

## Original Article

# Association between whole grain intake and stroke risk: evidence from a meta-analysis

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**Abstract:** Background: Researches of the relationships between dietary whole grains intake and risk of stroke have produced inconsistent results. We therefore conducted a meta-analysis to summarize the evidence from observed studies regarding the association between whole grain intake and stroke risk. Methods: Pertinent studies were identified by searching Web of Knowledge and PubMed up to May 2015. Random-effect model was used to combine the relative risk (RR) with the corresponding 95% confidence intervals (CI). Publication bias was estimated using Egger's regression asymmetry test. Results: Six prospective studies involving 1635 stroke cases and 247487 participants were included in this meta-analysis. Pooled results suggested that highest category of whole grain intake versus lowest category was significantly associated with reduced the risk of stroke [summary RR = 0.86, 95% CI = 0.73-0.99, I<sup>2</sup> = 0.0%]. Inverse associations were also found in the America population [summary RR = 0.81, 95% CI = 0.67-0.98, I<sup>2</sup> = 0.0%] and subgroup analysis of females [summary RR = 0.78, 95% CI = 0.63-0.97, I<sup>2</sup> = 0.0%]. No publication bias was found. Conclusion: Our analysis indicated that higher whole grain intake has a protective effect on stroke.

**Keywords:** Whole grain, stroke, meta-analysis

## Introduction

Stroke is a leading cause of mortality and morbidity in the world [1]. The rates of age-adjusted stroke mortality and disability-adjusted life years lost were higher in low-income countries than in middle-income or high-income countries [2]. Improving diet and lifestyle is critical for stroke risk reduction in the general population [3, 4]. In particular, a diet rich in whole grain food is highly recommended, because they are rich sources of fiber, K and antioxidant compounds, which through different mechanisms may have protective effects against stroke [5]. Up to date, a number of epidemiologic studies have been published to explore the relationship between whole grain intake and stroke risk. Only one study reported that higher whole grain intake could reduce the risk of stroke [6], while no significant associations were reported in 3 studies [7-9]. Furthermore, two studies found an increased but not significant association between whole grain intake and the risk of stroke [10, 11]. Considering the results are not consistent, we conducted a

comprehensive meta-analysis to evaluate the evidence from observational studies on whole intake with the risk of stroke.

## Methods

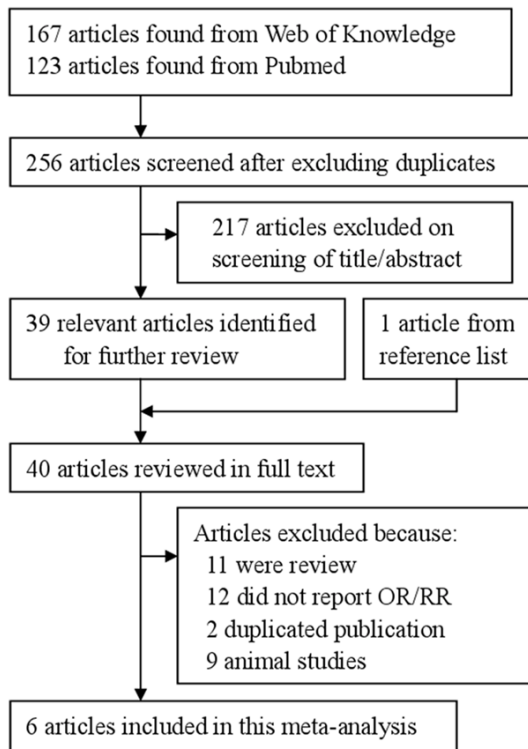
### Literature search strategies

Studies were identified by a literature search of PubMed and Web of Knowledge through May 2015. The following search strategy was used: 'whole grain' or 'diet' or 'lifestyle' in combined with 'stroke'. Furthermore, we reviewed citations from the retrieved articles and relevant reviews to identify additional studies. Two researchers searched the related articles and reviewed of all retrieved studies independently. Disagreements between the two researchers were resolved by consensus with a third reviewer.

