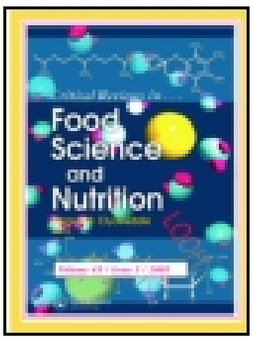

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REVIEW

Fish consumption and the risk of cardiovascular disease and mortality in patients with type 2 diabetes: a dose-response meta-analysis of prospective cohort studies

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ABSTRACT

We aimed to investigate the association of fish consumption with the risk of coronary heart disease (CHD), stroke and all-cause mortality in patients with type 2 diabetes (T2D). We systematically searched PubMed and Scopus from inception till June 2019. We included prospective cohort studies assessing the relation of fish intake with the risk of CHD, stroke and mortality in patients with T2D. Study-specific results were pooled with the use of a random-effects model. Nine prospective cohort studies with 57,394 diabetic patients were identified. The relative risks for the highest compared with the lowest category of fish consumption were 0.86 (95% CI 0.76, 0.96; $I^2 = 50\%$, $n = 8$) for all-cause mortality, and 0.61 (95% CI 0.29, 0.93; $I^2 = 68\%$, $n = 3$) for CHD. There was a monotonic inverse association, with a nadir at fish consumption of approximately 2–3 servings/week, in both analyses. A nonsignificant inverse association was found for stroke. In the analysis of all-cause mortality, a nonsignificant inverse association was found in studies that controlled for energy intake, suggesting that the observed inverse association was not an addition effect, but may be due to substituting other foods such as red and processed meat with fish.

KEYWORDS

Cardiovascular disease; coronary heart disease; fish; meta-analysis; mortality; type 2 diabetes

Introduction

Fish are one of the main cardioprotective food groups. Current literature presents convincing evidence for the inverse association between higher fish consumption and the risks of cardiovascular disease (CVD) (He et al. 2004; Jayedi, Zargar, and Shab-Bidar 2019) and all cause and CVD mortality (Jayedi, Shab-Bidar et al. 2018). Fish are rich in long-chain omega-3 polyunsaturated fatty acids (He 2009). Results from interventional studies have indicated that supplementation with omega-3 fatty acids can result in favorable cardioprotective changes in platelets aggregation, lipid profile, endothelial function, arrhytmatic activity, and inflammatory status (Sidhu 2003; Lavie et al. 2009).

However, despite the evidence regarding the inverse association of fish consumption with the risk of morbidity and mortality in the general population, such associations in patients with type 2 diabetes (T2D) have not been well investigated. T2D is accompanied by unfavorable cardiometabolic abnormalities such as insulin resistance and hyperglycemia (Laakso and Kuusisto 2014), high blood pressure (Cheung and Li 2012), serum lipoprotein abnormalities (Krauss 2004), and endothelial dysfunction (McEwen et al. 2010) and as a result, is associated with a higher risk of CVD (Abi Khalil et al. 2012).

The results demonstrated that supplementation with omega-3 fatty acids in patients with T2D has the same beneficial effects as those found in the general populations (McEwen et al. 2010). However, some interventional studies indicated that supplementation with omega-3 fatty acids may increase blood glucose levels in patients with T2D (Glauber et al. 1988; Friday et al. 1989). On the other hand, a meta-analysis of 16 prospective cohort studies indicated that higher intakes of both fish and long-chain omega-3 fatty acids were associated with a higher risk of developing T2D among the US populations, but not in European and Asian countries (Wallin et al. 2012). In addition, another recent meta-analysis of prospective cohort studies suggested that there was a potential U-shaped association between fish intake and the risk of all-cause and CVD mortality in Western countries (Jayedi, Shab-Bidar et al. 2018).

Current recommendations for fish consumption in patients with T2D are similar to those of the general population and have been developed based on investigations in the general population (Mann et al. 2004; Evert et al. 2014). Thus, assessing the association of fish intake with the risk of CVD and mortality in diabetic patients may help developing more detailed dietary recommendations for the prevention of CVD in patients with T2D. With regard to

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above-mentioned considerations, we aimed to summarize available evidence on the association of fish consumption with the risk of CVD and mortality in diabetic patients. Thus, the objective of this systematic review and dose-response meta-analysis of prospective cohort studies is to investigate the association of fish intake with the risk of all-cause mortality and CVD including coronary heart disease (CHD), stroke, and myocardial infarction (MI) in patients with T2D.

Methods

This report has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement (Moher et al. 2009). Also, we followed the 12-item PRISMA extension to write the abstract (Beller et al. 2013).

Search strategy

We systematically searched PubMed and Scopus databases up to June 2019. We used the following keywords for the systematic search: ('fish' OR 'fishes' OR 'seafood' OR 'fish protein' OR 'fish products') AND ('death' OR 'deaths' OR 'survival' OR 'mortality' OR 'fatal' OR 'event' OR 'events' OR 'prognosis' OR 'prognostic' OR 'outcome' OR 'stroke' OR 'cerebrovascular disease' OR 'intracranial hemorrhage' OR 'cerebral infarction' OR 'CVD' OR 'cardiovascular disease' OR 'cardiovascular' OR 'myocardial infarction' OR 'ischemic heart disease' OR 'coronary heart disease' OR 'CHD' OR 'IHD') AND ('prospective' OR 'prospectively' OR 'cohort' OR 'cohorts' OR 'longitudinal' OR 'observational' OR 'observation' OR 'Follow-up' OR 'nested' OR 'relative risk' OR 'hazard ratio' OR 'odds ratio' OR 'Follow-up') AND 'diabetes'. The reference lists of all relative articles and reviews were also manually searched. We limited our systematic search to articles published in English.

