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Original Article

Association between fiber intake and ischemic stroke risk: a meta-analysis of prospective studies

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Abstract: Objective: Epidemiological studies have suggested that dietary fiber intake is associated with the ischemic stroke risk; however, the outcomes are inconsistent. We therefore performed a meta-analysis of published studies to evaluate the association between dietary fiber intake and the ischemic stroke risk. Method: We searched Pubmed and EMBASE for prospective cohort studies providing quantitative estimates between dietary fiber intake and the ischemic stroke risk, until July 1, 2016. Summary relative risks (RRs) with 95% confidence intervals (CIs) were pooled by using a random-effects model. Categorical analysis, dose-response analysis, subgroup analysis, and heterogeneity and publication bias analyses were performed. Results: There were 338218 participants from eight prospective cohort studies, with 8852 cases of ischemic stroke. For the highest vs. lowest category, the RRs of ischemic stroke was 0.85 (95% CI: 0.79-0.91; I^2=4.5%, *p* for heterogeneity =0.40) for total dietary fiber intake, 0.94 (95% CI: 0.86-1.00; I^2=28.8%) for cereal fiber intake, 0.92 (95% CI: 0.86-0.99; I^2=47.3%) for vegetable fiber intake, 0.92 (95% CI: 0.86-0.99; I^2=0%) for fruit fiber intake, 0.87 (95% CI: 0.76-0.98; I^2=0%) for water-soluble fiber intake, and 0.91 (95% CI: 0.82-1.01; I^2=65.4%) for water-insoluble fiber intake. A nonlinear relationship was found of total dietary fiber intake with risk of ischemic stroke (*p* for nonlinearity =0.006). Conclusion: High dietary fiber intake was associated with a reduced risk of ischemic stroke, especially for cereal fiber, vegetable fiber, fruit fiber, and water-soluble fiber intakes.

Keywords: Fiber, ischemic stroke, meta-analysis, prospective cohort study

Introduction

Ischemic stroke, which is the most common type of stroke and accounts for about 70%-90% of all stroke cases, is increasing worldwide and becoming one of the most common non-communicable diseases. Ischemic stroke is known as a leading cause of serious somatic and cognitive lifetime disability in adults, which leads to a substantial morbidity as well as mortality, and is associated with enormous government expenditure [1-3]. It was estimated that the number of people with ischemic stroke was approximately 636,000 annually in the United States and there was 5.1 million Americans who were ischemic stroke survivors [2].

It is extensively recognized for the importance of modifiable risk factors in ischemic stroke etiology. Weight reduction, increased physical activity, and alcohol control are important for the prevention of ischemic stroke [4-6]. Moreover, dietary risk factors are believed to play an important role in the prevention and development of ischemic stroke, among which dietary fiber has received considerable interest. Epidemiological studies have suggested that dietary fiber intake is associated with the ischemic stroke risk; however, the outcomes are inconsistent [7-14].

Thus, we performed a meta-analysis of prospective cohort studies with the following objectives: (1) to summarize the epidemiologic evidence on the relationship between dietary fiber intake and the ischemic stroke risk; (2) to evaluate the dietary fiber intake in relation to the risk of ischemic stroke according to sources and types of fiber and characteristics of study populations; and (3) to assess the dose-response relationship between dietary fiber intake and the ischemic stroke risk.

Subjects and methods

We reviewed the literatures and performed this meta-analysis according to the guidelines of Meta-analysis of Observational Studies and

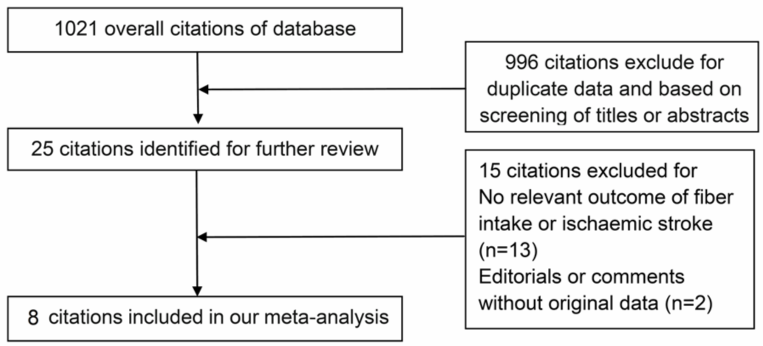

Figure 1. Flow diagram of included studies.

the statement of Preferred Reporting Items for Systemic Meta-analysis [15-17].

