WORLD JOURNAL OF GASTROENTEROLOGY, HEPATOLOGY AND ENDOSCOPY

Fish Consumption and Multiple Health Outcomes: An Umbrella Review of Meta-Analyses of Observational and Clinical Studies

Zhao H[1,2], Wang M[1], Zhong L[1], Peng X[3,1], Chen J[4], Yu Z[5], Liu X[1], Chen Y[1], Shi Y[1], Li Y[1] and Tang S[1*]

[1]Department of Gastroenterology, The First Affiliated Hospital, Jinan University, Guangzhou, P. R. China
[2]Department of Gastroenterology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, P. R. China
[3]Department of Endocrinology, Liuzhou People's Hospital, Liuzhou, Guangxi 545006, P. R. China
[4]Department of Cardiology, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, P. R. China
[5]Department of Nephrology, The First Affiliated Hospital, Jinan University, Guangzhou, P. R. China

Article Information

Article Type: Meta- Analysis
Journal Type: Open Access
Volume: 3 Issue: 6
Manuscript ID: WJGHE-3-141
Publisher: Science World Publishing

***Corresponding Author:**
Shaohui Tang,
Department of Gastroenterology,
The First Affiliated Hospital, Jinan University,
Guangzhou, P. R. China,
E-mail: tangshaohui206@163.com

Citation:
Tang S. (2021). Fish Consumption and Multiple Health Outcomes: An Umbrella Review of Meta-Analyses of Observational and Clinical Studies. World J Gastroenterol Hepatol Endosc. 3(6); 1-16

&Author Contribution

Min Wang, Hailiang Zhao, Lu Zhong, Xiaojuan Peng and Shaohui Tang contributed to the conception and design of the umbrella review. Min Wang, Hailiang Zhao, Lu Zhong and Xiaojuan Peng were involved in the acquisition and analysis of the data. Xiongxiu Liu, Yanfang Chen, Ying Shi and Yuting Li interpreted the results. Min Wang and Shaohui Tang drafted the manuscript. All authors: read and approved the final manuscript.

Received Date: 15 July 2021
Accepted Date: 27 July 2021
Published Date: 02 Aug 2021

ABSTRACT

Scope: To evaluate the current evidence of associations between consumption of fish and diverse health outcomes.

Methods and results: Meta-analyses and systematic reviews of randomized controlled trials and observational studies examining associations between fish consumption and human health outcomes were screened. The methodological quality of 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 non-significant associations and only 1 was harmful (myeloid leukemia). The methodological quality of the included meta-analyses was mostly high. 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, Macular Degeneration (AMD), inflammatory bowel disease (IBD), Crohn's disease (CD), triglycerides, vitamin D, HDL-cholesterol and multiple Sclerosis (MS)) and 8 no significant associations (colorectal cancer mortality, Esophageal adenocarcinoma (EAC), prostate cancer, renal cancer, ovarian cancer, hypertension, ulcerative colitis (UC) and rheumatoid arthritis) were evaluated as moderate/high quality of evidence. According to dose-response analyses, consumption of fish, especially fatty types, seems generally safe at 1-2 servings per week and could exert protective effects.

Conclusions: Overall, fish consumption often has beneficial or harmless associations with various health outcomes, but only about 34% of the associations were graded as moderate/high quality of evidence. Thus, more well conducted study is needed to verify these findings.

KEYWORDS: Fish Consumption; Health; Umbrella Review; Meta-Analysis; Systematic Review

INTRODUCTION

Fish, which is a rich source of various nutrients, is one of the most commonly consumed sustenance worldwide [1]. The per capita fish consumption is steadily increasing, especially in developed countries [2]. As such, 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 be protective 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, the fish types could be roughly divided into two categories: fatty fish and lean fish, among which the fatty fish is more popular worldwide [11]. In fatty fish, such as salmon, tuna, sardines, mackerel, and trout, a higher amount of n-3 PUFA, which is good fats unlike the bad saturated fat in most meats, is provided than in lean species including cod [5,12].

Recent epidemiological studies have investigated the relevance between consumption of fish and a wide series of outcomes, including mortality, cancers, cardiovascular disease, metabolic, cognitive disorders, and other health-related outcomes [13]. However, there have been inconsistent conclusions about the overall impact of fish consumption on health problems, and the precise roles of fish 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 capture comprehensively the breadth of health outcomes associated with fish consumption. Thus, 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

Literature search

For this umbrella review, we searched PubMed and Web of Science of Systematic Reviews for quantitative reviews of fish intake and health outcomes up to May 2021. The search terms were "fish" and ("systematic review" OR "meta-analysis"). We also carried out a manual screen of the references of eligible articles. The search was independently performed by three investigators (MW, HZ and XP) and any differences in the literature search were resolved through consensus.

Eligibility Criteria

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. Review articles without quantitative statistical analysis, RCTs including animal trials or in vitro studies, and studies on genetic polymorphisms related to fish consumption were excluded. Articles that were not published in English were also excluded. Because 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, omega-3 fatty acids, were also excluded. If multiple health outcomes were presented in a single article, we included each of these health outcomes separately. If a single meta-analysis divided the studies into cohort and case-control studies without a total estimated effect size that included both, we reported the results of cohort studies as it was less affected by recall and selection biases. If more than one published meta-analysis examined the exact same 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 (MW, HZ and LZ) extracted data separately. From each eligible meta-analysis, the following information was extracted: first author and publication year, outcome, the study design, number of studies included, total population, number of cases, type of exposure, measure of exposure, effect sizes (risk ratio, odds ratio, hazard ratio, 95% confidence intervals, and continuous outcomes). Finally, the type of effect model, publication bias by Egger's test, and dose-response analyses were abstracted when possible. Any discrepancies in the extracted data were resolved with discussion.

Assessment of Methodological Quality

The eleven items of Assessment of Multiple Systematic Reviews (AMSTAR) checklist were performed to evaluate reporting and methodological quality of all included systematic reviews and meta-analyses [17]. Each question can be answered with "yes," "no," "can't answer," and "not applicable." A "yes" scores one point, whereas the other answers score 0 points. An overall score of at least 8 points was defined as the cutoff value for high quality, 4-7points as moderate quality, and 3 points or less as low quality.

Evaluation of The Grading of Evidence

The grading of recommendations, assessment, development and evaluation (GRADE) was used to assess the quality of evidence for each outcome in each meta-analysis [18]. Included observational studies started at low-certainty evidence by default and then were downgraded or upgraded based on prespecified criteria. Downgrading criteria included study limitations (the weight of studies showed risk of bias by the NOS), inconsistency (substantial unexplained interstudy heterogeneity, $I2 \geq 50\%$ and $P < 0.10$), indirectness (presence of factors relating to the population, exposures, and outcomes that limit generalizability), imprecision [95% CIs were wide or crossed a minimally important difference of 5% (RR: 0.95–1.05) for all outcomes], and publication bias (significant evidence of small-study effects). Upgrading criteria included a large size effect (RR >2 or RR <0.5 in the absence of plausible confounders), a dose-response gradient, and attenuation by plausible confounding effects.

DATA ANALYSIS

The estimated summary effect with its corresponding 95% CI was abstracted from each eligible meta-analysis. The heterogeneity between studies was evaluated with Cochran's Q test and the I2 statistic. 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 check the primary articles.

RESULTS

Characteristics of Meta-Analyses

The search strategy was 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. Most of outcomes had more than one meta-analysis. The association between fish consumption and mortality were presented in Table 1 [19-27]. Table 2 presents the associations between consumption of fish and cancer outcomes [14,22,27-64]. The associations between fish consumption and CVD were presented in Table 3 [13,65-77]. Table 4 presents the associations between fish consumption and metabolic outcomes [78-87]. The associations between fish consumption and cognitive outcomes were presented in Table 5 [88-97]. Table 6 presents the associations between fish consumption and allergic outcomes [98-100]. The associations between fish consumption and other outcomes were 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 downgrading quality were absence of a registered protocol, nonsatisfactory reporting/evaluation of the risk of bias in primary studies, and inappropriate metanalytic methodology.