Eligibility and study selection

Two authors (AJ, SS) independently reviewed the titles and abstracts of all studies identified and selected eligible studies on the basis of the following criteria: (1) prospective cohorts, nested case-controls, or prospective reports within interventional studies conducted in patients with T2D; (2) measured and reported fish intake as exposure and in at least two categories; (3) reported the outcome of interest including all-cause mortality, CHD (fatal and/or nonfatal), stroke, and/or MI at follow-up; and (4) reported risk estimates (relative risk (RR) or hazard ratio or odds ratio) and the corresponding 95% confidence intervals (CIs) for each category of fish intake. Cross-sectional and retrospective studies, studies conducted in the general population, and studies without risk estimates were excluded.

Data extraction and assessment for study quality

Two authors (AJ, SS) independently reviewed the full texts of selected eligible studies, and extracted the following information from each eligible study: first author's name, publication year, location, follow-up duration, mean age and/or age range, gender, dietary assessment method, confounding covariates, exposure levels, number of participants/cases and reported risk estimates and their 95% CIs across categories of fish intake. When several adjustment models were reported in a given study, the model with the most confounding variables was selected and included in the meta-analysis. For studies without sufficient information for inclusion in dose-response analyses, we contacted with authors for additional information (Iimuro et al. 2012; Villegas et al. 2015; Zhang et al. 2018), but we did not receive any response from authors. The quality of eligible studies was assessed with use of a 9-point Newcastle-Ottawa scale (Stang 2010). Also, we used the NutriGrade scale to rate the quality of meta-evidence (Schwingshackl et al. 2016). Disagreements were resolved through discussion under supervision a third author (SS-B).

Data synthesis and statistical analysis

The RR and 95% CI were considered the effect size and the reported hazard ratios or odds ratios were considered as equal to RR. For the highest versus lowest category meta-analysis, we pooled the reported risk estimates for the highest compared to the lowest category of fish intake using the DerSimonian and Laird random-effects model (DerSimonian and Laird 1986). When separate risk estimates were reported across sex or other subgroups, we pooled subgroup-specific RRs using a fixed-effects model and included the pooled effect size in meta-analysis. We performed sensitivity analyses by serial exclusion of each study at one time to test the potential effect of each study on pooled RR. We tested between-studies heterogeneity using Cochrane's Q test of heterogeneity and the I^2 statistic (Higgins et al. 2003). We performed several subgroup analyses based on location, follow-up duration, mean age, and adjustments for main confounding variables to test the association in each subgroup and to find the potential sources of heterogeneity. We assessed potential publication bias using funnel plots asymmetry, and tested it by Egger's asymmetry test (Egger et al. 1997) and Begg's test (Begg and Mazumdar 1994).

We performed additional dose-response analyses using studies that reported sufficient information. For this purpose, studies were eligible for inclusion if they: (1) reported fish intake in at least three categories; (2) reported range or median/mean of each category; (3) reported the numbers of cases and participants/personyears in each category of fish intake; (4) reported adjusted RRs and their 95% CI across categories of fish intake; and (5) considered the lowest category as reference. When the numbers of cases and participants/personyears in each category were not reported, we divided the total number of cases and participants/personyears by the number of categories, if fish consumption was categorized as quantiles (Schwingshackl et al., 2017; Jayedi, Rashidy-Pour et al. 2018).

We measured the linear dose–response relation using generalized least squares trend estimation, according to the