Literature search strategy

A systematic database search of Pubmed (from 1966 to July 1, 2016), and EMBASE (from 1980 to July 1, 2016) were performed by using both MeSH words and free text words. The search words were combined with outcomes (ischemic stroke and cerebral infarction) and the risk factor (dietary fiber, fiber, and fibre). In addition, we searched the reference lists of relevant articles and reviews, comments, meeting abstracts, and clinical guidelines. No language restrictions were restricted.

Selection criteria

Two independent reviewers selected the relevant studies using the inclusion criteria. A third reviewer checked repeatability and discussed the disagreements. The inclusion criteria were as follows: 1) prospective cohort study; 2) adult population; 3) the risk factor was dietary fiber intake; 4) the outcome was ischemic stroke; 5) risk estimates (relative risk [RR] or hazard ratios [HR]) with the 95% confidence interval (CI) for dietary fiber intake as a continuous variable or each category of baseline dietary fiber intake were reported; and 6) follow-up of at least 2 years (mean or median). The studies which did not meet the inclusion criteria will be excluded. If more than one prospective cohort study including the same population, we included the prospective cohort study with the longest follow-up duration.

Data extraction

Two independent reviewers extracted data by using a standard data collection form. A third reviewer checked repeatability and discussed the disagreements. We extracted the following data: the last name of first author's, publication year, country of execution of cohort study, sex of participants, age range of participants, recruitment time, years of follow-up, number of ischemic stroke cases, cohort size, method of stroke ascertainment, method and type of dietary fiber ascertainment, adjustments, and risk estimates with corresponding CIs. The RRs and 95% CIs were extracted of greatest adjustments for potential confounders. The quality of included cohort studies were assessed by the nine-star Newcastle-Ottawa Scale.

Statistical analyses

For the categorical meta-analysis (highest vs. lowest of dietary fiber intake), we pooled RRs and 95% CIs to evaluate the associations between dietary fiber intake and the risk of ischemic stroke using both fix-effect and random-effect model. Possible heterogeneity among the included studies were accessed by Cochrane Q test and the Cochran I^2 statistics [18]. According to Higgins et al., I^2 values < 25% means low heterogeneity, I^2 values 25%-50% means moderate heterogeneity, and I^2 values > 75% means high heterogeneity [19].

For the dose-response meta-analysis of relationship between dietary fiber intake and the risk of ischemic stroke, the RR with 95% CI for an increase of 10 g/d dietary fiber intake was estimated. According to Greenland and Longnecker [20] and Orsini et al., [21] the reviewers calculated the trend from the correlated log RR estimated across categories of dietary fiber intake. For each included prospective cohort study, the median or mean dietary fiber intake for each category was assigned to each corresponding RR [22]. If the median or mean of dietary fiber intake was not provided, the midpoint data of each category was used [22]. If the highest category or the lowest category of dietary fiber intake was open-ended, we considered that the boundary had the same amplitude as the closest category [22]. The restricted cubic splines were used to access

