

Fish Consumption and Stroke Risk: A Meta-Analysis of Prospective Cohort Studies

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Background: Inconsistent results of the association between fish consumption and stroke risk have been indicated in previous epidemiological studies. Therefore, we performed a meta-analysis of prospective cohort studies to estimate the impact of fish consumption on stroke risk. **Methods:** The PubMed and EMBASE databases were searched through a computer search. Prospective cohort studies satisfying predetermined inclusion criterion were included. Random-effect model was adopted in this meta-analysis. Analysis of subgroup, sensitivity, publication bias, dose-response, power, and quality of evidence was also conducted. **Results:** Thirty one publications including 33 independent prospective cohort studies were identified in this meta-analysis. In the primary analysis of the highest versus lowest categories of fish consumption, pooled results indicated that a significant trend toward an inverse association between fish intake and stroke risk (HR = .90, 95% confidence interval [CI] .85-.96). Further subgroup analyses indicated an inverse association was more pronounced in the group of hemorrhagic stroke (HR=.88, 95% CI .80-.96), female (HR =.83, 95% CI .75-.92), and Asia-Pacific (HR = .87, 95% CI .80-.95). Both the funnel plot and Egger tests suggested no evidence of publication bias. Dose-response analysis showed a linear relationship between fish intake and stroke and the risk of stroke decreased by 2%-12% with increasing intake of fish up to 100-700 g/week. According to the NutriGrade scoring system, the level of metaevidence quality was moderate. **Conclusions:** Based on current evidence from prospective cohort studies, we concluded that fish consumption was associated with a decreased risk of stroke.

Key Words: Stroke—fish—risk—meta-analysis.

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Introduction

Health beneficial effects of fish on cardiac cerebral disease have gained growing interest in recent years. Fish, as one important component of diet, is a rich source of n-3 fatty acids, which may be protective against cardiovascular disease through lowering oxidative stress, blood pressure, inflammation, and improving vascular function.¹⁻³ Furthermore, fish provides additional nutrients, such as high quality proteins, vitamins, and minerals, which have been shown to play an important role in the prevention of cardiovascular disease.⁴ The association between fish consumption and stroke risk has been reported with inconsistent finding in a tremendous amount of epidemiological studies.⁵⁻³⁵ Additionally, they also raised questions that stroke risk with fish consumption may vary in stroke type, gender, and fish types. To shed light on this issue, several systematic review and meta-analyses had been conducted.³⁶⁻⁴¹ However, these reviews or meta-analyses

missed or excluded some important studies, and some new studies were published. Therefore, an updated meta-analysis of prospective cohort studies was performed.

Materials and Methods

We reported this study following the proposal for reporting Meta-analysis Of Observational Studies in Epidemiology group.⁴²

Eligibility Criteria

Prospective cohort studies which evaluated the association between fish intake and stroke risk in adult and reported specific data (ie, hazard ratios or rate ratios with their 95% confidence intervals [CIs]) were included. The outcome of interest is stroke incidence or death. If multiple publications from the same population or overlap data were found, we included the study with the longest years of follow-up or the most informative one for both exposure and outcome. Additionally, studies reporting unadjusted risk estimates were excluded.

Search Strategy

Published studies were identified in Embase and PubMed databases. The electronic search without language restriction was updated on March 23, 2018. Search items and detailed search processes were shown in Supplementary Table I. Additional search was supplemented by reviewing the reference lists of retrieved studies, review or meta-analysis related to this issue as well as the literatures citing the included studies in Google Scholar.

Data Collection

We extracted the following information including the first author of included studies, publication year, the county where population were recruited, name of cohort study, sex and age of population, years of follow-up, sample size, the method of exposure assessment, ascertainment of stroke, fish consumption levels, and corresponding risk estimates with 95% CIs in maximally multivariable-adjusted models, and confounding variables. Data were extracted by one author and checked by another author for accuracy.