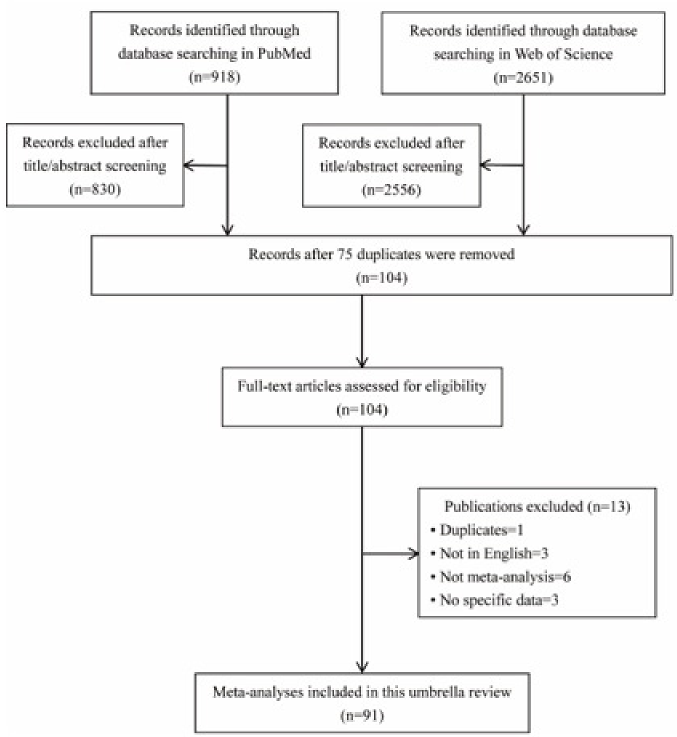

Figure 1: Flowchart of the selection process.

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
Mortality									
Significant associations									
All-cause mortality	fish	Schwingshackl2017	157688/NA	RR[a)]	0.95	0.92-0.98	39	39	0
All-cause mortality	fish	Schwingshackl2017	157688/NA	RR[b2)]	0.93	0.88-0.98	19	19	0
Prostate cancer–specific mortality	fish	Szymanski2010	740/49661	RR[a)]	0.37	0.18-0.74	4	4	0
CHD mortality	fish	Zheng2012	NA/315812	RR[b1)]	0.84	0.75-0.95	16	16	0
CHD mortality	fish	Zheng2012	NA/315812	RR[d)]	0.79	0.67-0.92	13	13	0
CVD mortality	fish	Jayedi2018	11720/331239	RR[c)]	0.96	0.94-0.98	8	8	0
Mortality of total aortic diseases	fish	Yamagishi2019	NA	HR[c)]	0.52	0.30-0.88	7	7	0
Aortic dissection mortality	fish	Yamagishi2019	NA	HR[c)]	0.4	0.18-0.89	3	3	0
Non-significant associations									
Total cancer mortality	fish	Zhang2017	NA	RR[a)]	0.99	0.94-1.05	10	10	0
Total cancer mortality	fish	Zhang2017	NA	RR[b2)]	0.98	0.92-1.05	10	10	0
CHD mortality	fish	Zheng2012	NA/315812	RR[e)]	0.83	0.68-1.01	5	5	0
Colorectal cancer mortality	fish	Geelen2007	NA	RR[a)]	1.02	0.90-1.16	4	4	0
Aortic aneurysm mortality	fish	Yamagishi2019	NA	HR[c)]	0.84	0.23-1.11	5	5	0

CI, confidence interval; MA, meta-analysis; NA, not available; HR, hazard ratio; RR, relative risk; MD, mean difference; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high density lipoprotein; a), Highest versus lowest/none; b1), 1serving/week; b2), 1serving/d; c), 1-2serving/week; d), 2-4serving/week; e), >5serving/week.

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^2	Egger test *p*-value
Significant associations													
Brain tumor	fish	Lian2017	NA	RR[a)]	0.83	0.70-0.99	9	1	8	0	Random	37.5	0.02
Brain tumor	fish	Lian2017	NA	RR[b)]	0.95	0.91-0.98	9	1	8	0	Random	51.7	NA
Esophageal cancer	fish	Jiang2013	NA	RRa)	0.69	0.57-0.85	18	2	16	0	Random	63.6	NA
ESCC	fish	Han2013	4508/NA	RR[a)]	0.81	0.66-0.99	17	3	14	0	Random	51.9	NA
Glioma	fish	Zhang2017	NA	RR[a)]	0.82	0.70-0.97	8	0	8	0	Random	43.6	0.088
Colorectal cancer	fish	Wu2012	NA	RR[a)]	0.88	0.80-0.95	41	22	19	0	Random	56.8	0.45
Liver cancer	fish	Huang2015	NA/3624	RR[a)]	0.82	0.71-0.94	10	5	5	0	Random	12.8	0.07
Liver cancer	fish	Huang2015	NA/3624	RR[c)]	0.94	0.91-0.98	10	5	5	0	Random	0	NA
Lung cancer	fish	Song2014	8799/17072	RRa)	0.79	0.69-0.92	20	3	17	0	Random	73	0.098
Myeloid leukemia	fish	Theodoros2019	416/NA	RR[a)]	1.74	1.22-2.47	3	3	0	0	Random	0.8	NA
NHL	fish	Yang2020	7696/NA	RR[a)]	0.8	0.68-0.94	9	2	7	0	Random	66.3	0.002
Oral cancer	fish	Yu2019	5211/7005	OR[a)]	0.74	0.64-0.85	15	2	13	0	Random	25.2	0.487
Non-significant associations													
Colon cancer	fish	Vieira2017	10512/NA	RR[b)]	0.91	0.80-1.03	11	11	0	0	Random	0	NA
Rectal cancer	fish	Vieira2017	3944/NA	RR[b)]	0.84	0.69-1.02	10	10	0	0	Random	15	NA
EAC	fish	Han2013	1610/NA	RR[a)]	0.86	0.61-1.22	6	1	5	0	Random	58.4	NA
Gastric cancer	fish	Wu2011	5323/NA	RR[a)]	0.87	0.71-1.07	17	2	15	0	Random	73.3	0.59
Leukemia	fish	Theodoros2019	2536/NA	RR[a)]	1.02	0.89-1.17	3	3	0	0	Random	0	NA
CLL/SLL	fish	Theodoros2019	1370/NA	RR[a)]	0.99	0.83-1.19	3	3	0	0	Random	0	NA
MM	fish	Theodoros2019	986/NA	RR[a)]	0.94	0.67-1.33	3	3	0	0	Random	30.2	NA

Prostate cancer	fish	Szymanski2010	NA/445820	RR[a)]	1.01	0.90-1.14	12	12	0	0	Random	NA	0.84
Thyroid cancer	fish	Cho2015	NA	RR[a)]	1.01	0.83-1.23	16	0	16	0	Random	58	NA
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^2	Egger test *p*-value
Renal cancer	fish	Bai2013	9324/608753	RR[a)]	0.99	0.92-1.07	15	3	12	0	Fixed	23.8	0.38
Ovarian cancer	fish	Jiang2014	NA	RR[a)]	1.04	0.89-1.22	5	5	0	0	Fixed	0	0.29
Breast cancer	fish	Wu2016	20810/914451	RR[a)]	1.04	0.97-1.12	18	18	0	0	Random	47.9	0.613
Breast cancer	fatty fish	Wu2016*	NA	RR[a)]	0.81	0.58-1.12	5	2	3	0	Random	87	NA
Breast cancer	lean fish	Wu2016*	NA	RR[a)]	1.09	1.00-1.19	4	2	2	0	Random	0	NA
Pancreatic cancer	fish	Jiang2019	4994/1794601	RR[a)]	1.04	0.95-1.13	13	13	0	0	Random	0	0.77
Endometrial cancer	fish	Hou2017	NA	RR[a)]	1.04	0.84-1.30	12	4	8	0	Random	80.4	NA
Endometrial cancer	fish	Hou2017	NA	RR[c)]	1	0.94-1.07	10	2	8	0	Random	81.7	NA
Bladder cancer	fish	Li2011	NA	RR[a)]	0.86	0.61-1.12	14	5	9	0	Random	85.4	NA

CI, confidence interval; MA, meta-analysis; NA, not available; OR, odds ratio; RR, relative risk; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; NHL, Non-Hodgkin's lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MM, multiple myeloma; a), Highest versus lowest/none; b), 1serving=100g/d; c), 1serving/week; *, Zhi-hui Wu.