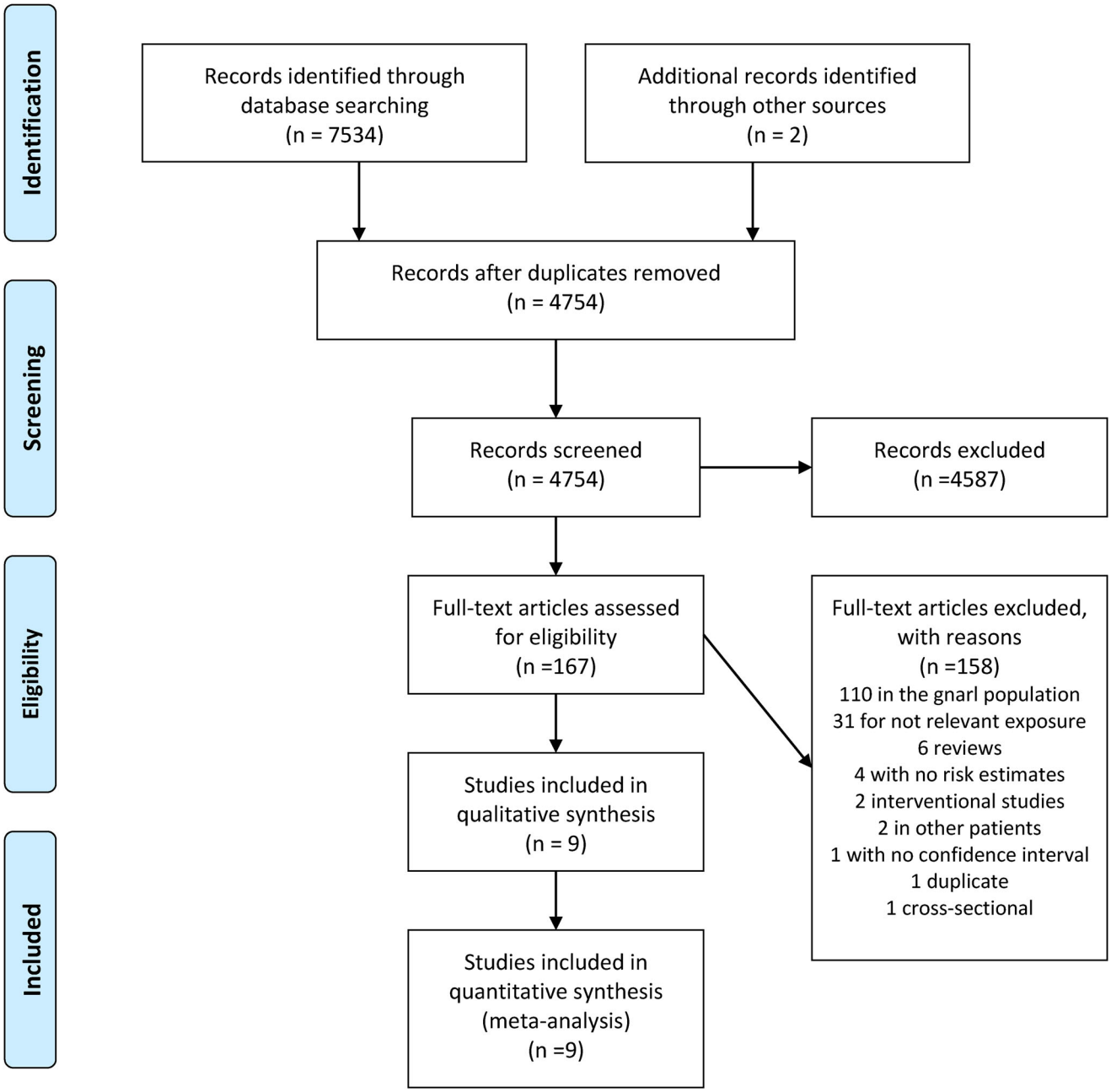


Figure 1. Literature search and study selection process for inclusion in meta-analysis of fish consumption and the risk of cardiovascular disease and mortality in patients with type 2 diabetes.

methods developed by Greenland and colleagues (Berlin, Longnecker, and Greenland 1993; Orsini, Bellocco, and Greenland 2006). The RR was calculated for a one serving/week (approximately 100 g) increment in fish consumption in each study. Study-specific results were combined with the use of a random-effects model. A potential nonlinear association was examined by modeling fish intake levels with the use of restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (Orsini et al. 2012). A *P* value for nonlinearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to 0. All analyses were conducted with Stata software, version 14 (Stata Corp., College Station, TX).

Results

We found 7534 studies through databases, plus two articles via hand searching. Of those, 2782 records were duplicates. We reviewed titles and abstracts of all remaining studies and as a result, another 4587 studies were excluded, yielded 167 studies for full-text assessing (Figure 1). Of the remaining 167 studies, nine prospective cohort studies with 57,394 patients with T2D were eligible for inclusion in the present meta-analysis (Feskens, Bowles, and Kromhout 1993; Hu et al. 2003; Trichopoulou et al. 2006; Iimuro et al. 2012; Strand et al. 2013; Villegas et al. 2015; Deng et al. 2018; Wallin et al. 2018; Zhang et al. 2018) (Table 1). Four prospective cohort studies were from the US (Hu et al. 2003;

Table 1. General characteristics of the studies included in meta-analysis of fish consumption and the risk of cardiovascular disease and mortality in patients with type 2 diabetes.

Author, years	Country	Follow-up duration (years)	Participants	Sex	Age	Diagnosis of type 2 diabetes	Outcome	Exposure assessment	Covariates	NOS score (ma× 9 points)
Deng et al. 2018	USA	10	1136	W/M	>18	Self-reported	All-cause mortality, CHD mortality, stroke mortality	FFQ	Age, sex, race/ethnicity, family income, the type of residential area, cigarette smoking, alcohol drinking, and the history of CVD, and the years of using insulin	8
Feskens, Bowles, and Kromhout 1993	Netherlands	17	83	W/M	64–87 years	Clinically diagnosed type 2 diabetes and glucose intolerance	CHD mortality	Cross-check dietary history method	Age and sex	5
Hu et al. 2003	USA	9	5103	W	49	Self-reported	All-cause mortality, CHD	FFQ	Age, smoking status, BMI, alcohol intake, parental history of myocardial infarction, menopausal status and postmenopausal hormone use, moderate to vigorous activities, multivitamin supplement use, vitamin E supplement use, history of HTN, hypercholesterolemia, duration of diabetes, hypoglycemic medication, *trans* fat, the ratio of PUFA to SFA, and dietary fiber	8
Iimuro, 2011	Japan	6	912	W/M	72	Clinically diagnosed type 2 diabetes	All-cause mortality	FFQ	Age, gender, Hb A1c, SBP, and history of CVD	7
Strand et al. 2013	Norway	4.8	317	W/M	62	Clinically diagnosed type 2 diabetes	Myocardial infarction	FFQ	Age, sex, fasting, current smoker, extent of CHD, left ventricular ejection fraction, serum TG, baseline ACS, baseline percutaneous coronary intervention, baseline coronary artery bypass graft surgery, and treatment with folic acid or vitamin B6 supplements	6
Trichopoulou et al. 2006	Greece	4.5	1013	W/M	> 20	Self-reported	All-cause mortality	FFQ	Age, gender, educational level, smoking, waist-to-height, hip circumference, MET score, total energy intake, treatment with insulin, treatment for HTN at enrollment, and treatment for hypercholesterolemia at enrollment	7
Villegas et al. 2015	USA	5.5	16452	W/M	52	Self-reported	Myocardial infarction	FFQ	Age, kcals/day, BMI, smoking, alcohol consumption, physical activity, income, education, insurance coverage, race, gender, and total meat intake per day	8
Wallin et al. 2017	Sweden	15	2225	W/M	45–84	Clinically diagnosed type 2 diabetes	All-cause mortality	FFQ	Age, sex, time since diabetes duration, BMI, physical activity, education, cigarette smoking, total energy intake, alcohol, history of high cholesterol, history of HTN and DASH diet	9
Zhang et al. 2018	USA	16	30153	W/M	62	Self-reported	All-cause mortality	FFQ	Age, BMI, race, education, marital status, smoking, alcohol, intake of total energy, red meat, SFA, vegetables, and fruit , physical activity, multivitamin use, aspirin use, history of HTN, history of high cholesterol level; and, in women, hormones use.	9

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; FFQ, food frequency questionnaire; HTN, hypertension; NOS, Newcastle Ottawa Scale; PUFA, poly unsaturated fatty acid; SBP, systolic blood pressure; SFA, saturated fatty acid, TG, triglycerides.