Risk of Bias Assessment and Quality of Meta-Evidence

To assess the risk of bias of prospective cohort studies, we adopted a risk of bias checklist introduced by Schwingshackl et al.⁴³ The quality of metaevidence was assessed by the NutriGrade Scoring System.⁴³ The NutriGrade Scoring System contains 8 subitems as follow: risk of bias (ascertainment of exposure, assessment of outcome, adequacy of follow-up duration, and adjusted basic model and outcome-relevant adjustments), precision, heterogeneity, directness, publication bias, funding bias, effect size, and dose-response. The score ranges from 0 to

10 points and the quality of metaevidence was grouped into 4 categories: very low (0-3.99), low (4-5.99), moderate (6-7.99), and high (≥ 8).

Statistical Analysis

Study-specific HR with 95% CI was pooled using a random-effects model.⁴⁴ In main analysis, a pooled risk estimate with 95% CI of highest versus lowest categories of fish consumption was calculated to confirm the association between fish intake and stroke risk. Results stratified by sex and stroke subtypes were considered as 2 separate reports. The heterogeneity measure was assessed by the I^2 statistic.⁴⁵ Funnel plot and the Egger asymmetry test was used to examine the publication bias.^{46,47} To investigate the robustness of overall finding, sensitivity analyses and power analysis were performed as described previously.^{48,49} Subgroup analysis was conducted according to sex, location, stroke subtypes, fish type, and length of follow-up.

Owing to the distinct cut-off points for fish consumption categories in different studies, we assumed that 1 serving/week was equivalent to 100 g/week,⁵⁰ except where otherwise specified in original studies. In further analysis, we performed a dose-response analysis with a one-stage robust error meta-regression model described by Xu and Doi.⁵¹ Estimates of HRs with 95% CIs for at least 2 categories of fish intake were required. When specific level of fish intake was specified for a range and no median level of exposure was reported, the midpoint of the interval was used. For the open-ended upper interval, the value is 1.5 times the low end of the interval.

All statistical analyses listed above were conducted with STATA 14.0 software (StataCorp, College Station, TX), except power analysis, which was performed by SAS version 9.3 (SAS Institute Inc, North Carolina, US).

Results

Literature Search

The process of study selection was shown in Supplementary Figure I. A total of 570 unique citations were identified based on the search strategy. After careful review, 110 remained for full-text assessment. Studies were excluded due to design of case-control, presentation format of comments, reviews, meta-analyses, conference abstract/summary, erratum, and note, crude relative risk estimates reported, no especially available data about stroke or fish intake, and studies with shorter follow-up years or duplicated data (Supplementary Table II). Five studies identified by additional search were found to be fulfilled the inclusion criteria.^{7,11,25,34,35} Finally, 31 publications were included in statistical analysis.⁵⁻³⁵

Basic Characteristics of Included Studies

The basic characteristics of included studies were presented in Supplementary Table III. Thirty one

publications contain 33 cohort studies. All studies were published in English. Year of publication dates from 1994 to 2018. The study population was derived from North America, Asia-Pacific, and Europe. Nearly all of the included studies concerned general populations, except one based on patients with type 2 diabetes.⁶ Twenty six studies enrolled both men and women,^{5-15,18-24,26,28,29,34,35} whereas 2 included only women^{16,25} and 5 studies only men.^{17,27,30-32} Definitions of cases were stroke incidence or mortality based on International Classification of Diseases or medical records. Twelve of the 31 studies involved stroke death event,^{5,7,12,20,21,24,25,27,28,30,34,35} while in the rest of included studies, the outcome of interest is total stroke event in an overwhelming majority of included studies.^{6,8-11,13-19,22,23,26,29,31,32-35} Data on fish habits were obtained through interviews using a general questionnaire or self-administered questionnaire. Confounding factors for consideration in original studies included basic characteristics of individuals, personal disease history, and dietary habits or lifestyles.