Table 1. Characteristics of the included studies

Study (country)	Sex/Age, y	Recruitment Time (Years of follow-up)	No of cases (cohort size)	Stroke Ascertainment	Calcium intake Assessment	RR (95% CI) for Highest vs. Lowest Category	Adjustments
Mozaffarian et al., 2003 (United States)	Female/Male, > 65	1989-1990 (8.6)	250 (3588)	Medical and radiological records	Validated FFQ	0.76 (0.60, 0.95)	Age, sex, education, diabetes, smoking, PA.
Oh et al., 2005 (United States)	Female, 30-55	1980 (18)	515(78779)	Medical and radiological records	FFQ	Total fiber: 0.78 (0.56, 1.09) Cereal fiber: 0.80 (0.57, 1.12) Vegetable fiber: 1.01 (0.74, 1.38) Fruit fiber: 0.87 (0.63, 1.21)	Age, BMI, smoking, alcohol intake, parental history of myocardial infarction, history of hypertension, hypercholesterolemia, and diabetes, menopausal status and postmenopausal hormone use, aspirin use, multivitamin use, vitamin E supplement, physical activity, energy, and carbohydrate intake.
Weng et al., 2008 (China)	Female/Male, > 40	1990-1993 (10.6)	132 (1772)	Verified Self-reported, Medical and radiological records, death certificate	Validated FFQ	0.85 (0.54-1.33)	Age, sex, hypertension, antihypertensive drugs, diabetes, area, central obesity, alcohol intake, smoking, sex-smoking habit interaction, BMI, self-report heart disease, physical activity, hypercholesterolemia, hypertriglyceridemia, fibrinogen, apolipoprotein B, and plasminogen.
Larsson et al., 2009 (Finland)	Male, 50-69	1985-1988 (13.6)	2702 (26556)	Medical records	Validated FFQ	Total fiber: 1.01 (0.85, 1.19) Cereal fiber: 1.06 (0.91, 1.23) Vegetable fiber: 0.86 (0.76, 0.99) Fruit fiber: 0.91 (0.80, 1.04) Water-soluble fiber: 0.86 (0.73, 1.02) Water-insoluble fiber: 1.03 (0.87, 1.21)	Age, supplementation, smoking, BMI, blood pressures, serum total cholesterol, serum high-density lipoprotein cholesterol, histories of diabetes and coronary heart disease, physical activity, and intakes of alcohol, total energy, folate and magnesium.
Kokubo et al., 2011 (Japan)	Female/Male, 45-65	1995 and 1998 (10.4)	910 for male and 518 for female (86387)	Medical records	Validated FFQ	Total fiber: Male: 0.94 (0.66, 1.34) Total fiber: Female: 0.73 (0.55, 0.97) Water-soluble fiber: 0.73 (0.47, 1.14) Water-insoluble fiber: 0.62 (0.40, 0.98)	Age, sex, alcohol, BMI, hypertension, diabetes, hypercholesterolemic drug use, exercise, dietary intakes of fruits, vegetables, fish, sodium, isoflavone and energy, and public health center.
Wallström et al., 2012 (Sweden)	Female/Male, 44-73	1991-1996 (13.5)	401 for male and 518 for female (20674)	Swedish National Patient Register and the National Cause of Death Register, and the Stroke Register in Malmö	Validated FFQ	Total fiber: Male: 0.69 (0.49, 0.96) Female: 0.73 (0.52, 1.04)	Age, method version, total energy intake, season, BMI, smoking, education, alcohol, blood pressure, antihypertensive and antihyperlipidemic treatment, and PA.
Larsson et al., 2014 (Sweden)	Female/Male, 45-83	1998 (10.3)	2722 (96677)	Swedish Inpatient Register and the Swedish Cause of Death Register	Validated FFQ	Total fiber: 0.89 (0.79, 1.01) Cereal fiber: 0.96 (0.85, 1.09) Vegetable fiber: 0.87 (0.77, 0.98) Fruit fiber: 0.90 (0.80, 1.02)	Age, sex, education, family history of myocardial infarction, smoking, PA, BMI, history of hypertension, aspirin use, total energy intake, and alcohol consumption.
Threapleton et al., 2015 (United States)	Female, 35-69	1990 (14.4)	184 (27373)	Medical and mortality records	Validated FFQ	Total fiber: 0.88 (0.72, 1.07) Cereal fiber: 0.89 (0.80, 1.00) Vegetable fiber: 1.02 (0.92, 1.13) Fruit fiber: 0.97 (0.86, 1.09) Water-soluble fiber: 0.93 (0.77, 1.13) Water-insoluble fiber: 0.90 (0.78, 1.03)	Age, education, cigarette, cigar, and pipe smoking, non occupational PA, occupational PA, BMI, multivitamin use, alcohol, energy, energy-adjusted mono- and polyunsaturated fat, and vegetable and fruit intakes.

BMI: body mass index; BP: blood pressure; PA, physical activity; RR: relative risk.