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^2	Egger test *p*-value
Cardiovascular outcomes													
Significant associations													
Stroke	fish	Zhao2018	NA	HR[a)]	0.9	0.85-0.96	33	33	0	0	Random	39.2	0.084
Stroke	lean fish	Qin2018	NA	RR[a)]	0.81	0.67-0.99	4	4	0	0	Random	0	0.324
Hemorrhagic stroke	fish	Zhao2018	NA	HR[a)]	0.88	0.80-0.96	13	13	0	0	Random	0	0.084
Acute coronary syndrome	fish	Yinko2014	8517/408305	RR[a)]	0.78	0.70-0.88	19	11	8	0	Random	0	0.6
Myocardial infarction	fish	Jayedi2019	NA/398221	RR[a)]	0.73	0.59-0.87	11	11	0	0	Random	72	NA
CHD	fish	Bechthold2017	NA	RR[b)]	0.88	0.79-0.99	15	15	0	0	Random	40	NA
Heart failure	fish	Angela2017	7945/NA	RR[a)]	0.89	0.80-0.99	8	8	0	0	Random	18	NA
Heart failure	fish	Angela2017	NA	RR[b)]	0.8	0.67-0.95	7	7	0	0	Random	20	NA
Cerebrovascular disease	fish	Chowdhury2012	25320/675048	RR[a)]	0.88	0.84-0.93	21	21	0	0	Random	18.5	0.05
Cerebrovascular disease	fish	Chowdhury2012	24612/650210	RR[d)]	0.94	0.90-0.98	18	18	0	0	Random	22	0.05
Cerebrovascular disease	fish	Chowdhury2012	16890/394958	RR[e)]	0.88	0.81-0.96	8	8	0	0	Random	20	0.05
Cerebrovascular disease	fatty fish	Chowdhury2012	2695/62799	RR[a)]	0.84	0.72-0.98	4	4	0	0	Random	10.1	0.05
Triglycerides	fish	Alhassan2017	596/1128	MD	−0.11mmol/L	−0.18-−0.04	14	0	0	14	Random	0	NA
Triglycerides	fatty fish	Alhassan2017	438/831	MD	−0.11mmol/L	−0.19-−0.03	12	0	0	12	Random	7	NA
HDL-cholesterol	fish	Alhassan2017	584/1104	MD	0.06mmol/L	0.02-0.11	13	0	0	13	Random	28	NA
HDL-cholesterol	fatty fish	Alhassan2017	438/831	MD	0.08mmol/L	0.04-0.13	12	0	0	12	Random	0	NA
Non-significant associations													
Stroke	fatty fish	Qin2018	NA	RR[a)]	0.88	0.74-1.04	5	5	0	0	Random	26.2	0.891
CHD	fish	Bechthold2017	16732/NA	RR[a)]	0.94	0.88-1.02	22	22	0	0	Random	52	NA
Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I^2	Egger test *p*-value
Ischemic stroke	fish	Zhao2018	NA	HR[a)]	0.96	0.89-1.03	15	15	0	0	Random	27.9	0.084
Cerebrovascular disease	lean fish	Chowdhury2012	2695/62799	RR[a)]	1.03	0.90-1.19	4	4	0	0	Random	0	0.05
Triglycerides	lean fish	Alhassan2017	158/297	MD	−0.09mmol/L	−0.26-0.04	2	0	0	2	Random	0	NA
HDL-cholesterol	lean fish	Alhassan2017	146/273	MD	−0.02mmol/L	−0.10-0.06	1	0	0	1	Random	NA	NA
Atrial fibrillation	fish	Li2017	NA	RR[a)]	1.01	0.94-1.09	6	6	0	0	Random	0	NA
Atrial fibrillation	fish	Li2017	NA	RR[c)]	0.99	0.96-1.02	6	6	0	0	Random	23	NA
Hypertension	fish	Schwingshackl2017	NA/83612	RR[a)]	1.01	0.92-1.10	8	8	0	0	Random	57	NA
Hypertension	fish	Schwingshackl2017	NA	RR[b)]	1.07	0.98-1.16	7	7	0	0	Random	74	NA
Venous thromboembolism,	fish	Zhang2020	NA	RR[a)]	1.02	0.93-1.11	6	6	0	0	Random	33	0.176

CI, confidence interval; MA, meta-analysis; NA, not available; HR, hazard ratio; RR, relative risk ; MD, mean difference ;CHD, coronary heart disease ;CVD, cardiovascular disease ; HDL, high density lipoprotein; a), Highest versus lowest/none; b), 1serving=100g/d; c)1serving/week; d), 2-4 versus ≤1 servings a week; e), ≥5 versus ≤1 servings a week.

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
Significant associations										
Metabolic Syndrome	fish	Kim2015	NA	RR[a)]	0.71	0.58-0.87	2	2	0	0
Metabolic Syndrome	fish	Kim2015	NA	RR[c)]	0.94	0.90-0.98	2	2	0	0
Type 2 diabetes	fatty fish	Namazi2019	NA	RR[a)]	0.89	0.82-0.98	5	5	0	0
Vitamin D	fish	Lehmann2015	NA	MD[a)]	4.4nmol/L	1.7-7.1	9	0	0	9
Vitamin D	fish	Lehmann2015	NA	MD[d)]	3.8 nmol/L	0.6-6.9	10	0	0	10
Vitamin D	fish	Lehmann2015	NA	MD[e)]	8.3nmol/L	2.1-14.5	4	0	0	4
Vitamin D	fatty fish	Lehmann2015	NA	MD[a)]	6.8nmol/L	3.7-9.9	7	0	0	7
Non-significant associations										
Type 2 diabetes	fish	Schwingshackl2017	NA/45029	RR[a)]	1.04	0.95-1.13	16	16	0	0
Type 2 diabetes	fish	Schwingshackl2017	NA	RR[b)]	1.09	0.93-1.28	15	15	0	0
Type 2 diabetes	lean fish	Namazi2019	NA	RR[a)]	1.03	0.87-1.22	5	5	0	0
Vitamin D	lean fish	Ulrike2015	NA	MD[a)]	1.9nmol/L	−2.3-6.0	7	0	0	7

CI, confidence interval; MA, meta-analysis; NA, not available; RR, relative risk; MD, mean difference; a), Highest versus lowest/none; b), 1serving=100g/d; c), 1serving/week; d), short-term studies (4–8 week); e), long-term studies (6month or 23 week).