Main Analysis

The multivariable-adjusted HRs for each study and pooled results were presented in [Figure 1](#). The pooled adjusted HR of stroke risk for the highest versus lowest categories fish consumption was .90 (.85-.96). There was no significant heterogeneity ($I^2 = 39.2\%$). In further analysis, there was borderline significant association between fish consumption and stroke mortality (HR = .92, 95% CI .84-1.02),^{5,7,12,20,21,24,25,27,28,30,34,35} without significant evidence of heterogeneity observed ($I^2 = 24.1\%$).

Stratifying Analysis

[Table 1](#) shows the results of the subgroup meta-analysis by sex, location, stroke subtypes, length of follow-up, and fish type. In subtype analyses, differential associations were observed for men and women. For men, the HR was .97 (.84-1.11) in pooled analysis of twelve studies.^{9,11,12,14,15,19,27-32} Correspondingly, the pooled risk estimate for women was .83 (.75-.92).^{9,11,12,14-16,19,22,25,29}

In subgroup analysis by geographic region, a significantly inverse relation with stroke risk was found in Asia-Pacific (HR = .87, 95% CI .80-.95),^{7,12,18,20,21,24,26-28} but not in North America group (HR = .90, 95% CI .75-1.06)^{5,10,11,15,23,25,29,30,31} or and Europe group (HR = .84, 95% CI .87-1.01).^{6,8,9,13,14,16,17,19,22,32-35}

In subgroup analysis by stroke subtype, the significant inverse association was more pronounced in hemorrhagic stroke group (HR = .88, 95% CI .80-.96),^{11-16,19,21,23,24,26,28,33} while results revealed a nonsignificant trend toward an inverse association between fish intake and ischemic stroke (HR = .96, 95% CI .89-1.03).^{9,10-16,19,21,23,24,26,28,33}

In subgroup analysis by length of follow-up, a cutoff of 10 years was used. The pooled estimates of risk was .89 (.83-.95) for studies with more than 10 years of

follow-up^{6,7,9,11,12,14-17,19-21,23-30,32-35} and .97 (.83-1.13) for those with a follow-up period of less than 10 years.^{5,8,10,12,18,22,31}

In subgroup analysis by fish type, a non-significant inverse trend was revealed for lean fish (HR=.84, 95% CI .70-1.00),^{6,8,9,16,17} fatty fish (HR = .89, 95% CI .79-1.01)^{6,8,9,16,17,22} or shellish fish (HR = .96, 95% CI .83-1.11).^{6,8,12,22,27}

Test Heterogeneity

The results of heterogeneity test were shown in [Table 1](#). Values of I^2 range from .0% to 53.2%.

Sensitivity Analyses

One study was omitted from sensitivity analyses at a time and then the remainder of included studies was pooled. The results of sensitivity analyses were shown in Supplementary Table IV. The overall result was not influenced by any studies, indicating our result was robust.

Publication Bias

Based on the Egger's regression test, there was no indication of publication bias (P for Egger's test = .084). As shown in the Begg's funnel plot ([Fig 2](#)), there was no asymmetry observed.

Power Analysis

Power analysis was performed based on the method described by Cafri et al.⁴⁹ The power was 85.6% to detect a HR of .90 for highest versus lowest category of fish intake (Supplementary Table V).

Dose-Response Analysis

Dose-response analysis shows there was no evidence of a nonlinear dose-response association between fish intake and stroke ($P = .45$). As shown in [Figure 3](#), lower risk in stroke appeared graded with increasing intake of fish, with a trend toward 4% lower risk in stroke with a 200 g/week increment, 7% lower risk with a 400 g/week increment, 10% lower risk in stroke with a 600 g/week increment, and 12% lower risk in stroke with a 700 g/week increment (Supplementary Table VI). In further analysis by stroke subtype, similar trend was observed for hemorrhagic stroke (Supplementary Figure II), while not in ischemic stroke (Supplementary Figure III).