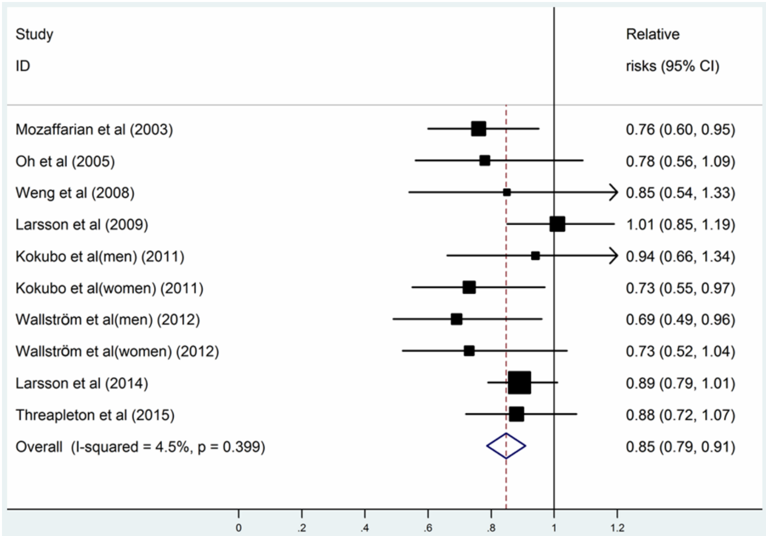

Figure 2. Dietary dietary fiber intake and the ischemic stroke risk (H vs. L).

the potential nonlinear dose-response associations between dietary fiber intake and the risk of ischemic stroke [23, 24].

We used subgroup analyses to identify the association between the risk of ischemic stroke and the characteristics of relevant cohorts as potential interference. Funnel plot asymmetry, Begg's tests, Egger's tests, and "trim and fill" procedure were used to access the publication bias of meta-analysis [25-27]. All statistical analyses were performed with STATA version 11.0 (Stata, College Station, Texas, USA). All statistical tests were considered $P < 0.05$ to be statistically significant.

Results

Figure 1 showed the process of literature search. There were 1021 studies selected from systematic database search of the Pubmed and Embase databases. After assessments of titles and abstracts, we excluded 996 articles. After evaluating titles and abstracts, we identified 25 articles that met the inclusion criteria. Several articles were excluded because lacking of substantive data. Eight prospective cohort studies met the inclusion criteria for the final meta-analysis [7-14].

Study characteristics

Table 1 lists the characteristics of the included studies. There were 338218 participants with 8852 cases of ischemic stroke in our meta-analysis. The included studies were from five different countries (three from the United States, two from Sweden, and one each from China, Finland, and Japan). Five studies included both men and women, whereas two studies included only women, and one study included only men. The age of the participants included was more than 30 years. The length of follow-up ranged from 8.6 to 18 years. All studies used food-frequency questionnaires (FFQ) for assessment of dietary fiber intake. The median intake of dietary fiber was 35.8 g/day for the highest categories and 5.8 g/day for the lowest categories. The most frequent adjustments for potential confounders included age, body mass index (BMI), smoking status, alcohol consumption, physical activity, total energy intake, diabetes, and hypertension.

Main analysis

Eight prospective cohort studies including 338218 participants and 8852 cases of ischemic stroke were included in this meta-analysis. The result showed a statistically significant inverse relationship between higher dietary fiber intake and the risk of ischemic stroke. And there was 15% lower risk among the participants with the highest intake of dietary fiber than among those with the lowest intake (RR, 0.85; 95% CI, 0.79-0.91) (**Figure 2**), with non-significant heterogeneity across studies (I^2= 4.5%, p for heterogeneity =0.40).

Five studies provided results for the type of dietary fiber. For the highest vs. lowest category, the RRs of ischemic stroke was 0.94 (95% CI: 0.86-1.00; I^2=28.8%) for cereal fiber intake, 0.92 (95% CI: 0.86-0.99; I^2=47.3%) for vegetable fiber intake, 0.92 (95% CI: 0.86-0.99; I^2= 0%) for fruit fiber intake, 0.87 (95% CI: 0.76-0.98; I^2=0%) for water-soluble fiber intake, and 0.91 (95% CI: 0.82-1.01; I^2=65.4%) for water-insoluble fiber intake (**Figure 3**).