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
Significant associations										
Depression	fish	Li2016	NA/102785	RR[a)]	0.83	0.74-0.93	26	10	0	16
Dementia	fish	Bakre2018	3139/40668	[RR]a)	0.8	0.74-0.87	8	6	2	0
Alzheimer disease	fish	Zeng2017	NA	RR[a)]	0.8	0.65-0.97	7	7	0	0
Alzheimer disease	fish	Zeng2017	NA	RR[b)]	0.88	0.79-0.99	7	7	0	0
MS	fish	Rezaeizadeh2020	2370/7170	RR[a)]	0.77	0.64-0.92	6	6	0	0
Non-significant associations										
mild cognitive impairment	fish	Zeng2017	NA	RR[a)]	1.03	0.78-1.37	2	2	0	0

CI, confidence interval; MA, meta-analysis; NA, not available; OR, odds ratio; RR, relative risk; a), Highest versus lowest/none; b), 1serving/week.

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
Significant associations										
Current Asthma	fish	Papamichael2018	NA	OR[a)]	0.75	0.60-0.95	3	3	0	0
Current Wheeze	fish	Papamichael2018	NA	OR[b)]	0.62	0.48-0.80	2	2	0	0
Current Asthma	fatty fish	Papamichael2018	NA	OR[c)]	0.35	0.18-0.67	2	2	0	0
Eczema	fish	Zhang2016	NA/13823	RR[g)]	0.61	0.47-0.80	4	4	0	0
Allergic rhinitis	fish	Zhang2016	NA/9987	RR[g)]	0.54	0.36-0.81	3	3	0	0
Non-significant associations										
Current Wheeze	fish	Papamichael2018	NA	OR[D)]	0.81	0.64-1.02	9	9	0	0
Asthma	fish	Yang2013	NA	RR[e)]	0.9	0.69-1.18	2	2	0	0
Sensitization	fish	Zhang2016	NA/3099	RR[f)]	0.88	0.65-1.21	2	2	0	0
Eczema	fish	Zhang2016	NA/15945	RR[f)]	0.88	0.75-1.04	10	10	0	0
Allergic rhinitis	fish	Zhang2016	NA/32589	RR[f)]	0.95	0.62-1.45	3	3	0	0
Wheeze	fish	Zhang2016	NA/42096	RR[f)]	0.94	0.83-1.07	8	8	0	0
Asthma	fish	Zhang2016	NA/37295	RR[f)]	0.94	0.75-1.18	4	4	0	0
Wheeze	fish	Zhang2016	NA/8597	RR[g)]	0.94	0.77-1.14	2	2	0	0
Asthma	fish	Zhang2016	NA/8902	RR[g)]	0.84	0.69-1.02	3	3	0	0

CI, confidence interval; MA, meta-analysis; NA, not available; OR, odds ratio; RR, relative risk; a), children (0-4 years old) for 'All fish' intake versus 'No Fish'; b), children (0-4.5 years old) for 'All Fish' intake versus 'No Fish'; c), 'Fatty Fish' intake versus 'No Fatty Fish' in children (8-14 years); d),children (0-13 years old) for 'All Fish' intake versus 'No Fish'; e), Highest versus lowest in adults; f), maternal fish intake during pregnancy; g), fish intake in infancy.

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
Significant associations										
AMD	fish	Dinu2018	NA/237464	RR[a)]	0.82	0.75-0.90	8	8	0	0
IBD	fish	Mozaffari2019	823/41601	ES[a)]	0.68	0.46-1.00	6	1	5	0
CD	fish	Mozaffari2019	NA	ES[a)]	0.54	0.31-0.96	5	1	4	0
Hip fracture	fish	Sadeghi2019	NA	ES[a)]	0.88	0.79-0.98	6	4	2	0
Non-significant associations										
UC										
Rheumatoid arthritis	fish	Giuseppe 2014	3346/174702	RR[a)]	0.96	0.91-1.01	7	3	4	0

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; AMD, age-related macular degeneration; CI, confidence interval; MA, meta-analysis; NA, not available; OR, odds ratio; RR, relative risk; ES, estimated size; a), Highest versus lowest/none.

Mortality

High consumption of fish decreased the risk of all-cause mortality (RR: 0.95; 0.92-0.98) and prostate cancer mortality (RR: 0.37; 95% CI: 0.18, 0.74) [21,22]. Moreover, compared with the lowest fish intake (<1 serving/month or 1-3 servings/month) (1 serving = 100g), either low (1 serving/week) (RR: 0.84; 95% CI: 0.75, 0.95) or moderate fish consumption (2-4 servings/week) (RR: 0.79; 95% CI: 0.67, 0.92), but not high fish consumption (>5 servings/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]. Besides, an increment in fish consumption was 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 that 1 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 1 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), colorectal cancer (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 their 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 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 observed only for females [39]; when the subgroup analysis was conducted by geographic location, a protective effect was only observed in HCC and lung cancer for Asian, as well as oral cancer and ESCC for European [28,32, 39,43].

According to dose-response analyses, fish intake of 1 serving per week was associated with a decreased risk of brain cancer (RR: 0.95; 0.91-0.98) and HCC (RR: 0.94; 95% CI: 0.91, 0.98) [29,32]. There was no relevance between of high intake of fish with 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]. Also, fish consumption was associated with a significant reduced risk of ovarian cancer among studies conducted in Europe (RR: 0.71; 95% CI: 0.61, 0.82) and Australia (RR: 0.76; 95% CI: 0.63, 0.92), and studies adjusted for 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; 0.80, 0.99), myocardial infarction (MI) (RR: 0.73; 95% CI: 0.59, 0.87), stroke (HR, 0.90; 95% CI: 0.85, 0.96), 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 2 servings a week 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 increasing of fish up to 1-7 servings/week [69]. Also, an increase of 1 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 1 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].

Comparing the highest to the lowest categories, a small association 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 that the intake of 1 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 that consumption of fish, especially fatty fish, was associated with a moderately significant reduction in plasma triglycerides levels (MD: -0.11 mmol/L; 95% CI: -0.18, 0.04) and an increase in 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 mean difference 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 of fish showed a higher mean difference 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 mean difference of 6.8 nmol/L (MD: 6.8 nmol/L; 95% CI: 3.7, 9.9), whereas for lean fish the mean difference 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 1 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 (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 (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]. Also, analyses of high versus low consumption of fish indicated that dementia risk was reduced by 20% (RR: 0.80; 95% CI: 0.74, 0.87) regardless of income level, and dose-response models showed that fish consumption could decrease the risk of dementia by 16%, 22%, 23% for low level consumers (consumed fish once weekly) (RR: 0.84; 95% CI: 0.72, 0.98), middle level consumers (≥twice weekly) (RR: 0.78; 95% CI: 0.68, 0.90), and high level consumers (≥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 1 serving per week (RR: 0.88; 95% CI: 0.79, 0.99) [95]. Increasing fish intake had no obvious effect on the risk of mild cognitive impairment (MCI) (RR: 1.03; 95% CI: 0.78, 1.37) [95]. Fish consumption was associated with a decreased risk of multiple sclerosis (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 does not affect any atopic outcome in children and adults, whereas total fish or fatty fish consumption during infancy period seem 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]. Besides, fish consumption was inversely associated with risk of hip fracture (ES, 0.88; 95% CI: 0.79, 0.98) [102]. Moreover, consumption of fish conferred a beneficial effect on the development of macular degeneration (AMD) (RR: 0.82; 95% CI: 0.75, 0.90), no matter 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 I2 <25%; 8% had very high heterogeneity, with I2 >75%; and 42% had moderate-to-high heterogeneity, with I2 ranging from 25%-75%. The individual studies within each meta-analysis varied by many factors, including the geography and human race, the procession difference, the method of ascertaining of fish consumption, measurement of fish consumption, duration of follow-up, and assessment of outcome. The remaining 6% of the included meta-analyses did not publish the heterogeneity of the studies included in the specific comparison and were not able to be reanalyzed using a random or fixed model.