Quality of Meta-Evidence

According to the NutriGrade scoring system, a total of 7.7 points were awarded, indicating that the level of meta-evidence was moderate (Supplementary Table VII).

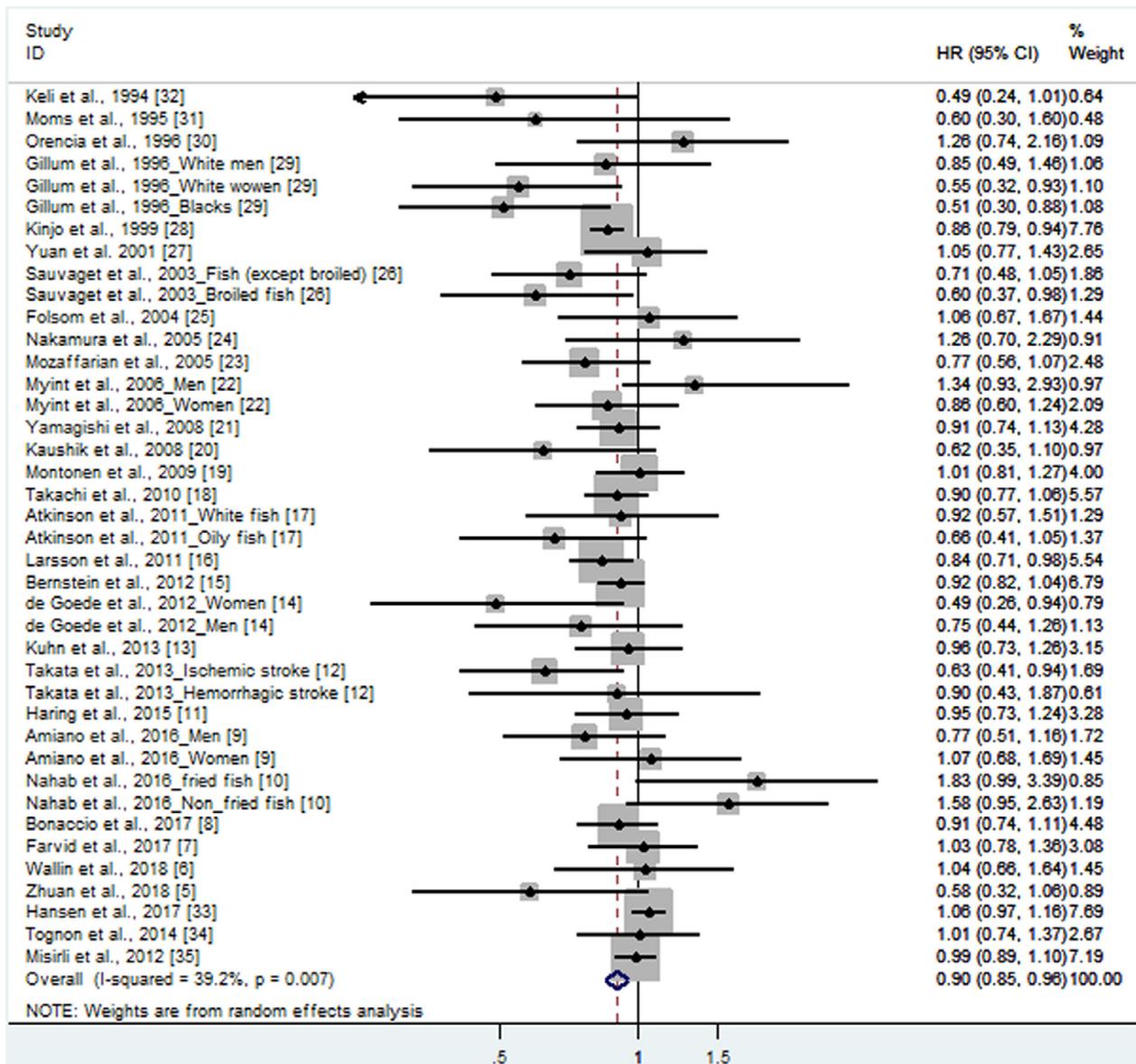


Figure 1. Forest plot for the association between stroke risk and fish consumption.