### Eligibility criteria

Our meta-analysis included prospective studies or case-control studies that reported the association between whole grain intake and the risk

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**Figure 1.** The detailed steps of our literature search.

of stroke. All studies should be written in English. The outcome measure was stroke. The exposure of interest was the intake of whole grain. All included studies provided the relative risk (RR) or hazard ratio (HR) or odds ratio (OR) and the corresponding 95% confidence intervals (CI), or provided enough data to calculate them. If several papers from the same study had been published, we only included the most complete or most recent paper.

### Data extraction

The following information was extracted from each study: the first author's last name, year of publication, study design, sex, geographic locations, number of cases and participants. The RR estimates and 95% CI for whole grain intake and stroke risk were also extracted, and confounding factors adjusted for in the analysis. For studies that reported results from various covariate analyses, we abstracted the estimates based on the model that included the most potential confounders. Otherwise, we abstracted the crude RR estimates. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

### Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the association between whole grain intake and the risk of stroke. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [12]. The  $I^2$  was used to assess the between-study heterogeneity, and  $I^2$  values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [13], respectively. Subgroup analysis was performed to assess the association between whole grain intake and stroke risk in some subgroup analyses. Publication bias was estimated using Egger's regression asymmetry test [14]. Sensitivity analysis [15] was conducted to describe how robust the pooled estimator is to removal of individual studies. All the statistical analyses were performed with STATA version 10.0. Two-tailed  $P < 0.05$  was accepted as statistically significant.

## Results

### Search results and study characteristics

We searched 123 articles from Pub Med and 167 articles from the Web of Knowledge, and 40 articles were reviewed in full after reviewing the title or abstract. At the end, 6 articles [6-11] involving 1635 stroke cases were used in this meta-analysis. All the included studies were prospective design. The detailed steps of our literature search are shown in **Figure 1**. The characteristics of these included studies are presented in **Table 1**. There are 5 studies come from United States and 1 from Finland.

### Highest whole grain intake vs. lowest intake analysis

For whole grain intake and stroke risk, data from 6 prospective studies were used including 1635 stroke cases. Only one of the included studies reported an inverse association of whole intake with the risk of stroke, while no significant association was reported in 5 studies. Our pooled results suggested that highest category of whole grain intake versus lowest category was significantly associated with reduced the risk of stroke [summary RR = 0.86, 95% CI = 0.73-0.99,  $I^2 = 0.0\%$ ] (**Figure 2**).

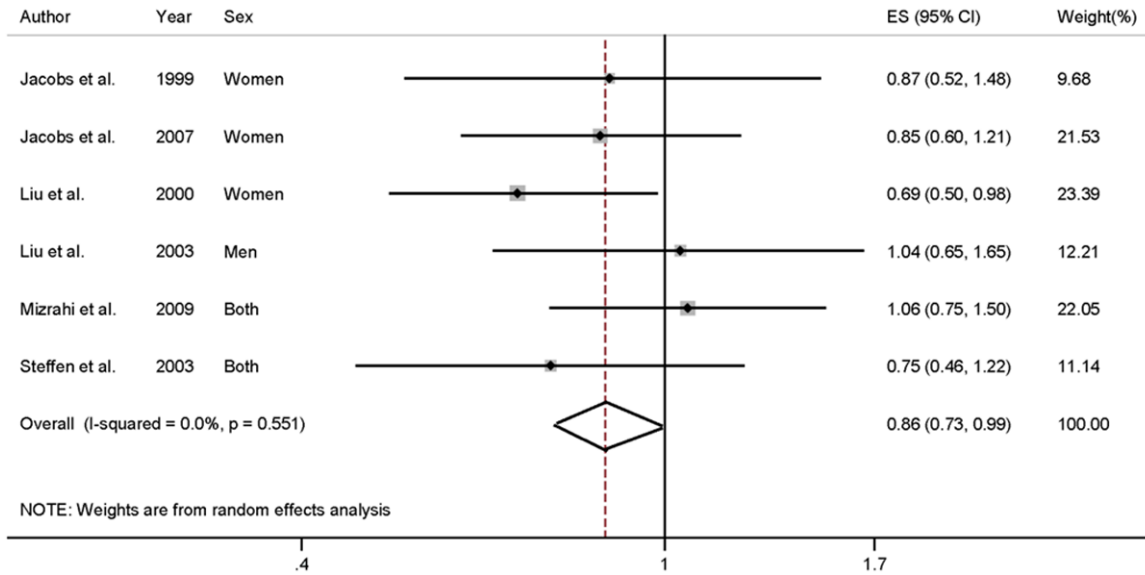
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**Table 1.** Characteristics of included studies on whole grain and stroke risk