Subgroup analyses

Subgroup analyses according to gender, geographical region, length of follow-up, and cohort

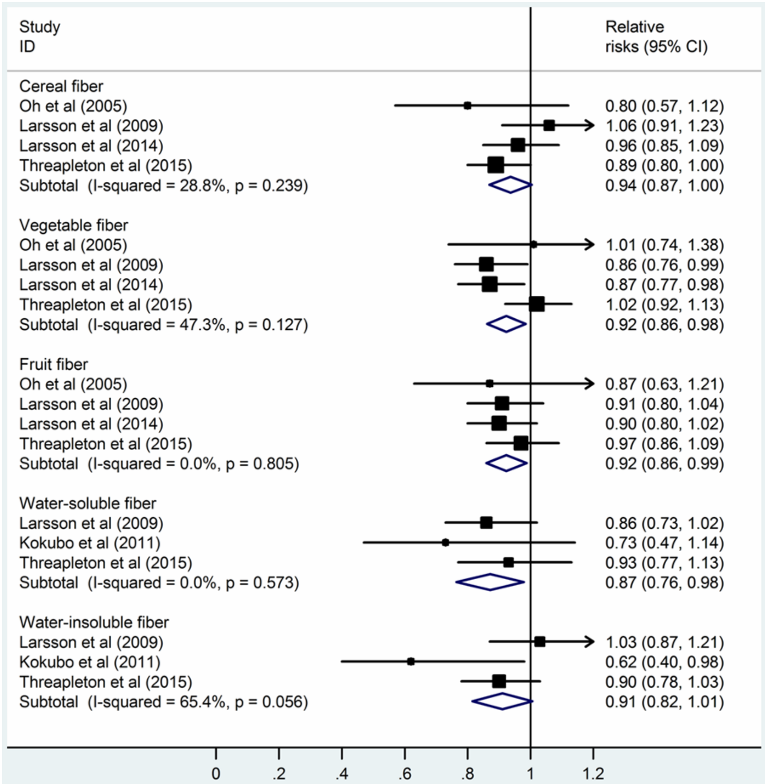

Figure 3. Subtype dietary fiber intake and the ischemic stroke risk (H vs. L).

size were performed (**Table 2**). The results showed that there was an statistically significant inverse association between dietary fiber intake and the risk of ischemic stroke in studies of both men and women (RR=0.85, 95% CI 0.76-0.94, I^2=0%, *p* for heterogeneity =0.47) and in studies of only women (RR=0.80, 95% CI 0.69-0.91, I^2=0%, *p* for heterogeneity =0.68), but not in studies of only men (RR=0.91, 95% CI 0.78-1.03, I^2=0%, *p* for heterogeneity =0.09). Moreover, subgroup analysis show that an inverse association between dietary fiber intake and the risk of ischemic stroke was observed in Asian populations (RR=0.80, 95% CI 0.64-0.96, I^2=0%, *p* for heterogeneity =0.57), in American populations (RR=0.81, 95% CI 0.70-0.93, I^2=0%, *p* for heterogeneity =0.61) and in European populations (RR=0.88, 95% CI 0.80-0.96, I^2=50.5%, *p* for heterogeneity =0.11). And stratifying by follow-up duration, the results showed that there was an statistically significant inverse association between dietary fiber intake and the risk of ischemic stroke in studies with more than 13 years of follow-up (RR=0.84, 95% CI 0.75-0.92, I^2= 31.4%, *p* for heterogeneity =0.20), and in studies with less than 13 years of follow-up (RR=0.86, 95% CI 0.77-0.91, I^2=0%, *p* for heterogeneity =0.58).

Publication bias

Visual examination of the funnel plot showed non-asymmetry (**Figure 4A**). Moreover, The Begg's and Egger's tests did not show any substantial asymmetry (*P*=0.66 for Begg's test and *P*=0.31 for Egger' tests). The "trim and fill" analysis showed no possible missing studies (**Figure 4B**).

Dose-response meta-analysis

Dose-response meta-analysis showed that there was not statistically significant relationship between dietary fiber intake and the risk of ischemic stroke (RR=0.90; 95% CI: 0.80 to 1.01) with moderate heterogeneity among studies (I^2=62.0%, *p* for heterogeneity =0.03) (**Figure 5A**). Further nonlinear dose-response analysis showed evidence of a nonlinear association between dietary fiber intake and the risk of ischemic stroke ($p_{nonlinearity}$ < 0.01) (**Figure 5B**).