Discussion

In this updated meta-analysis with 31 publications involving 33 prospective cohort studies, we found that higher intake of fish was associated with a decreased risk of stroke and a significantly linear relationship between fish intake and stroke.

Subgroup analyses indicated the observed health effect of fish intake on stroke risk was modified by stroke subtype, sex, and geographic region. A significant beneficial association between fish intake and stroke risk was observed in women and the Asia-Pacific group, but not in men, Europe, or North America. Our result is in agreement with a systematic review and meta-analysis which compared risk factor profiles between intracerebral hemorrhage and ischemic stroke in Chinese and White populations.⁵² This review

indicated that Chinese and Whites bear different risk from the same risk factor.⁵² With reference to the gender difference on this issue, it may be partly explained by hormonal factors and lifestyles.

In terms of stroke subtype, a significant inverse association was found between fish consumption and hemorrhagic stroke, while the association was attenuated with ischemic stroke. The significance of these findings is unclear. Compared with ischemic strokes, hemorrhagic strokes are generally associated with lower morbidity and higher mortality.⁵³ Thus, if there had been no measurement error for exposure and misclassification for outcome happened, our finding was conceivable due to the different nature of their pathogenesis. These differences also arouse interesting in mechanism variation underlying the different pathological types of stroke. Further studies,

Table 1. Results of subgroup analysis and heterogeneity test

Group	Number of studies	Summary HR (95% CI)	Heterogeneity I ²
All studies	31	.90 (.85-.96)	39.2%
<i>Geographic region</i>			
Asia-Pacific	9	.87 (.80-.95)	14.5%
Europe	13	.84 (.87-1.01)	27.4%
North America	9	.90 (.75-1.06)	53.2%
<i>Sex</i>			
Male	12	.97 (.84-1.11)	24.1%
Female	10	.83 (.75-.92)	7.3%
<i>Type of stroke</i>			
Ischemic stroke	15	.96 (.89-1.03)	27.9%
Hemorrhagic stroke	13	.88 (.80-.96)	.0%
<i>Type of fish</i>			
Lean fish	5	.84 (.70-1.00)	.0%
Fatty fish	6	.89 (.79-1.01)	.0%
Shellish	5	.96 (.83-1.11)	.0%
<i>Follow-up years</i>			
≥10	24	.89 (.83-.95)	41.7%
<10	8	.97 (.83-1.13)	44.2%

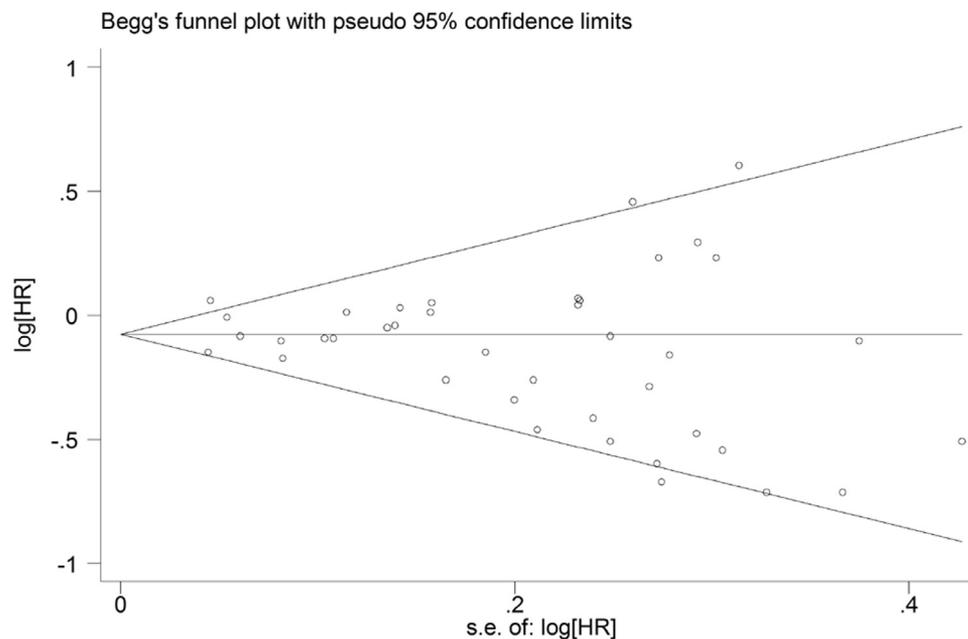
Abbreviations: CI, confidence interval.