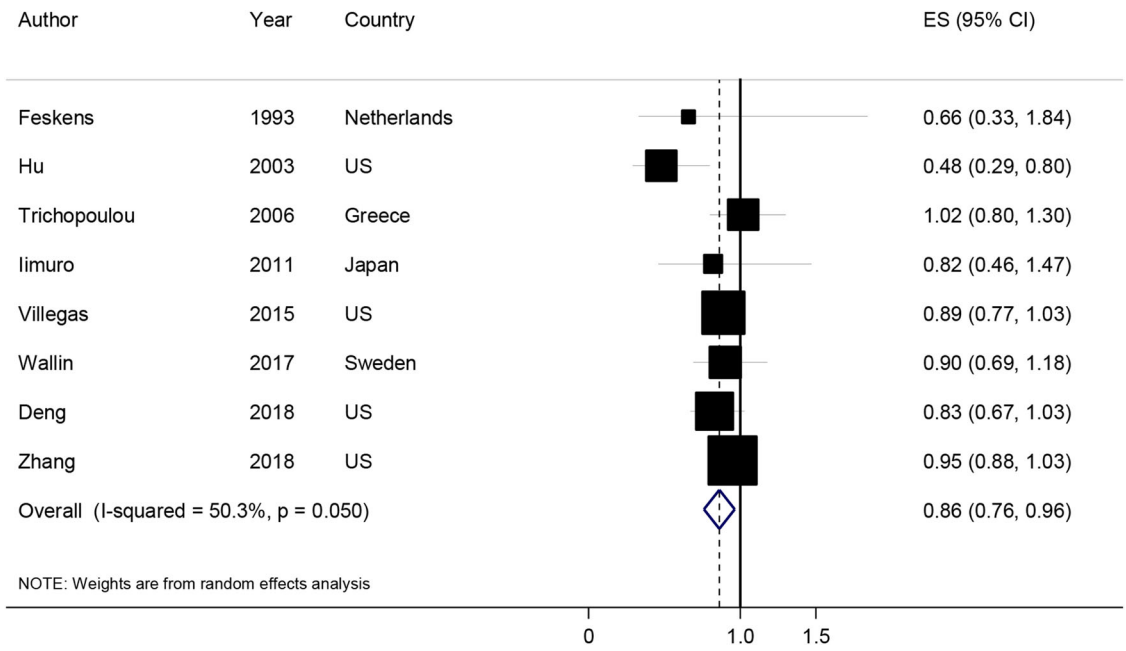


Figure 2. Relative risk of all-cause mortality for the highest compared with the lowest category of fish intake. EE: effect size.

Villegas et al. 2015; Deng et al. 2018; Zhang et al. 2018), four studies were from Europe (Feskens, Bowles, and Kromhout 1993; Trichopoulou et al. 2006; Strand et al. 2013; Wallin et al. 2018), and one from Asia (Iimuro et al. 2012). One study was a prospective evaluation within an interventional study (Iimuro et al. 2012), and the remainders were prospective cohort studies. One study on fish consumption and the risk of MI was conducted in diabetic patients with a history of CHD at baseline (Strand et al. 2013), and other eight studies were conducted among the general diabetic populations. One study included only women (Hu et al. 2003), and the rest included both sexes. Follow-up durations were between 4.8 and 17 years. One study performed cross-check evaluation for dietary assessment (Feskens, Bowles, and Kromhout 1993), and other studies used food frequency questionnaire (FFQ). Only two studies controlled for duration of diabetes in their multivariable analyses (Hu et al. 2003; Deng et al. 2018). Based on the Newcastle Ottawa Scale, two studies were at low quality (<7 stars) (Feskens, Bowles, and Kromhout 1993; Strand et al. 2013), and the remainders were at high quality. General characteristics of the studies included in the present review are presented in Table 1, and the reported RRs and the number of cases and participants/personyears in each category of fish consumption in primary studies are provided in Supplementary information Table 1.

All-cause mortality

We identified eight prospective cohort studies with 57,077 patients with T2D that were eligible for the analysis of fish intake and the risk of all-cause mortality (Feskens, Bowles, and Kromhout 1993; Hu et al. 2003; Trichopoulou et al. 2006; Iimuro et al. 2012; Villegas et al. 2015; Deng et al. 2018; Wallin et al. 2018; Zhang et al. 2018). Because some of the primary studies assessed the association of fish intake with mortality risk in their subgroup analyses and presented it in their supplemental materials, the exact numbers of deaths in diabetic subgroups were not reported in these studies and thus, we were unable to calculate total number of cases.