PUBLICATION BIAS

Egger's regression test was used in this umbrella review. Of the 36 included meta-analyses that reported a P value for publication bias, three reported statistical evidence for publication bias. These included CHD mortality (P=0.018), NHL (P=0.002) and brain tumor (P=0.02) [23,29,45]. The remaining meta-analyses did not report significant publication bias. However, it is very likely that unmeasured publication bias exists in many of the summary estimates we have presented 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, metabolic syndrome, AMD, IBD, CD, and MS), 2 positive associations (vitamin D, HDL-cholesterol) and 9 nonsignificant associations (comprising colorectal cancer mortality, EAC, prostate cancer, renal cancer, ovarian cancer, hypertension, VTE, UC and rheumatoid arthritis) showed moderate/high epidemiologic evidence.

15 additional inverse associations (mortality of total aortic diseases, aortic dissection mortality, brain cancer, esophageal cancer, colorectal cancer, liver cancer, lung cancer, stroke, hemorrhagic stroke, myocardial infarction, heart failure, depression, dementia, Alzheimer disease and hip fracture) and 1 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, atrial fibrillation, type 2 diabetes, asthma, sensitization, eczema, allergic rhinitis, wheeze and mild cognitive impairment) 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, cardiovascular disease, metabolic, cognitive, allergic, 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, metabolic syndrome, 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 colorectal cancer mortality, EAC, prostate cancer, renal cancer, ovarian cancer, hypertension, UC and rheumatoid arthritis, 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

In this umbrella review, the results showed that 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 colorectal cancer 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 a 227g fish per week [107]. It was worth noting that subgroup analysis by geographic location showed a significant association of fish consumption with all-cause mortality for studies conducted only in Asia, but not in Europe [21]. The different results appeared possibly due to different dietary pattern of fish in Asian population and Western population, of which the former has 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 diseases and its subtype aortic dissection mortality, total cancer mortality and aortic aneurysm mortality, 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 higher intake of fish and we observed 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) recommends a higher intake of fish, for which we also found an inverse association with the risk of brain cancer, esophageal cancer, colorectal cancer, liver cancer and lung cancer, but the quality of evidence was low [29,32,38,39,42,109]. Also, we 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]. Probably, heavy metals, which is frequently linked to increased intake of fish, leads 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, previous meta-analysis has indicated that an increase of 1 serving/week 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].

Consumption and Cardiovascular Outcomes

Recommendations for improving the cardiovascular health of all Americans with a dietary pattern including consumption of fish at least 1 to 2 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 that 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, VTE [75,77].

Our results also confirmed the inverse association of fish consumption with the risk of stroke, hemorrhagic stroke, myocardial infarction, heart failure, and the null association with ischemic stroke, CHD, atrial fibrillation, but quality of evidence for these associations was low, indicating that 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 human 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 rheumatoid arthritis [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 a higherserum25(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 metabolic syndrome, AMD, IBD and CD but no association between fish consumption and UC was found, for which we found moderate quality of evidence [79,103,106].

Although we also observed a reduced risk of MS, depression, dementia, Alzheimer disease and hip fracture, and a null association of type 2 diabetes and mild cognitive impairment with consumption of fish, respectively, 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 affect health conditions are not well-established, fish containing 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, 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 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]. Besides, fish is also a good source of vitamins D, which has been linked to inverse T2DM risk [125]. Probably, considering the synergic effect of many components in fish, such asn-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

This umbrella review systematically collects and evaluates information from multiple meta-analyses and systematic reviews on all clinical outcomes for fish consumption. In this analysis, we systematically search scientific databases by a strong search strategy. Besides, the extent of publication bias and heterogeneity were analyzed. Furthermore, the quality of included systematic reviews was evaluated by AMSTAR, and the categorization of the evidence was assessed by GRADE classification.

But there are also some limitations that should be considered. Firstly, this umbrella reviewer lied on existing systematic reviews and meta-analyses. As a result, the quality is directly related to the quality of the included articles. Secondly, even though the total number of included studies in the meta-analysis was large, potential publication bias should be taken into account. Thirdly, a form of reverse causation may occur through reporting bias. Fourthly, some health-related outcomes were inadequately covered, and we have emphasized this gap. Fifthly, no reanalysis was performed since we did not examine the primary articles when dose-response meta-analyses were absent. 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, atrial fibrillation, type 2 diabetes, asthma, sensitization, eczema, allergic rhinitis, wheeze and mild cognitive impairment did not show significant associations, and the quality of evidence was low or very low, further research is needed.

CONCLUSIONS

Taken together in this umbrella review, the relevance between fish consumption and multiple health outcomes have been examined in a large number of meta-analyses. Evidence indicates that 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, metabolic syndrome, AMD, IBD, CD, triglycerides and MS), 2 positive associations (vitamin D, HDL-cholesterol) and 8 nonsignificant associations (colorectal cancer mortality, EAC, prostate cancer, renal cancer, ovarian cancer, hypertension, UC and rheumatoid arthritis). According to dose-response analyses, consumption of fish, especially fatty types, seems generally safe at 1-2 servings per week and could exert obvious protective effects. 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 Australian Dietary Guidelines, Dietary Guidelines for Americans and European Food Safety Authority (EFSA) Dietary Guidelines [108,126,127]. Additional multicenter high quality RCTs with large sample size are needed to verify these findings in the future.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ROLE OF FUNDING

This work was supported by the Health Commission Funding Project of Hunan Province grant B2019145, Science and Technology Funding Project of Chenzhou City grant zdyf201848, and Science and Technology Funding Project of Hunan Province grant 2017SK4010. The content of the paper is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

References

1. Xu M, Fang YJ, Chen YM, Lu MS, Pan ZZ, Yan B, Zhong X, Zhang CX. Higher freshwater fish and sea fish intake is inversely associated with colorectal cancer risk among Chinese population: a case-control study. Sci Rep 2015; 5: 12976.
2. Moratal S, Dea-Ayuela MA, Cardells J, Marco-Hirs NM, Puigcercós S, Lizana V, López-Ramon J. Potential Risk of Three Zoonotic Protozoa (Cryptosporidium spp., Giardia duodenalis, and Toxoplasma gondii) Transmission from Fish Consumption. Foods. 2020; 9(12): 1913.
3. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol 2005; 6(12): 1191-7.
4. Raatz SK, Silverstein JT, Jahns L, Picklo MJ. Issues of fish consumption for cardiovascular disease risk reduction. Nutrients 2013; 5(4): 1081-97.
5. He K. Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease--eat fish or take fish oil supplement? Prog Cardiovasc Dis 2009; 52(2): 95-114.
6. Bourre JM. Dietary omega-3 fatty acids for women. Biomed Pharmacother 2007; 61(2-3): 105-12.
7. Del Brutto OH, Mera RM, Gillman J, Castillo PR, Zambrano M, Ha JE. Dietary Oily Fish Intake and Blood Pressure Levels: A Population-Based Study. J Clin Hypertens (Greenwich) 2016; 18(4): 337-41.
8. Rajaram S, Haddad EH, Mejia A, Sabate J. Walnuts and fatty fish influence different serum lipid fractions in normal to mildly hyperlipidemic individuals: a randomized controlled study. Am J Clin Nutr 2009; 89(5): 1657S-63S.
9. Helland A, Bratlie M, Hagen IV, Mjos SA, Sornes S, Ingvar Halstensen A, Brokstad KA, Sveier H, Rosenlund G, Mellgren G, et al. High intake of fatty fish, but not of lean fish, improved post-

prandial glucose regulation and increased the n-3 PUFA content in the leucocyte membrane in healthy overweight adults: a randomised trial. Brit J Nutr 2017; 117(10): 1368-78.