Discussion

There were 338218 participants with 8852 cases of ischemic stroke included in our meta-analysis. In this meta-analysis, we found that dietary fiber intake is inversely associated with the ischemic stroke risk, especially for cereal fiber, vegetable fiber, fruit fiber, and water-soluble fiber intakes. A nonlinear relationship was found of total dietary fiber intake with risk of ischemic stroke.

Several plausible mechanisms have been proposed for this relationship. In experimental studies, higher fiber intake may affect serum lipid levels, postprandial absorption, blood pressure, and insulin sensitivity [9, 28, 29]. First, many studies suggested that four different types of dietary water-soluble fiber (β-glucan, psyllium, guar gum, and pectin) may affect lipid profile [30, 31]. Moreover, a dose-

Table 2. Subgroup analyses of Relative Risk of ischemic stroke

	No of studies	RR (95%CI)	I^2 (%)	Q Statistic	*P* Value for Heterogeneity	*P* Value Between Groups
Gender						
Male	3	0.91 (0.78, 1.03)	57.6	4.72	0.09	0.44
Female	4	0.80 (0.69, 0.91)	0	1.53	0.68	
Both	3	0.85 (0.76, 0.94)	0	1.52	0.47	
Geographical region						
United States	3	0.81 (0.70, 0.93)	0	0.97	0.61	0.54
European	2	0.88 (0.80, 0.96)	50.5	6.06	0.11	
Asian	3	0.80 (0.64, 0.96)	0	1.14	0.57	
Length of follow-up (years)						
≥ 13	5	0.84 (0.75, 0.92)	31.4	7.28	0.20	0.68
< 13	5	0.86 (0.77, 0.91)	0	1.97	0.58	
No. of cohort						
≥ 50,000	5	0.84 (0.76, 0.93)	29.6	7.10	0.21	0.86
< 50,000	3	0.85 (0.76, 0.94)	0	2.30	0.51	