The analysis indicated that highest compared to the lowest category of fish intake was associated with a 14% lower risk of all-cause mortality in patients with T2D (RR: 0.86, 95% CI 0.76, 0.96), with moderate evidence of heterogeneity, $I^2 = 50\%$, $P_{\text{heterogeneity}} = 0.05$ (Figure 2). We sequentially removed each study from the pooled analysis, but the pooled RR remained significant (RR range: 0.83–0.92). In the sensitivity analysis, one large prospective cohort study, the Nurses' Health Study (Hu et al. 2003), accounted for all of the observed heterogeneity and when this study was eliminated from the pooled analysis, the heterogeneity disappeared and the association changed to 0.92 (95% CI 0.87, 0.98; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.81$).

In the subgroup analyses, the association was significant only in studies with younger participants with a mean age of <60 years (RR: 0.83, 95% CI 0.69, 0.98, $n = 4$) compared with >60 years, studies with follow-up duration of >10 years (RR: 0.93, 95% CI 0.86, 0.99, $n = 4$) compared with <10 years, studies with higher number of participants (>2000 vs <2000: 0.84, 95% CI 0.68, 0.99, $n = 4$ *vs* 0.88, 95% CI 0.74, 1.02, $n = 4$), ands among the US studies (RR: 0.82, 95% CI 0.68, 0.97, $n = 4$) compared with European and Asian studies (Table 2). The association was significant independent of smoking status and alcohol consumption, but was not significant when we controlled for body mass index, physical activity, and intakes of energy and saturated fats (Table 2). There was no evidence of publication bias with Egger's test ($p = 0.08$) and Begg's test ($p = 0.26$) (Supplementary information Figure 1). The quality of the evidence was rated moderate on the basis of the NutriGrade score (NutriGrade score = 6, Supplementary information Table 2).

Table 2. Subgroup analyses of fish intake and the risk of all-cause mortality in patients with type 2 diabetes.

	n	RR (95%CI)	I^2(%), $P_{heterogeneity}$ [a]	$P_{between}$ [b]
All studies	8	0.86 (0.76–0.96)	50, 0.05	–
Age (mean)				
<60	4	0.83 (0.69–0.98)	62, 0.03	0.09
≥60	4	0.94 (0.87–1.02)	0, 0.67	
Geographical region				
US	4	0.82 (0.67–0.97)	76, 0.05	0.84
Europe	3	0.94 (0.77–1.11)	0, 0.60	
Asia	1	0.82 (0.31–1.33)	–	
Follow-up duration				
≤10 years	4	0.81 (0.58–1.04)	71, 0.02	0.17
>10 years	4	0.93 (0.86–0.99)	0, 0.57	
Number of participants				
<2000	4	0.88 (0.74–1.02)	0, 0.60	0.74
>2000	4	0.84 (0.68–0.99)	75, 0.007	
Adjustments				
Body mass index				
Yes	5	0.87 (0.73–1.00)	69, 0.01	0.30
No	3	0.82 (0.66–0.99)	0, 0.91	
Smoking				
Yes	6	0.86 (0.75–0.98)	63, 0.02	0.53
No	2	0.77 (0.35–1.91)	0, 0.73	
Alcohol consumption				
Yes	5	0.84 (0.72–0.97)	69, 0.01	0.62
No	3	0.95 (0.74–1.17)	0, 0.57	
Physical activity				
Yes	5	0.87 (0.73–1.00)	69, 0.01	0.30
No	3	0.82 (0.69–0.99)	0, 0.91	
Saturated fat intake				
Yes	2	0.73 (0.27–1.19)	92, 0.001	
No	6	0.82 (0.66–0.99)	0, 0.91	0.30
Energy intake				
Yes	3	0.94 (0.88–1.00)	0, 0.60	
No	5	0.75 (0.58–0.92)	40, 0.16	0.01

[a]*P*-heterogeneity within subgroups with the use of a random-effects model.
[b]*P*-heterogeneity between subgroups with the use of a fixed-effects model.

Three studies reported sufficient data for dose-response analyses (Hu et al. 2003; Deng et al. 2018; Wallin et al. 2018), and the results demonstrated that each one serving/week (approximately 100 g/week) increment in fish consumption was associated with a 9% lower risk of all-cause mortality (RR: 0.91, 95% CI 0.87, 0.96), with no evidence of heterogeneity, $I^2 = 0\%$, $P_{heterogeneity} = 0.55$ (Figure 3a). A nonlinear dose-response analysis indicated that the risk of all-cause mortality decreased linearly to an intake of approximately 2–3 servings/week fish consumption, with no further changes in effect estimate ($P_{nonlinearity} = 0.007$, Figure 3b).

Cardiovascular disease

Four prospective cohort studies with 8781 patients with T2D and 791 cases of CHD, 376 cases of MI, and 372 cases of stroke were included in the analyses of fish intake and the risk of CVD (Hu et al. 2003; Strand et al. 2013; Deng et al. 2018; Wallin et al. 2018). A strong inverse association was found between higher fish consumption and the risk of CHD in patients with T2D (RR: 0.61, 95% CI 0.29, 0.93; $I^2 = 68\%$, $P_{heterogeneity} = 0.05$) in the analysis of three prospective cohort studies (Supplementary information Figure 2) (Hu et al. 2003; Deng et al. 2018; Wallin et al. 2018). The quality of the evidence was rated low on the basis of the NutriGrade score (NutriGrade score = 5.2, Supplementary information Table 2). However, nonsignificant inverse associations were found for MI and stroke in the analyses of two prospective cohort studies (Supplementary information Figure 3).

Three studies were eligible for dose-response analyses of CHD (Hu et al. 2003; Deng et al. 2018; Wallin et al. 2018). A one serving/week increment in fish consumption was associated with an 8% lower risk of CHD (RR: 0.92, 95%CI 0.86, 0.98; $I^2 = 0\%$, $P_{heterogeneity} = 0.50$) (Figure 4a). Similar to the analysis of all-cause mortality, the risk of CHD decreased linearly to an intake of 2–3 servings/week, and then reached plateau ($P_{nonlinearity} = 0.15$, Figure 4b).