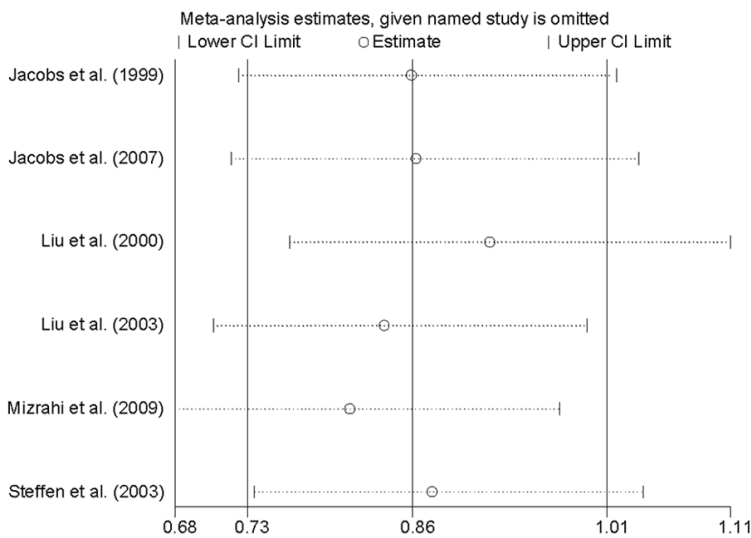
Study, year	Ref.	Study name	Country	Participants (cases)	Follow-up (years)	Age (years)	RR (95% CI) for highest versus lowest category	Adjustment for covariates
Jacobs et al. 1999	[7]	The Iowa Women's Health Study	United States	38740 (1779)	9	55-69	0.87 (0.52-1.48)	Adjusted for age, total energy intake, educational attainment, marital status, high blood pressure, diabetes, heart disease, cancer, BMI, waist-to-hip ratio, physical activity, smoking, alcohol intake, vitamin supplements, estrogen replacement therapy use, total fat, saturated fat, intake of fruits and vegetables, intake of red meat, and intake of fish and seafood.
Jacobs et al. 2007	[8]	The Iowa Women's Health Study	United States	27312 (2934)	17	55-69	0.85 (0.60-1.21)	Adjusted for age, energy intake, BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, refined grain, coffee, red meat, fish and seafood, and total fruit and vegetables.
Liu et al. 2000	[6]	The Nurses' Health Study	United States	75521 (761)	12	38-63	0.69 (0.50-0.98)	Adjusted for age, BMI, cigarette smoking, alcohol intake, parental or family history of myocardial infarction before the age of 60 y, self-reported history of hypertension or hypercholesterolemia, menopausal status, protein intake, aspirin use, use of multiple vitamin or vitamin E supplements, vigorous activity.
Liu et al. 2003	[10]	The Physicians' Health Study	United States	86190 (1869)	5.5	40-84	1.04 (0.65-1.65)	Adjusted for age, cigarette smoking, alcohol intake, physical activity, BMI, history of type 2 diabetes, high cholesterol, and hypertension, and use of multivitamins.
Mizrahi et al. 2009	[11]	The Finnish Mobile Clinic Health Examination Survey	Finland	3932 (344)	24	40-74	1.06 (0.75-1.50)	Adjusted for age, sex, BMI, smoking, physical activity, serum cholesterol level, blood pressure and energy.
Steffen et al. 2003	[9]	The Atherosclerosis Risk in Communities (ARIC) Study	United States	15792 (535)	11	45-64	0.75 (0.46-1.22)	Adjusted for age at baseline, BMI, race, sex, time-dependent energy intake, education, smoking status, pack-years of smoking, physical activity, alcohol intake, and hormone replacement in women.

