACS, cerebrovascular disease, triglycerides, MetS, AMD, IBD, and CD, for which fish consumption reduced their risks; for vitamin D and HDL-cholesterol, whose levels were raised by fish consumption; and for CRC mortality, EAC, prostate cancer, renal cancer, ovarian cancer, hypertension, UC, and RA, whose risks were not related to fish consumption. For the other outcomes, the quality of evidence was low or very low, which might be explained by the high proportion of meta-analyses that included fewer than five studies or had high heterogeneity.

### *Outcome interpretation*

#### **Fish consumption and mortality outcomes**

The results showed a higher intake of fish was associated with a decreased risk of all-cause mortality, prostate cancer mortality, and CVD mortality but no association between fish consumption and CRC mortality was found, for which we found moderate quality of evidence (21,22,25,27). Our results support the recommendation made by the recent 2015–2020 Dietary Guidelines for Americans to consume more than 227 g fish per week (107). It is worth noting that subgroup analysis by geographic location showed a significant association of fish consumption with all-cause mortality for studies conducted in Asia, but not in Europe (21). The different results appeared possibly due to the different dietary pattern of fish consumption in Asian and Western populations, of which the former have a higher intake, which may impact the significance of the results (25).

Although intake of fish had a protective effect on the risk of CHD mortality (low and moderate fish consumption, not high fish consumption), total aortic disease and its subtype aortic dissection mortality, total cancer mortality, and aortic aneurysm mortality, the quality of evidence was only low and further investigation is needed (23,24,26).

#### **Fish consumption and cancer outcomes**

Our findings confirm Australian Dietary Guidelines recommendations for a higher intake of fish, and we observed a moderate quality of evidence for an inverse association with oral cancer, glioma, NHL, and ESCC,

and a nonsignificant association with prostate cancer, renal cancer, ovarian cancer, and EAC (22,28,30,43,45,47,48,108).

The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) recommend a higher intake of fish, for which we also found an inverse association with the risk of brain cancer, EC, CRC, liver cancer, and lung cancer, but the quality of evidence was low (29,32,38,39,42,109). We also found low quality of evidence for a positive association of fish intake with the risk of myeloid leukemia, and a null association with the risk of colon cancer, rectal cancer, gastric cancer, leukemia, CLL/SLL, MM, thyroid cancer, breast cancer, pancreatic cancer, endometrial cancer, and bladder cancer (36,44,51,53,55,56,62,63). It may be that heavy metals, which are frequently linked to the increased intake of fish, lead to the increased risk of myeloid leukemia in the highest fish consumption levels (44,110,111). These results indicate that more studies are needed. Additionally, a previous meta-analysis indicated an increase of one serving/week of salted fish intake, but not fresh fish, was significantly associated with an increased risk of gastric cancer (50). This may be because highly salted or smoked fish products can contain chemical carcinogens (112).

#### **Fish consumption and cardiovascular outcomes**

Recommendations for improving the cardiovascular health of all Americans with a dietary pattern including consumption of fish at least one to two servings per week, are included in the guidelines of the American Heart Association (AHA) Goals and Metrics Committee of the Strategic Planning Task Force issued 2020 Impact Goals (113). This information accords with our results which show a higher intake of fish was associated with a decreased level or risk of ACS, cerebrovascular disease and triglycerides, and an increased level of HDL-cholesterol, for which we found high quality of evidence (65,66,74). Particularly, fatty fish, but not lean fish could play an important role in the prevention of cerebrovascular diseases (66). In addition, we found moderate quality evidence that consumption of fish was not significantly associated with the risk of hypertension and VTE (75,77).

Our results also confirmed the inverse association of fish consumption with the risk of stroke, hemorrhagic stroke, MI, and HF, and a null association with ischemic stroke, CHD, and AF, but the quality of evidence for these associations was low, indicating further investigation is needed (67–70,73). Interestingly, lean fish, but not fatty fish, could confer a decreased risk of stroke, which was

somewhat opposite to the general knowledge that fatty fish is “better” than lean fish (13). Nevertheless, a Norwegian diet study gives a possible explanation that lean fish contains more iodine, selenium, and less energy than fatty fish, which are beneficial to health (114). Generally, both fatty fish and lean fish are good for cardiovascular and cerebrovascular health, and frequent consumption of fatty fish is better than lean fish.