Discussion

To our knowledge, this is the first systematic review and meta-analysis of prospective cohort studies to investigate the association of fish consumption with the risk of CVD and mortality in diabetic patients. The results suggested that higher fish consumption was associated with a 14% and a 39% lower risk of all-cause mortality and CHD, respectively. A one serving/week increment in fish intake was associated with a 9% and 8% lower risks of all-cause mortality and CHD, respectively. A nonsignificant inverse association was found for MI and stroke in the analyses of two prospective cohort studies.

Our results in patients with T2D are similar to those of the general population which have indicated that higher fish consumption was associated with a lower risk of CHD (Jayedi, Zargar, and Shab-Bidar 2019) and all-cause and

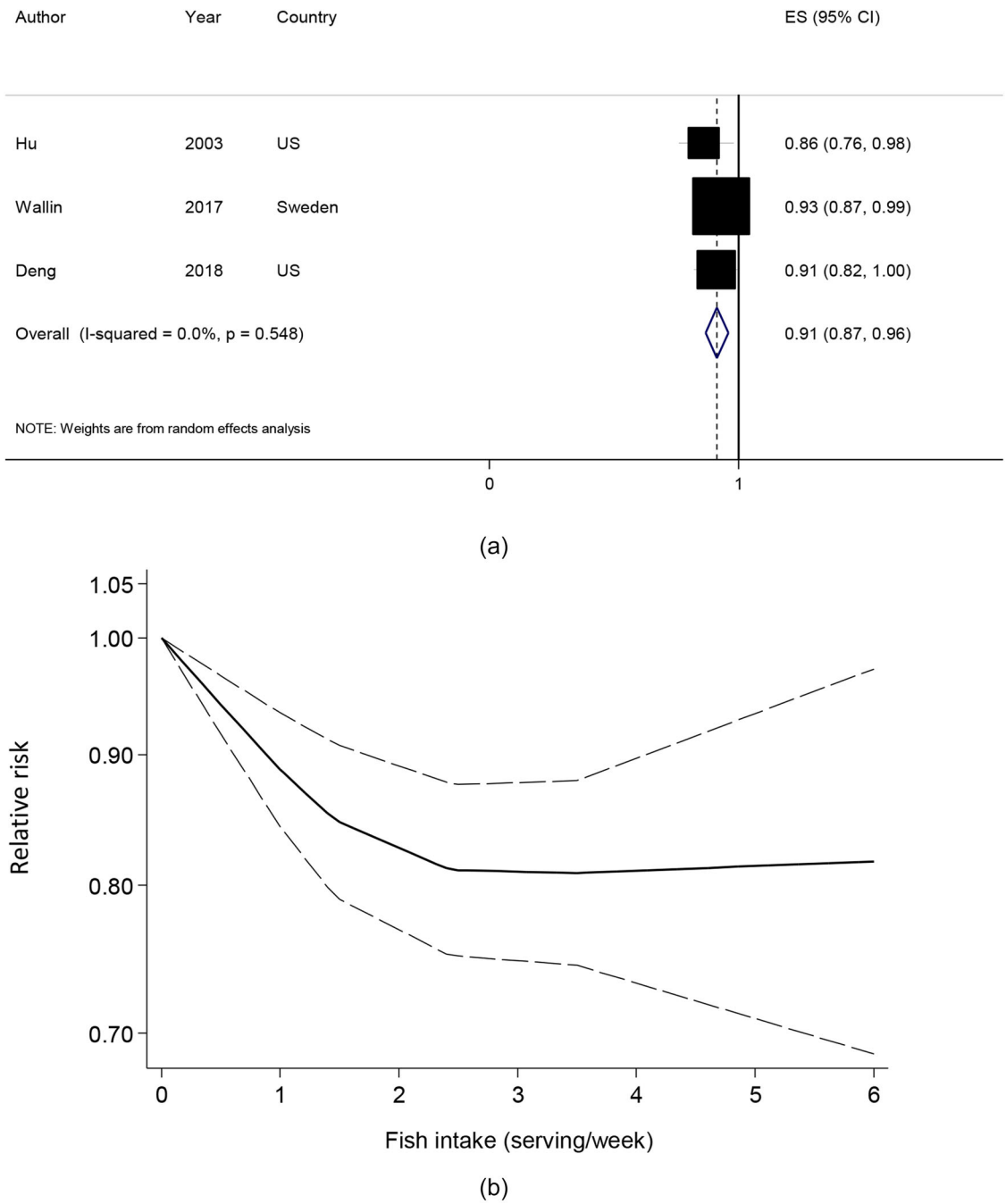
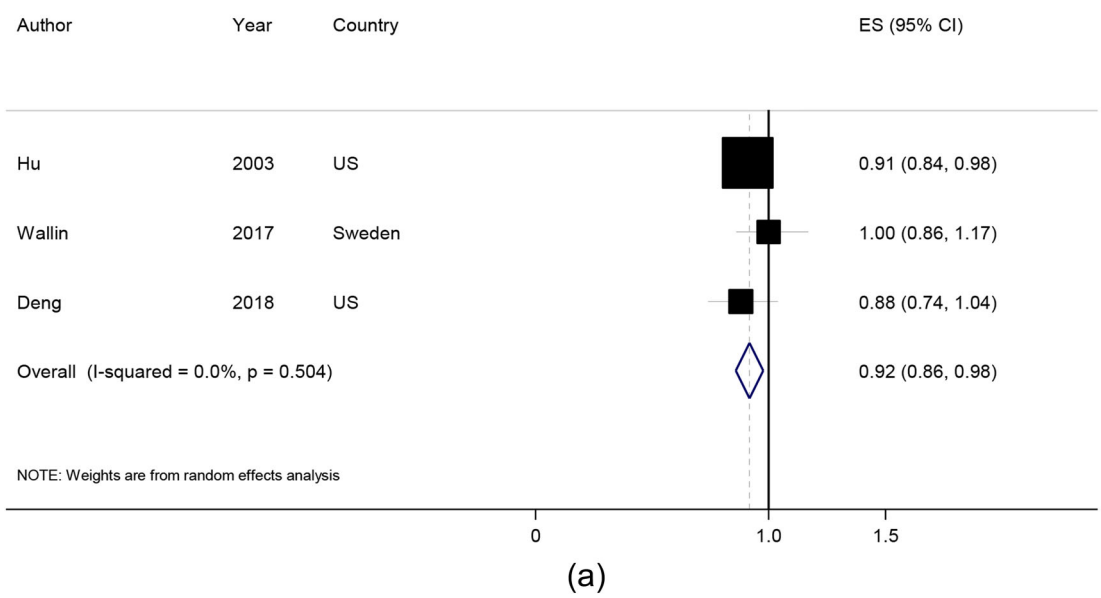