10. Brown MD, Hart CA, Gazi E, Bagley S, Clarke NW. Promotion of prostatic metastatic migration towards human bone marrow stoma by Omega 6 and its inhibition by Omega 3 PUFAs. Brit J Cancer 2006; 94(6): 842-53.
11. Welch AA, Lund E, Amiano P, Dorronsoro M, Brustad M, Kumle M, Rodriguez M, Lasheras C, Janzon L, Jansson J, et al. Variability of fish consumption within the 10 European countries participating in the European Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2002; 5(6B): 1273-85.
12. Nahab F, Pearson K, Frankel MR, Ard J, Safford MM, Kleindorfer D, Howard VJ, Judd S. Dietary fried fish intake increases risk of CVD: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Public Health Nutr 2016; 19(18): 3327-36.
13. Qin ZZ, Xu JY, Chen GC, Ma YX, Qin LQ. Effects of fatty and lean fish intake on stroke risk: a meta-analysis of prospective cohort studies. Lipids Health Dis 2018; 17(1): 264.
14. Yu XF, Zou J, Dong J. Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies. World J Gastroentero 2014; 20(41): 15398-412.
15. Ioannidis JP. Why most discovered true associations are inflated. Epidemiology 2008; 19(5): 640-8.
16. Corrigan-Curay J, Sacks L, Woodcock J. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. Jama 2018; 320(9): 867-8.
17. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007; 7: 10.
18. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, Atkins D, Kunz R, Brozek J, Montori V, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011; 64(12): 1311-6.
19. Wan Y, Zheng J, Wang F, Li D. Fish, long chain omega-3 polyunsaturated fatty acids consumption, and risk of all-cause mortality: a systematic review and dose-response meta-analysis from 23 independent prospective cohort studies. Asia Pac J Clin Nutr 2017; 26(5): 939-56.
20. Zhao LG, Sun JW, Yang Y, Ma X, Wang YY, Xiang YB. Fish consumption and all-cause mortality: a meta-analysis of cohort studies. Eur J Clin Nutr 2016; 70(2): 155-61.
21. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi AM, Knuppel S, Iqbal K, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2017; 105(6): 1462-73.
22. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr 2010; 92(5): 1223-33.
23. Zheng J, Huang T, Yu Y, Hu X, Yang B, Li D. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. Public Health Nutr 2012; 15(4): 725-37.
24. Yamagishi K, Iso H, Shimazu T, Tamakoshi A, Sawada N, Matsuo K, Ito H, Wakai K, Nakayama T, Kitamura Y, et al. Fish intake and risk of mortality due to aortic dissection and aneurysm: A pooled analysis of the Japan cohort consortium. Clin Nutr (Edinburgh, Scotland) 2019; 38(4): 1678-83.
25. Jayedi A, Shab-Bidar S, Eimeri S, Djafarian K. Fish consumption and risk of all-cause and cardiovascular mortality: a dose-response meta-analysis of prospective observational studies. Public Health Nutr 2018; 21(7): 1297-306.
26. Zhang Z, Chen GC, Qin ZZ, Tong X, Li DP, Qin LQ. Poultry and Fish Consumption in Relation to Total Cancer Mortality: A Meta-Analysis of Prospective Studies. Nutr cancer 2018; 70(2): 204-12.
27. Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. Am J Epidemiol 2007; 166(10): 1116-25.
28. Hu S, Yu J, Wang Y, Li Y, Chen H, Shi Y, Ma X. Fish consumption could reduce the risk of oral cancer in Europeans: A meta-analysis. Arch Oral Biol 2019; 107: 104494.
29. Lian W, Wang R, Xing B, Yao Y. Fish intake and the risk of brain tumor: a meta-analysis with systematic review. Nutr J 2017; 16(1): 1.
30. Zhang Z, Xin J. Dietary fresh fish and processed fish intake and the risk of glioma: A meta-analysis of observational studies. Cell Mol Biol (Noisy-le-grand) 2019; 65(8): 48-53.
31. Lei H, To C, Lei U. Association between fish intake and glioma risk: a systematic review and meta-analysis. J Int Med Res 2020; 48(8): 300060520939695.
32. Huang RX, Duan YY, Hu JA. Fish intake and risk of liver cancer: a meta-analysis. PloS One 2015; 10(1): e0096102.
33. Gao M, Sun K, Guo M, Gao H, Liu K, Yang C, Li S, Liu N. Fish consumption and n-3 polyunsaturated fatty acids, and risk of hepatocellular carcinoma: systematic review and meta-analysis. Cancer Causes Control 2015; 26(3): 367-76.
34. Wang CB, Fu QX, Liu HY, Wang R. Fish consumption doesn't reduce the risk of hepatocellular carcinoma. Int J Clin Exp Med 2015; 8(7): 10825-34.
35. Luo J, Yang Y, Liu J, Lu K, Tang Z, Liu P, Liu L, Zhu Y. Systematic review with meta-analysis: meat consumption and the risk of Pharm Therap hepatocellular carcinoma. Aliment 2014; 39(9): 913-22.
36. Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, Greenwood D, Norat T. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol 2017; 28(8): 1788-802.
37. Pham NM, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Wakai K, Nagata C, Inoue M, Tsugane S, et al. Fish consumption

and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2013; 43(9): 935-41.