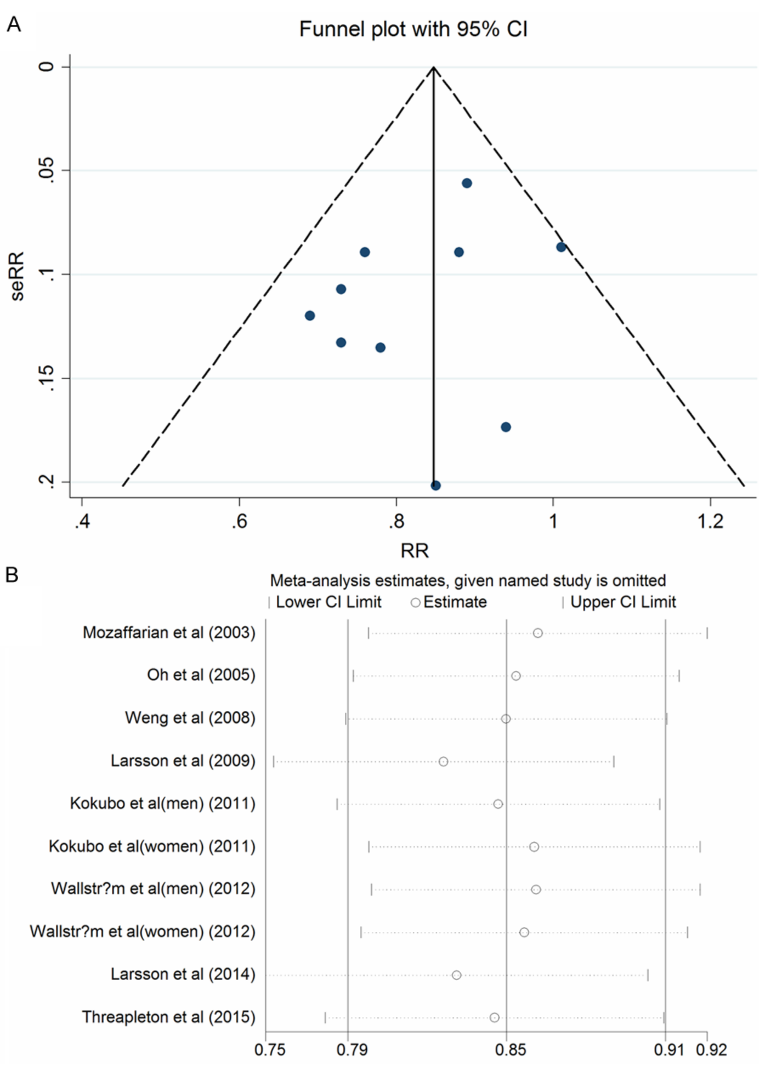

Figure 4. Funnel plot (A) and sensitivity analysis (B) for meta-analysis.

response meta-analysis showed that 2-10 g/day increase in water-soluble fiber may decrease total cholesterol (-0.045; 95% CI -0.054, -0.035 mmol/L) and LDL-cholesterol (-0.057; 95% CI -0.070, -0.044 mmol/L) [32]. Second, fiber-rich foods contented lower energy, which may affect body weight regulation [31]. Several observational studies showed that higher whole grains intake was associated with lower BMI and body weight [33]. Third, Several studies reported that higher fiber intake may improve postprandial glucose value and long-term glucose metabolism [34]. A meta-analysis of nine prospective cohort studies showed that higher cereal fiber intake could reduce diabetes risk (RR=0.67; 95% CI, 0.62-0.72) [35]. Fourth, many observational studies focused on the relationship between dietary fiber intake and blood pressure. A meta-analysis performed by Whelton et al. showed dietary fiber intake was associated with a signifi-

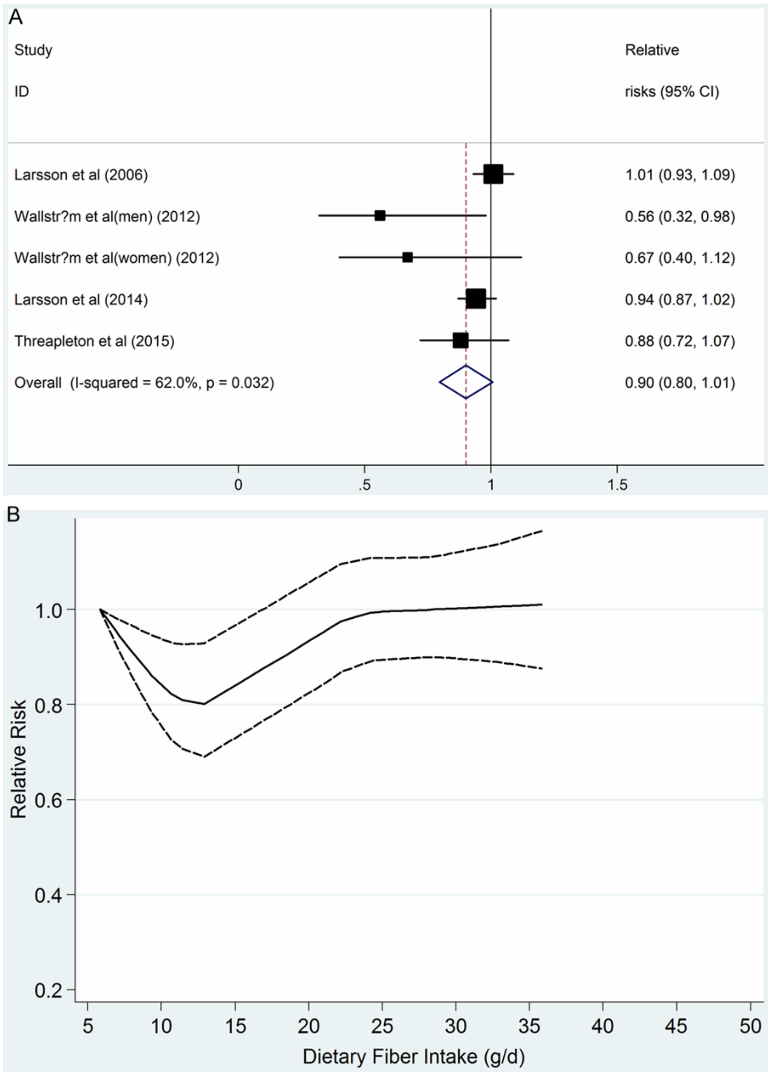

Figure 5. Linear (A) and nonlinear (B) dose-response relationship between dietary fiber intake and the ischemic stroke risk.