Figure 3. (a) Relative risk of all-cause mortality for a one-serving/week increment in fish consumption. EE: effect size. (b). Dose-response association between fish consumption and the risk of all-cause mortality in patients with type 2 diabetes ($P_{\text{nonlinearity}} = 0.007$).

CVD mortality (Jayedi, Shab-Bidar et al. 2018) in the general population. There are several biological mechanisms that could explain the inverse associations found in the present meta-analysis. T2D is accompanied by series of cardiometabolic abnormalities including insulin resistance, dyslipidemia, and hypertension and proinflammatory status (Martín-Timón et al. 2014; Leon and Maddox 2015).

Fish, especially fatty fish, are the main dietary source of long-chain omega-3 fatty acids in human diet. Results from interventional studies have indicated that supplementation with omega-3 fatty acids can reduce serum triglyceride levels in the general population and in patients with T2D (Harris 1999; Krauss et al. 2000), can cause a modest increase in high-density lipoprotein cholesterol levels (Balk et al. 2006), and can reduce platelet aggregation (Westerveld et al., 1993; Axelrod et al. 1994). Omega-3 fatty acids have antithrombotic (Robinson and Stone 2006) and antiarrhythmic properties (De Caterina et al. 2003) and thus, independent of their effect on lipid profile, can reduce CVD risk. They can improve insulin sensitivity (Gao et al. 2017), and can reduce the incidence of diabetes-related neuropathy and nephropathy (De Caterina et al. 2007). In addition, omega-3 fatty acids have substantial anti-inflammatory (Calder 2015) and immune-modulatory properties (Calder 2013), and can improve endothelial function (Brown and Hu 2001).



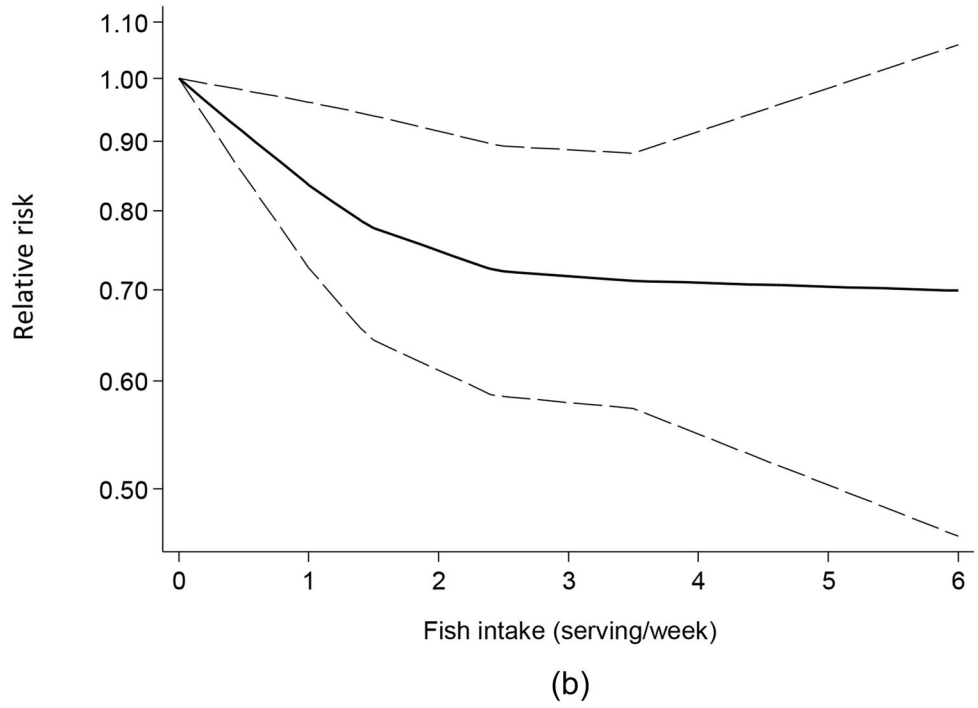


Figure 4. (a) Relative risk of coronary heart disease for a one-serving/week increment in fish consumption in patients with type 2 diabetes. EE: effect size. (b). Dose-response association between fish consumption and the risk of coronary heart disease in patients with type 2 diabetes ($P_{nonlinearity} = 0.15$).