both experimental research and observational studies, are warranted to consolidate and extend these findings.

With regard to different type of fish intake, the most common definition of fish intake among the included studies was "fatty vs. lean fish vs. shellfish." In our meta-analysis, there were no significant associations between stroke risk and any specific-types of fish. Of note, only few studies were included in subgroup analysis. The null results were may be the result of insufficient statistical power. In fatty fish, a higher amount of fatty acids were

provided than in lean species.¹⁰ Therefore, the favorable effect of fish intake depending on the species needs further study.

To date, data are still limited regarding the effect of the method used for fish prepared on the relationship between fish intake and stroke risk. In a cohort of people living in Hiroshima and Nagasaki, Sauvaget et al reported almost daily intake of broiled fish was associated with a significant 40% reduction in stroke death for the first time.²⁶ Finding from the Cardiovascular Health Study of

**Figure 2.** Begg's funnel plot for assessment of publication bias.

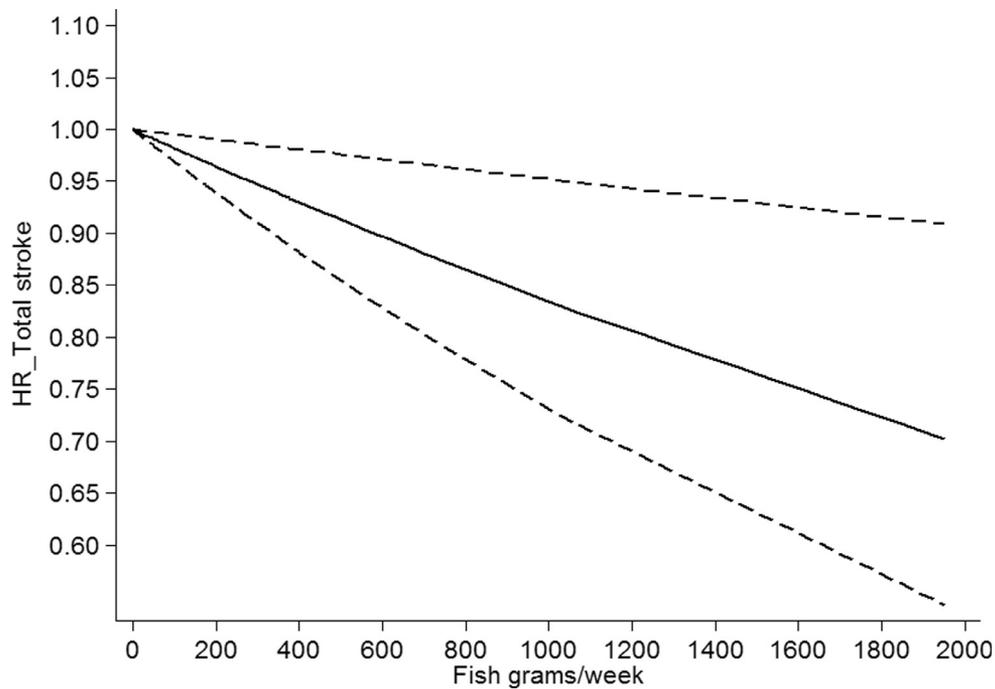


Figure 3. Dose-response relationships between stroke risk and fish consumption.