Abbreviations: Ref. = reference; BMI = body mass index; CI = confidence interval; RR = relative risk.

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**Figure 2.** The forest plot between highest versus lowest categories of whole grain intake and stroke risk.



**Figure 3.** Analysis of influence of individual study on the association between whole grain intake and stroke risk. Open circle, the pooled RR, given named study is omitted. Horizontal lines represent the 95% CIs.

For the stratified analysis by geographic locations, we only combined the results for American, while 1 study was come from Finland. The association was significant in the America population [summary RR = 0.81, 95% CI = 0.67-0.98,  $I^2 = 0.0\%$ ]. In subgroup analyses for follow-up duration (< 10 years or  $\geq 10$  years), inverse association of whole grain intake with the risk of stroke was only found in the duration of  $\geq 10$  years [summary RR = 0.84, 95% CI = 0.69-

0.99,  $I^2 = 7.7\%$ ], but not in the duration of < 10 years [summary RR = 0.96, 95% CI = 0.68-1.36,  $I^2 = 0.0\%$ ]. When we conducted the subgroup analysis by sex, significant association was only significant in the females [summary RR = 0.78, 95% CI = 0.63-0.97,  $I^2 = 0.0\%$ ], but not in the males.

### Sensitivity analysis and publication bias

Sensitivity analysis showed that no individual study had excessive influence on the association of whole grain intake and stroke risk (**Figure 3**). Egger's test ( $P = 0.836$ ) showed no evidence of significant publication bias between

whole grain intake and the risk of stroke was found.

### Discussion

Findings from this meta-analysis indicated that highest category of whole grain intake versus lowest category was significantly associated with the reduced risk of stroke. Inverse association was also found in American, but not in the

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other populations. The associations were also significant in the group of follow-up duration  $\geq 10$  years and females.

Previous study had reported that whole grain intake has a protective effect against coronary heart disease [16]. A meta-analysis suggested that an increment of three servings daily of whole grains could reduce the risk of colorectal cancer [17]. Furthermore, whole grain intake had an inverse association with type 2 diabetes risk [18]. Several potential mechanisms for the observed association have been proposed. Whole-grain foods contain fiber, vitamins, minerals, and other phytochemicals that are removed during the refining process [19-22]. Many of these compounds can support the antioxidant defense and thereby reduce the damaging effects of chronic inflammation via several mechanisms [23, 24]. It has been suggested that these molecules also can mount an antioxidant defense in animal cells (after intake by the animal) by inducing gene expression of similar genes for antioxidant and detoxification enzymes [25]. Thus, we think it is plausible that whole grain intake may reduce the risk of stroke.

A major strength of this study was the large number of cases and participants included from prospective studies, allowing a much greater possibility of reaching reasonable conclusions and conducting subgroup analysis. And prospective studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case-control studies. Second, no evidence of between-study heterogeneity and no publication bias were found, indicating that our results are stable. However, some limitations in this meta-analysis should be concerned. First, although we extracted the RR that reflected the greatest degree of control for potential confounders, the extent to which they were adjusted and the possibility that the observed association was due to unmeasured or residual confounding should be considered. Second, for the subgroups of geographic locations, five of the six included studies come from American. And the association was significant in the America population for whole grain intake and the risk of stroke. There is only one study come from Finland. So, we did not combine the results for other countries. Due to this limitation, the results are applicable to the America population, but can-

not be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between whole grain intake and stroke risk. Finally, for the subgroup analysis of follow-up duration, we found a significant association in the follow-up duration  $\geq 10$  years, but not in the  $< 10$  years. Therefore, further studies should be  $\geq 10$  years to assess the association between whole grain intake and the risk of stroke.

In summary, results from this meta-analysis suggested that higher intake of whole might have a protective effect on stroke.

### Disclosure of conflict of interest

None.

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