With regard to blood glucose control, some interventional studies have indicated that supplementation with omega-3 fatty acids may rise blood glucose levels in patients with T2D (Glauber et al. 1988; Friday et al. 1989). However, two meta-analyses of randomized controlled trials indicated that fish oil supplementation has no adverse effects on blood glucose control in patients with T2D (Friedberg et al. 1998; Montori et al. 2000).

Although the results showed that higher fish consumption may reduce mortality risk in patients with T2D, the subgroup analysis according to adjustment for energy intake indicated a nonsignificant association in the subgroup of studies that controlled for energy intake. The pooled RRs were 0.75 (0.58, 0.92) for the five studies that controlled for energy intake versus 0.94 (0.88, 1.00) for three studies without such adjustment. This observation may suggest that the observed inverse association between fish consumption and all-cause mortality risk was not an addition effect, but an effect of substituting other foods such as red and processed meat with fish. A large prospective cohort study indicated

that replacing processed meat with a combination of poultry, eggs, fish, pulses, nuts, and low-fat dairy was associated with lower risks of all-cause and CVD mortality (van den Brandt 2019). However, only three studies were available in the subgroup with adjustment for energy intake and thus, further research in needed to test the association between fish consumption and mortality risk in patients with T2D.

There are some limitations that could attenuate our final conclusions and should be considered when interpreting the results. First, this is a meta-analysis of observational studies. Almost all primary studies included in the present review reported the results of the subgroup analyses within a larger cohort study in the general population and have not been developed to investigate diet-disease associations in patients with T2D. Thus, the findings are subject to be affected by recall, selection, and reverse causality biases. Several important confounding variables including duration of diabetes, presence of other comorbidities such as renal disorders, and diabetes treatment were not assessed in the primary studies and were not included in their multivariable analyses. Thus, we were unable to control for these important confounders. Of the nine studies included in the present work, only two studies controlled for duration of diabetes (Hu et al. 2003; Deng et al. 2018). Second, only one study, the Nurses' Health Study (Hu et al. 2003), performed multiple dietary assessments during follow-up period, and the remainders assessed baseline dietary intakes. Thus, the seasonal and interpersonal variations, as well as dietary variations due to incidence of other comorbidities during follow-up period did not consider in almost all primary studies. Third, we have a few numbers of studies in the subgroup analyses of all-cause mortality and in the analyses of CHD, MI, and stroke. In addition, the quality of the evidence was rated moderate for all-cause mortality and low for CHD. Thus, further observational studies are needed to confirm our findings. Fourth, of the nine studies included in the present review, three studies included <1000 participants (Feskens, Bowles, and Kromhout 1993; Iimuro et al. 2012; Strand et al. 2013), and other two cohorts were performed on about 1000 diabetic patients (Trichopoulou et al. 2006; Deng et al. 2018). Thus, the magnitude of the associations may have been affected by low statistical power. Fifths, as mentioned earlier, of the nine studies included in the present meta-analysis, seven studies reported the results of the subgroup of diabetes patients within a larger prospective cohort study in the general population (Hu et al. 2003; Trichopoulou et al. 2006; Strand et al. 2013; Villegas et al. 2015; Deng et al. 2018; Wallin et al. 2018; Zhang et al. 2018). They used FFQs that were developed and validated for using in the general population. Thus, using dietary assessment tools that were developed for using in the general population to assess dietary intakes in diabetic patients may result in inaccurate assessment of dietary intakes (Jenab et al. 2009; Hedrick et al. 2012). Only one study used diabetes-specific FFQ to assess dietary intakes (Iimuro et al. 2012). Sixth, the subgroup analyses of all-cause mortality indicated that the association became nonsignificant after controlling for body mass index, physical activity, and intakes of saturated fats and energy. However, the number of studies was relatively low in the subgroups and thus, further studies are needed to test the associations with considering all potential confounding variables. Finally, publication bias tests did not show any evidence of bias in the analysis of all-cause mortality. However, the funnel plot showed some evidence of asymmetry. Thus, the results are likely to be affected by publication bias and as a result, we may have reached an inaccurate estimation of the magnitude of the associations.

The present meta-analysis has several strengths. This is a first try, to our knowledge, that systematically gathered existing evidence on the association of fish consumption with the risk of CVD and mortality in diabetic patients. As mentioned earlier, current recommendations for fish consumption in patients with T2D (2 servings/week) are similar to those of the general population and have been developed based on investigations in the general population (Mann et al. 2004; Evert et al. 2014). In this work, we summarized all available evidence and found that there was an inverse association between fish consumption and the risk of CHD and mortality in diabetic patients. We found a strong inverse association in the analysis of CHD, which confirmed protective effects of fish and their long-chain omega-3 fatty acids in the prevention of CVD in diabetic patients. We performed dose-response analysis in the analyses of CHD and total mortality, which confirmed current recommendations for fish consumption in patients with T2D (2 servings/week).

Conclusions

The present meta-analysis of nine prospective cohort studies suggested that higher fish consumption was associated with lower risks of CHD and all-cause mortality in patients with T2D, with the best protective effects at fish consumption of approximately 2–3 servings/week. A nonsignificant inverse association was found in the analyses of MI and stroke. There are some limitations including low number of participants in some original studies, using dietary assessment tools that were developed for using in the general populations to assess dietary intakes in patients with T2D, inadequate adjustment for potential confounding variables, and low number of studies included in the analyses and thus, further prospective cohort studies are needed to present more strong evidence for the observed results in the present study.

Disclosure statement

None.

Author contributions

Research idea and study design: AJ; data acquisition: AJ, SS; data analysis/interpretation: AJ, AA, and SS-B; statistical analysis: AJ, supervision: SS-B. SS-B is the guarantor. All authors have read and approved the final manuscript. All authors had full access to all the data and

take responsibility for the integrity of the data and the accuracy of the data analysis.

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