38. Wu S, Feng B, Li K, Zhu X, Liang S, Liu X, Han S, Wang B, Wu K, Miao D, et al. Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis. Am J Med 2012; 125(6): 551-9 e5.
39. Song J, Su H, Wang BL, Zhou YY, Guo LL. Fish consumption and lung cancer risk: systematic review and meta-analysis. Nutr Cancer 2014; 66(4): 539-49.
40. Gnagnarella P, Caini S, Maisonneuve P, Gandini S. Carcinogenicity of High Consumption of Meat and Lung Cancer Risk Among Non-Smokers: A Comprehensive Meta-Analysis. Nutr Cancer 2018; 70(1): 1-13.
41. Salehi M, Moradi-Lakeh M, Salehi MH, Nojomi M, Kolahdooz F. Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. Nutr Rev 2013; 71(5): 257-67.
42. Jiang G, Li B, Liao X, Zhong C. Poultry and fish intake and risk of esophageal cancer: A meta-analysis of observational studies. Asia Pac J Clin Oncol 2016; 12(1): e82-91.
43. Han YJ, Li J, Huang W, Fang Y, Xiao LN, Liao ZE. Fish consumption and risk of esophageal cancer and its subtypes: a systematic review and meta-analysis of observational studies. Eur J Clin Nutr 2013; 67(2): 147-54.
44. Sergentanis TN, Ntanasis-Stathopoulos I, Tzanninis IG, Gavriatopoulou M, Sergentanis IN, Dimopoulos MA, Psaltopoulou T. Meat, fish, dairy products and risk of hematological malignancies in adults - a systematic review and meta-analysis of prospective studies. Leuk Lymphoma 2019; 60(8): 1978-90.
45. Yang L, Shi WY, Xu XH, Wang XF, Zhou L, Wu DP. Fish consumption and risk of non-Hodgkin lymphoma: A meta-analysis of observational studies. Hematology 2020; 25(1): 194-202.
46. Wang YZ, Wu QJ, Zhu J, Wu L. Fish consumption and risk of myeloma: a meta-analysis of epidemiological studies. Cancer Causes Control. 2015; 26: 1307-14.
47. Bai HW, Qian YY, Shi BY, Li G, Fan Y, Wang Z, et al. The association between fish consumption and risk of renal cancer: a meta-analysis of observational studies. PloS One. 2013; 8: e81939.
48. Jiang PY, Jiang ZB, Shen KX, Yue Y. Fish intake and ovarian cancer risk: a meta-analysis of 15 case-control and cohort studies. PloS One. 2014; 9: e94601.
49. Kolahdooz F, van der Pols JC, Bain CJ, Marks GC, Hughes MC, Whiteman DC, et al. Meat, fish, and ovarian cancer risk: Results from 2 Australian case-control studies, a systematic review, and meta-analysis. Am J Clin Nutr. 2010; 91: 1752-63.
50. Fang X, Wei J, He X, An P, Wang H, Jiang L, et al. Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. Eur J Cancer. 2015; 51: 2820-32.
51. Wu S, Liang J, Zhang L, Zhu X, Liu X, Miao D et al. Fish consumption and the risk of gastric cancer: systematic review and meta-analysis. BMC Cancer. 2011; 11: 26.
52. Poorolajal J, Moradi L, Mohammadi Y, Cheraghi Z, Gohari-Ensaf F. Risk factors for stomach cancer: a systematic review and meta-analysis. Epidemiol Health. 2020; 42: e2020004.
53. Cho YA, Kim J. Dietary Factors Affecting Thyroid Cancer Risk: A Meta-Analysis. Nutr Cancer. 2015; 67: 811-7.
54. Liu ZT, Lin AH. Dietary factors and thyroid cancer risk: a meta-analysis of observational studies. Nutr Cancer. 2014; 66: 1165-78.
55. Li Z, Yu J, Miao Q, Sun S, Sun L, Yang H, et al. The association of fish consumption with bladder cancer risk: a meta-analysis. World J Surg Oncol. 2011; 9: 107.
56. Wu J, Zeng R, Huang J, Li X, Zhang J, Ho JC, et al. Dietary Protein Sources and Incidence of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Studies. Nutrients. 2016; 8: 730.
57. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ. 2013; 346: f3706.
58. Zhihui W, Weihua Y, Zupei W, Jinlin H. Fish consumption and risk of breast cancer: meta-analysis of 27 observational studies. Nutr Hosp. 2016; 33: 282.
59. Nindrea RD, Aryandono T, Lazuardi L, Dwiprahasto I. Protective Effect of Omega-3 Fatty Acids in Fish Consumption Against Breast Cancer in Asian Patients: A Meta-Analysis. Asian Pac J Cancer Prev. 2019; 20: 327-32.
60. Kim AE, Lundgreen A, Wolff RK, Fejerman L, John EM, Torres-Mejia G, et al. Red meat, poultry, and fish intake and breast cancer risk among Hispanic and Non-Hispanic white women: The Breast Cancer Health Disparities Study. Cancer Causes Control. 2016; 27: 527-43.
61. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: a systematic literature review and meta-analysis. Cancer Causes Control. 2007; 18: 967-88.
62. Hou R, Yao SS, Liu J, Wang LL, Wu L, Jiang L et al. Dietary n-3 polyunsaturated fatty acids, fish consumption, and endometrial cancer risk: a meta-analysis of epidemiological studies. Oncotarget. 2017; 8: 91684-93.
63. Jiang W, Wang M, Jiang HZ, Chen GC, Hua YF. Meta-analysis of fish consumption and risk of pancreatic cancer in 13 prospective studies with 1.8 million participants. PloS One. 2019; 14: e0222139.
64. Qin B, Xun P, He K. Fish or long-chain (n-3) PUFA intake is not associated with pancreatic cancer risk in a meta-analysis and systematic review. J Nutr. 2012; 142: 1067-73.
65. Leung YSS, Stark KD, Thanassoulis G, Pilote L. Fish consumption and acute coronary syndrome: a meta-analysis. Am J Med. 2014; 127: 848-57.
66. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic

review and meta-analysis. BMJ. 2012; 345: e6698.

67. Djousse L, Akinkuolie AO, Wu JH, Ding EL, Gaziano JM. Fish consumption, omega-3 fatty acids and risk of heart failure: a meta-analysis. Clin Nutr. 2012; 31: 846-53.

68. Jayedi A, Zargar MS, Shab-Bidar S. Fish consumption and risk of myocardial infarction: a systematic review and dose-response meta-analysis suggests a regional difference. Nutr Res. 2019; 62: 1-12.

69. Zhao W, Tang H, Yang X, Luo X, Wang X, Shao C, et al. Fish Consumption and Stroke Risk: A Meta-Analysis of Prospective Cohort Studies. Journal of stroke and cerebrovascular diseases. J Stroke Cerebrovasc Dis. 2019; 28: 604-11.

70. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knuppel S, Iqbal K, et al. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2019; 59: 1071-90.

71. Larsson SC, Orsini N. Fish consumption and the risk of stroke: a dose-response meta-analysis. Stroke. 2011; 42: 3621-3.

72. Xun P, Qin B, Song Y, Nakamura Y, Kurth T, Yaemsiri S, et al. Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. Eur J Clin Nutr. 2012; 66: 1199-207.

73. Li FR, Chen GC, Qin J, Wu X. DietaryFish and Long-Chain n-3 Polyunsaturated Fatty Acids Intake and Risk of Atrial Fibrillation: A Meta-Analysis. Nutrients. 2017; 9: 955.

74. Alhassan A, Young J, Lean MEJ, Lara J. Consumption of fish and vascular risk factors: A systematic review and meta-analysis of intervention studies. Atherosclerosis. 2017; 266: 87-94.

75. Schwingshackl L, Schwedhelm C, Hoffmann G, Knuppel S, Iqbal K, Andriolo V, et al. Food Groups and Risk of Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Adv Nutr. 2017; 8: 793-803.

76. Yang B, Shi MQ, Li ZH, Yang JJ, Li D. Fish, Long-Chain n-3 PUFA and Incidence of Elevated Blood Pressure: A Meta-Analysis of Prospective Cohort Studies. Nutrients. 2016; 8: 58.

77. Zhang Y, Ding J, Guo H, Liang J, Li Y. Associations of Fish and Omega-3 Fatty Acids Consumption With the Risk of Venous Thromboembolism. A Meta-Analysis of Prospective Cohort Studies. Front Nutr. 2020; 7: 614784.

78. Lehmann U, Gjessing HR, Hirche F, Mueller-Belecke A, Gudbrandsen OA, Ueland PM, et al. Efficacy of fish intake on vitamin D status: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2015; 102: 837-47.

79. Kim YS, Xun P, He K. Fish consumption, long-chain omega-3 polyunsaturated fatty acid intake and risk of metabolic syndrome: a meta-analysis. Nutrients. 2015; 7: 2085-100.

80. Schwingshackl L, Hoffmann G, Lampousi AM, Knuppel S, Iqbal K, Schwedhelm C, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol. 2017; 32: 363-75.

81. Yang X, Li Y, Wang C, Mao Z, Zhou W, Zhang L, et al. Meat and fish intake and type 2 diabetes: Dose-response meta-analysis of prospective cohort studies. Diabetes Metab. 2020; 46: 345-52.

82. Namazi N, Brett NR, Bellissimo N, Larijani B, Heshmati J, Azadbakht L et al. The association between types of seafood intake and the risk of type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. Health Promot Perspect. 2019; 9: 164-73.

83. Zhou Y, Tian C, Jia C. Association of fish and n-3 fatty acid intake with the risk of type 2 diabetes: a meta-analysis of prospective studies. Br J Nutr. 2012; 108: 408-17.

84. Wallin A, Di Giuseppe D, Orsini N, Patel PS, Forouhi NG, Wolk A et al. Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. Diabetes Care. 2012; 35: 918-29.

85. Xun P, He K. Fish Consumption and Incidence of Diabetes: meta-analysis of data from 438,000 individuals in 12 independent prospective cohorts with an average 11-year follow-up. Diabetes Care. 2012; 35: 930-8.

86. Muley A, Muley P, Shah M. ALA, fatty fish or marine n-3 fatty acids for preventing DM?: a systematic review and meta-analysis. Curr Diabetes Rev. 2014; 10: 158-65.