cant -1.65 mmHg (95% CI, -2.70, -0.61) reduction in diastolic blood pressure [36]. And a significant reduction in both diastolic blood pressure and systolic blood pressure was observed in included studies of patients with hypertension (systolic blood pressure -5.95 mmHg, diastolic blood pressure -4.20 mmHg) and in included studies with a duration of intervention ≥8 weeks (systolic blood pressure -3.12 mmHg, diastolic blood pressure -2.57 mmHg) [36]. Another meta-analysis showed fiber intake (average dose of 11.5 g/day) may reduce systolic blood pressure (1.13 mmHg) and diastolic blood pressure (1.26 mmHg) [37]. Fifth, many studies reported dietary fiber intake may impact markers of systemic inflammation, such as interleukin-6, tumor necrosis factor-a receptor-2, plasma fibrinogen, and hs-CRP [38-41].

In addition, several previous meta-analyses investigated the associations between dietary fiber intake and the risk of total stroke. Threapleton et al. [42]. performed a meta-analysis in 2013 including eight cohort (only fatal events reported in 2 studies, only one study reported just ischemic stroke risk, 5 publications reported stroke incidence data) and reported that total dietary fiber intake was inversely associated with risk of total stroke, with significant evidence of heterogeneity between studies (RR of per 7 g/day, 0.93; 95% CI, 0.88-0.98; I^2=59%). Another dose-response meta-analysis performed by Zhang et al. [43] in 2013 showed no evidence of a nonlinear relationship between total dietary fiber intake and risk of total stroke (*p* for nonlinearity =0.15). And the increment in dietary fiber intake was associated with decreased risk of total stroke in a dose-response meta-analysis (RR 0.90, 95% CI 0.82-0.99 for per 5 g/day, 0.84, 0.75-0.94 for per 10 g/day, and 0.77, 0.66-0.91 for per 15 g/day). However, the results of these two previous meta-analyses contradict our results. Our dose-response meta-analysis showed that there was not statistically significant relationship between dietary fiber intake and the risk of ischemic stroke (RR=0.90; 95% CI: 0.80-1.01). And further nonlinear dose-response analysis showed evidence of a nonlinear association between dietary fiber intake and the risk of ischemic stroke. The reasonable explanation of conflicting results may be due to the different pathogenesis of ischemic stroke and hemorrhagic stroke. The combination of ischemic stroke and hemorrhagic stroke may affect the reliability of their conclusion. Moreover, our meta-analysis only focuses on ischemic stroke, which conducted comprehensive literature search (to July 1, 2016) and included four more cohort studies than the meta-analysis performed by Threapleton et al. [42] and Zhang et al. [43], that thereby further strengthened our association.

Potential limitations of this meta-analysis should be considered. Because our meta-analysis was based on observational studies, the residual confounding factors should be concerned. It is hard to exclude the possibility that other risk factors could explain the observed relationship between dietary fiber intake and the ischemic stroke risk. However, most of the cohort studies were adjusted for a wide range of potential confounding factors, including age, BMI, smoking status, alcohol consumption, physical activity, total energy intake, diabetes, and hypertension. Only few studies adjusted for supplement intake or medication. Therefore it is difficult to exclude the opportunity that specific effects of nutrients or other beneficial food components present in the patient's diet were responsible for the observed association. We should be careful to explain the conclusions of the meta-analysis.

In summary, in our meta-analysis, we found a significant inverse relationship between dietary fiber intake and the ischemic stroke risk, especially for cereal fiber, vegetable fiber, fruit fiber, and water-soluble fiber intakes. A nonlinear relationship was found of total dietary fiber intake with risk of ischemic stroke. Further well-design cohort studies should be conducted to quantitatively assess the dose-response relationship between dietary fiber intake and the risk of ischemic stroke.

Disclosure of conflict of interest

None.

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