4775 elderly individuals aged 65-98 showed consumption of tuna/other fish was inversely associated with total stroke, whereas a higher risk of stroke was associated with fried fish/fish sandwich consumption.²⁴ Similarly, 2 another studies found a nonsignificant higher risk of stroke was associated with fried fish consumption, with a trend toward 83%¹⁰ or 25%⁶ increment risk. The mechanisms depended on the preparation were unclear. In the preparation method of frying, nutrient composition of fish meal was greatly altered. Also, the amounts of trans-fatty acids and lipid oxidation products which may contribute to cardiovascular risk, increased with the increase of both heating temperature and time during the cooking process.²⁴ Additionally, increased energy intake would accompany with fried fish consumption compared with nonfried fish and daily habit of fried fish intake may be associated with some unhealthy dietary patterns.¹⁰ Thus it is conceived that an increased risk of stroke was associated with fried fish intake.

Safety concerns for fish intake were adverse effects of heavy metals and other chemical pollutants, like methylmercury, polycyclic aromatic hydrocarbons, organochlorine pesticides, and polychlorinated biphenyl.^{54,55} These chemicals can impair neurological development and teratogenesis and influence endocrine and immune system function. However, these contaminants usually presented at a high level in some older, larger, carnivorous fish and marine mammals, and people can reduce exposure to contaminants through some specially prepared method.⁵⁶ Additionally, according to a recent comprehensive review, the benefit from fish intake with guidelines proposed the FDA and Environmental Protection Agency far overshadow the risks.⁵⁶

Our study has an important implication. Stroke remains a major public health problem, which is the leading cause of permanent disability and death. It is estimated that approximately 2.4 million strokes occur and 1.1 million stroke-related deaths in China in each year.⁵⁷ Globally, in 2015 there were 6.326 million stroke deaths.⁵⁸ The vast burden due to stroke indicates effective prevention strategies are highly warranted. In our study, we found an inverse and linear association between fish intake and stroke risk. The quality of metaevidence is moderate. Therefore, based on current evidence with safety concerns listed above, daily fish consumption may represent an effective strategy for preventing stroke.

The relationship between fish intake and stroke has been reported controversial results. To clarify this issue, several meta-analyses have been published.³⁶⁻⁴¹ Previous meta-analyses indicated that fish consumption confers a lower risk of stroke, particularly ischemic stroke and women. Although our main finding generally concurs with those of previous studies, the discrepancies between current study and previous study are remarkable (Supplementary Table VI). First, the current study included almost twice as many participants than the latest meta-analysis published in 2017. Second, all included studies were prospective cohort design. Case-control studies were excluded but included in some previous studies.^{37-39,41} Third, we performed a dose-response analysis with new model described by Xu and Doi.⁵¹ Using this model, distribution of cases and person-years (noncases) for each level of exposure is unnecessary. Therefore, more studies could be included in dose-response analysis and a more accurate estimate could reach. Forth, subgroup results should be interpreted cautiously because

of the limited number of included studies in previous studies, especially in dose-response analysis. Finally, power analysis and assessment of quality of metaevidence was done. However, some limitations are worthy of consideration. One potential limitation is the effect of residual confounders. Biases produced by confounding factors either exaggerate or obscure the strength of the real association, regardless of the fact great efforts to adjust for possible confounding factors were made in original studies. A second limitation is misclassification of fish intake, as information on fish habits was derived from a food frequency questionnaire at baseline.

Conclusions

In summary, our meta-analysis provides further evidence that fish consumption is associated with a decreased risk of stroke. Further studies are necessary to clarify the disparities of gender-effect, geographic region, and type of stroke on the association between fish intake and stroke.

Conflicts of Interest

The authors declare no conflict of interest.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jstrokecerebrovasdis.2018.10.036](https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.036).

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