### **Fish consumption and other outcomes**

In this umbrella review, we found high quality evidence that consumption of fish was associated with an increased level of vitamin D, while it was not significantly associated with the risk of RA (78,101). A randomized intervention trial came to similar conclusions concerning the beneficial association between fish intake and the level of vitamin D (115). In particular, long-term fish consumption or consumption of fatty fish resulted in higher serum 25(OH)D concentrations than short-term or lean fish, respectively (78). Moreover, our findings showed that higher consumption of fish was associated with a decreased risk of MetS, AMD, IBD, and CD but no association between fish consumption and UC was found, for which we found a moderate quality of evidence (79,103,106).

Although we also observed a reduced risk of MS, depression, dementia, AD, and hip fracture, and a null association of T2DM and MCI with consumption of fish, respectively, the quality of evidence for these associations was low and further investigation is needed (80,88,94,95,97,102).

### **Possible mechanisms**

Although the precise mechanisms by which fish consumption beneficially affects health are not well-established, fish is a rich source of n-3 PUFA, vitamins, essential amino acids, and trace elements, which exert chemopreventive activity, anti-carcinogenic, anti-inflammatory, and synergistic antioxidant properties, which may at least partly explain its protective effects (116-119). For example, fish is a good source of trace elements, especially selenium, which may have synergistic antioxidant effects against all-cause mortality (21). In addition, n-3 PUFA, which has antiarrhythmic properties and reduces serum triacylglycerol (TAG) and platelet aggregation, has been observed to play an important role in the protective effect of fish on CHD risk (120,121). Also, it has been shown that higher consumption of n-3 PUFA may be associated with lower risk of cancer,

partially due to its favorable effects of chemopreventive activity, including inhibition of eicosanoid biosynthesis derived from arachidonic acid, promotion of vasodilation, attenuation of inflammation, inhibition of mutations, and enhancement of cell apoptosis (122-124). Fish is also a good source of vitamin D, which has been linked to inverse T2DM risk (125). Considering the synergic effect of many components in fish, such as n-3 PUFA, trace elements, amino acid, and vitamins, comprehensive analysis of the potential mechanism behind the association between fish consumption and health is necessary.

### **Strengths and limitations**

There are also some restrictions that should be considered. Firstly, this umbrella reviewer relied on existing systematic reviews and meta-analyses. As a consequence, the quality of the included articles might impact the quality of systematic reviews and meta-analyses directly. Secondly, although a large number of studies were included in the present meta-analysis, potential publication bias should also be considered. Thirdly, reporting bias might cause a form of reverse causation, and fourthly, a number of health-related outcomes were inappropriately covered, and this gap has been emphasized. Fifthly, due to the lack of a dose-response meta-analysis, we did not examine the original article and therefore did not conduct a re-analysis, and finally, we did not go back to original publications and re-calculate meta-analyses and we do not have information about confounding. The outcomes such as total cancer mortality, aortic aneurysm mortality, CHD mortality, colon cancer, rectal cancer, gastric cancer, leukemia, CLL/SLL, MM, thyroid cancer, breast cancer, pancreatic cancer, endometrial cancer, bladder cancer, ischemic stroke, CHD, AF, T2DM, asthma, sensitization, eczema, allergic rhinitis, wheeze, and MCI did not show significant associations, and the quality of evidence was low or very low. Further research is required.

### **Conclusions**

Taken together, in this umbrella review, the relevance between fish consumption and multiple health outcomes has been examined in several meta-analyses. Evidence indicates fish consumption often has beneficial or harmless associations with various health outcomes. Although the methodological quality of the included meta-analyses was mostly high, the quality of evidence was moderate/high

only for 15 inverse associations (all-cause mortality, prostate cancer mortality, CVD mortality, glioma, NHL, ESCC, oral cancer, ACS, cerebrovascular disease, MetS, AMD, IBD, CD, triglycerides, and MS), two positive associations (vitamin D and HDL-cholesterol), and eight nonsignificant associations (CRC mortality, EAC, prostate cancer, renal cancer, ovarian cancer, hypertension, UC, and RA). According to dose-response analyses, consumption of fish, especially fatty types, seems generally safe at one to two servings per week and could exert obvious protective effects. Our findings strongly support the important role of fish as part of a healthy diet, which was recommended by the dietary guidelines in various countries, such as Australian Dietary Guidelines, Dietary Guidelines for Americans, and European Food Safety Authority (EFSA) Dietary Guidelines (108,126,127). Additional multicenter high quality RCTs with a large sample size are needed to verify these findings in the future.

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### Footnote

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-6515/coif>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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