87. Tian S, Xu Q, Jiang R, Han T, Sun C, Na L et al. Dietary Protein Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cohort Studies. Nutrients. 2017; 9.

88. Li F, Liu X, Zhang D. Fish consumption and risk of depression: a meta-analysis. J Epidemiol Community Health. 2016; 70: 299-304.

89. Molendijk M, Molero P, Sanchez-Pedreno FO, Van der Does W, Martinez-Gonzalez AM. Diet quality and depression risk: A systematic review and dose-response meta-analysis of prospective studies. J Affect Disord. 2018; 226: 346-54.

90. Grosso G, Micek A, Marventano S, Castellano S, Mistretta A, Pajak A, et al. Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. J Affect Disord. 2016; 205: 269-81.

91. Yang Y, Kim Y, Je Y. Fish consumption and risk of depression: Epidemiological evidence from prospective studies. Asia Pac Psychiatry. 2018; 10: e12335.

92. Cao L, Tan L, Wang HF, Jiang T, Zhu XC, Lu H, et al. Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies. Mol Neurobiol. 2016; 53: 6144-54.

93. Wu S, Ding Y, Wu F, Li R, Hou J, Mao P. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. Neurosci Biobehav Rev. 2015; 48: 1-9.

94. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G, et al. Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. Public Health Nutr. 2018; 21: 1921-32.

95. Zeng LF, Cao Y, Liang WX, Bao WH, Pan JK, Wang Q, et al. An exploration of the role of a fish-oriented diet in cognitive decline: a systematic review of the literature. Oncotarget. 2017; 8: 39877-95.

96. Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2016; 103: 330-40.
97. Rezaeizadeh H, Mohammadpour Z, Bitarafan S, Harirchian MH, Ghadimi M, Homayon IA. Dietary fish intake and the risk of multiple sclerosis: a systematic review and meta-analysis of observational studies. Nutr Neurosci 2020;1-9.
98. Yang H, Xun P, He K. Fish and fish oil intake in relation to risk of asthma: a systematic review and meta-analysis. PloS One. 2013; 8(11): e80048.
99. Papamichael MM, Shrestha SK, Itsiopoulos C, Erbas B. The role of fish intake on asthma in children: A meta-analysis of observational studies. Pediatr Allergy Immunol. 2018; 29: 350-60.
100. Zhang GQ, Liu B, Li J, Luo CQ, Zhang Q, Chen JL, et al. Fish intake during pregnancy or infancy and allergic outcomes in children: A systematic review and meta-analysis. Pediatr Allergy Immunol 2017; 28:152-61.
101. Di Giuseppe D, Crippa A, Orsini N, Wolk A. Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Res Ther 2014; 16: 446.
102. Sadeghi O, Djafarian K, Ghorabi S, Khodadost M, Nasiri M, Shab-Bidar S. Dietary intake of fish, n-3 polyunsaturated fatty acids and risk of hip fracture: A systematic review and meta-analysis on observational studies. Crit Rev Food Sci Nutr. 2019; 59: 1320-33.
103. Dinu M, Pagliai G, Casini A, Sofi F. Food groups and risk of age-related macular degeneration: a systematic review with meta-analysis. Eur J Nutr. 2019; 58: 2123-43.
104. Zhu W, Wu Y, Meng YF, Xing Q, Tao JJ, Lu J. Fish Consumption and Age-Related Macular Degeneration Incidence: A Meta-Analysis and Systematic Review of Prospective Cohort Studies. Nutrients 2016; 8: 743.
105. Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. Arch Ophthalmol. 2008; 126: 826-33.
106. Mozaffari H, Daneshzad E, Larijani B, Bellissimo N, Azadbakht L. Dietary intake of fish, n-3 polyunsaturated fatty acids, and risk of inflammatory bowel disease: a systematic review and meta-analysis of observational studies. Eur J Nutr 2020; 59: 1-17.
107. Hauk L. DGAC Makes Food-Based Recommendations in the 2015-2020 Dietary Guidelines for Americans. Am Fam Physician. 2016; 93: 525.
108. Santo K, Hyun K, de Keizer L, Thiagalingam A, Hillis GS, Chalmers J, et al. The effects of a lifestyle-focused text-messaging intervention on adherence to dietary guideline recommendations in patients with coronary heart disease: an analysis of the TEXT ME study. Int J Behav Nutr Phys Act 2018; 15: 45.
109. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008; 67: 253-6.
110. Bosch AC, O'Neill B, Sigge GO, Kerwath SE, Hoffman LC. Heavy metals in marine fish meat and consumer health: a review. J Sci Food Agric. 2016; 96: 32-48.
111. Zhou Q, Gu Y, Yue X, Mao G, Wang Y, Su H, et al. Combined toxicity and underlying mechanisms of a mixture of eight heavy metals. Mol Med Rep. 2017; 15: 859-66.
112. Chen W, Weisburger JH, Fiala ES, Spratt TE, Carmella SG, Chen D, et al.Gastric carcinogenesis: 2-chloro-4-methylthiobutanoic acid, a novel mutagen in salted, pickled Sanma hiraki fish, or similarly treated methionine. Chem Res Toxicol. 1996; 9:58-66.
113. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010; 121: 586-613
114. Alexander J, Frøyland L, Hemre GI, Jacobsen BK, Lund E, Meltzer HM, et al. A comprehensive assessment of fish and other seafood in the Norwegian diet. Report from Norwegian Scientific Committee for Food Safety 2007.
115. Graff IE, Oyen J, Kjellevold M, Froyland L, Gjesdal CG, Almas B, et al. Reduced bone resorption by intake of dietary vitamin D and K from tailor-made Atlantic salmon: A randomized intervention trial. Oncotarget 2016; 7: 69200-15.
116. Rangel-Huerta OD, Aguilera CM, Mesa MD, Gil A. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomakers: a systematic review of randomised clinical trials. Br J Nutr. 2012; 107 Suppl 2: S159-70.
117. Pilz S, Tomaschitz A, Drechsler C, Zittermann A, Dekker JM, Marz W. Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. Curr Drug Targets. 2011; 12: 88-96.
118. Militante JD, Lombardini JB. Treatment of hypertension with oral taurine: experimental and clinical studies. Amino Acids. 2002; 23: 381-93.
119. D'Elia L, Iannotta C, Sabino P, Ippolito R. Potassium-rich diet and risk of stroke: updated meta-analysis. Nutr Metab Cardiovasc Dis. 2014; 24: 585-7.
120. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. J Lipid Res 1989; 30: 785-807.
121. von Schacky C. n-3 fatty acids and the prevention of coronary atherosclerosis. Am J Clin Nutr. 2000; 71(1 Suppl): 224S-7S.
122. Rose DP, Connolly JM. Omega-3 fatty acids as cancer chemopreventive agents. Pharmacol Ther 1999; 83: 217-44.
123. Tapiero H, Ba GN, Couvreur P, Tew KD. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. Biomed Pharmacother. 2002; 56: 215-22.
124. Hilakivi-Clarke L, Olivo SE, Shajahan A, Khan G, Zhu Y, Zwart A,

Cho E, et al. Mechanisms mediating the effects of prepubertal (n-3) polyunsaturated fatty acid diet on breast cancer risk in rats. J Nutr. 2005; 135(12 Suppl): 2946S-52S.

125. Pannu PK, Piers LS, Soares MJ, Zhao Y, Ansari Z. Vitamin D status is inversely associated with markers of risk for type 2 diabetes: A population based study in Victoria, Australia. PloS One. 2017; 12: e0178825.

126. McGuire S. U.S. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. Adv Nutr. 2011; 2: 293-4.

127. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on health benefits of seafood (fish and shellfish) consumption in relation to health risks associated with exposure to methylmercury. EFSA J 2014; 12: 3761.