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Meta-Analysis of the Association Between Whole and Refined Grain Consumption and Stroke Risk Based on Prospective Cohort Studies

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Abstract

The association between whole and refined grain consumption and stroke risk remains unclear. A search using MEDLINE and EMBASE databases was performed through February 29, 2016. Seven prospective studies with a total of 446 451 subjects and 5892 stroke events were included. The summary relative risk (SRR) of stroke for the high versus low consumption was 0.95 (95% confidence interval [CI] = 0.83-1.14) for total grains, 0.92 (95% CI = 0.72-1.17) for whole grains, and 0.99 (95% CI = 0.84-1.16) for refined grains. Diets rich in whole grains were inversely associated with ischemic stroke risk (SRR = 0.75, 95% CI = 0.60-0.95). Our meta-analysis revealed that whole and refined grain consumption is not associated with total stroke risk; however, whole grain consumption is associated with reduced ischemic stroke risk.

Keywords

whole grains, stroke, meta-analysis, refined grains, relative risk

Introduction

Stroke is the second leading cause of mortality in both developed and developing countries; its prevalence and disability burden are expected to increase in future decades.[1] Lifestyle and dietary factors play important roles in stroke prevention.[2,3] Specifically, whole grains have received considerable attention due to their effects on vascular health.[4,5] Whole grains, which include whole wheat, dark breads, oats, brown rice, rye, barley, and bulgur, consist of 3 botanically defined parts: the bran, germ, and endosperm. During refining, the outer bran and germ portions are removed. These portions of whole grains represent important sources of dietary fiber, vitamins, minerals, and phytochemicals. It is has been postulated that the consumption of whole grains

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reduces the risk of hypertension,[4,5] weight gain and obesity,[6-9] and type 2 diabetes,[10-12] which are risk factors of stroke.

Epidemiological studies focusing on the association between whole grain consumption and stroke risk have produced mixed results.[13-19] A recent meta-analysis[20] of 6 prospective cohort studies revealed that high whole grain consumption was significantly associated with reduced stroke risk (summary relative risk [SRR] = 0.86, 95% confidence interval [CI] = 0.73-0.99]. However, this meta-analysis did not examine risk association based on stroke subtype or stroke outcome (incidence or mortality). In the current meta-analysis, we quantitatively assessed such association using dose-response and high versus low grain consumption analyses.

Methods

Literature Search

We followed standard criteria for analyzing observational studies.[20] Two authors (JGC and QFH) performed a systematic literature search through February 29, 2016, using MEDLINE and EMBASE databases. Key words included (1) stroke, subarachnoid hemorrhage, brain ischemia, intracranial hemorrhages, or cerebral hemorrhage and (2) whole grain, cereals, grains, wheat, rice, oats, rye, barley, triticale, millet, or bread. To identify additional relevant studies, we reviewed the reference lists of retrieved articles. We included studies published in English. Any disagreements were resolved by a third reviewer (QL).

Study Selection

The inclusion criteria consisted of prospective cohort studies (1) examining the association between whole and refined grains (or total grains) and stroke and its subtypes and (2) reporting relative risk (RR), odds ratio, or hazard ratio and the corresponding 95% CIs. We included one study[14] that incorporated breakfast cereals, because breakfast cereals represent a major source of both whole and refined grains. Multiple reports from the same cohort study were reviewed, and studies with the longest follow-up periods were included. Additionally, we excluded studies that examined the effects of individual grains, such as white rice, brown rice, and oats. Animal, in vitro, case-control, and ecological studies; case reports; and literature reviews were excluded. To determine whether an article met the inclusion criteria, 2 authors (JGC and QFH) independently reviewed all relevant articles. Any disagreements were resolved by a third reviewer (QL).

Data Extraction

Two authors (JGC and QFH) extracted the following information from each study: author's name, study location, publication year, number of participants, age of participants, length of follow-up, exposure type and quantity, number of cases, definition of outcome, adjustments used within analyses, and RR estimates with corresponding 95% CIs. Separate risk estimates for men and women and for stroke subtypes provided by one study were treated as separate studies.

Assessment of Study Quality

Two authors (JGC and QFH) independently evaluated the quality of the observational studies using the Newcastle-Ottawa Quality Assessment Scale (NOS).[21] NOS consists of 3 quality parameters: selection (maximum 4 stars), comparability (maximum 2 stars), and outcome (maximum 3 stars). A maximum of 9 stars reflects the highest quality. A total score of 7 or more was used to indicate high-quality studies.

Statistical Methods

To calculate SRR and 95% CI for high versus low grain consumption analysis and dose-response analysis, we used the random-effects model, accounting for heterogeneity across studies.[22] Statistical heterogeneity among studies was assessed using the Q statistic. Additionally, we evaluated the proportion of the total variation in study estimates that was due to heterogeneity (I^2).[23] Results for the Q statistic were defined as heterogeneous when $P < .10$. I^2 values of approximately 25%, 50%, or 75% were considered to represent low, moderate, and high heterogeneity, respectively. Pooled estimates were only presented if I^2 did not exceed our prespecified cutoff point of 75%.

We performed subgroup analyses based on sex, geographic area, stroke outcome, and stroke subtypes. We attempted to carry out subgroup analyses based on length of follow-up and adjustments for confounding factors; however, the number of studies was too low to perform these analyses. Sensitivity analyses were performed by excluding one study and calculating the pooled estimate for the remainder of the studies to evaluate whether the results were significantly affected by a single study.

Dose-response analyses were conducted according to the method reported in earlier studies,[24,25] which requires information on the distribution of cases and person years or noncases and the relative risks with their variance estimates for at least 3 quantitative categories of use. The median or mean of each consumption level was assigned to the corresponding relative risk for each study. If such values were not reported, we used the estimated midpoint between the upper and lower boundaries in each category as the average intake level. When the lowest category was open-ended, it was considered to be zero. When the highest category was open-ended, we assumed the size of the open-ended interval to be the same as that of the adjacent interval. When studies reported grain consumption in grams per day, we used 30 g as a serving size for both whole and refined grains.[26] Dose-response results in the forest plots were presented for a 3-serving-per-day increment in grain consumption.

Publication bias was assessed with funnel plots and Egger' regression asymmetry tests; potential publication bias was considered at $P < .10$.[27] We used STATA, version 11.0 (College Station, TX) for all data analyses. P values were 2-sided. Statistical significance was set a $P < .05$ unless otherwise specified.

Results

Search Results and Study Characteristics

The search strategy identified 1054 potentially relevant publications, of which 1014 articles were excluded based on the title and abstract (see Supplementary Figure 1, available online at http://aph.sagepub.com/supplemental). Forty full-text articles were assessed. No studies were obtained from the reference list search. Twenty-four studies were excluded either because the outcomes did not include stroke events or because the exposure of interest was not whole and refined grains. Two studies reported the same population, 3 studies did not report RRs and/or 95% CIs, 2 studies were had a case-control design,[28,29] and 1 study reported continuous levels of consumption.[30] Therefore, a total of 7 prospective cohort studies were included in our meta-analysis.

As shown in Table 1, the 7 studies were published between 2000 and 2013, and involved a total of 446 451 subjects (3932 to 215 000) and 5892 stroke cases (146 to 3281). Of the 7 studies, 5 were conducted in the United States and 2 were conducted in Finland.[17,18] The length of follow-up ranged from 5.5 to 24 years, with a median of 11.4 years. All studies used validated semiquantitative food frequency questionnaires to collect dietary information from the participating subjects. According to NOS, all studies were of high quality (NOS ≥ 7).

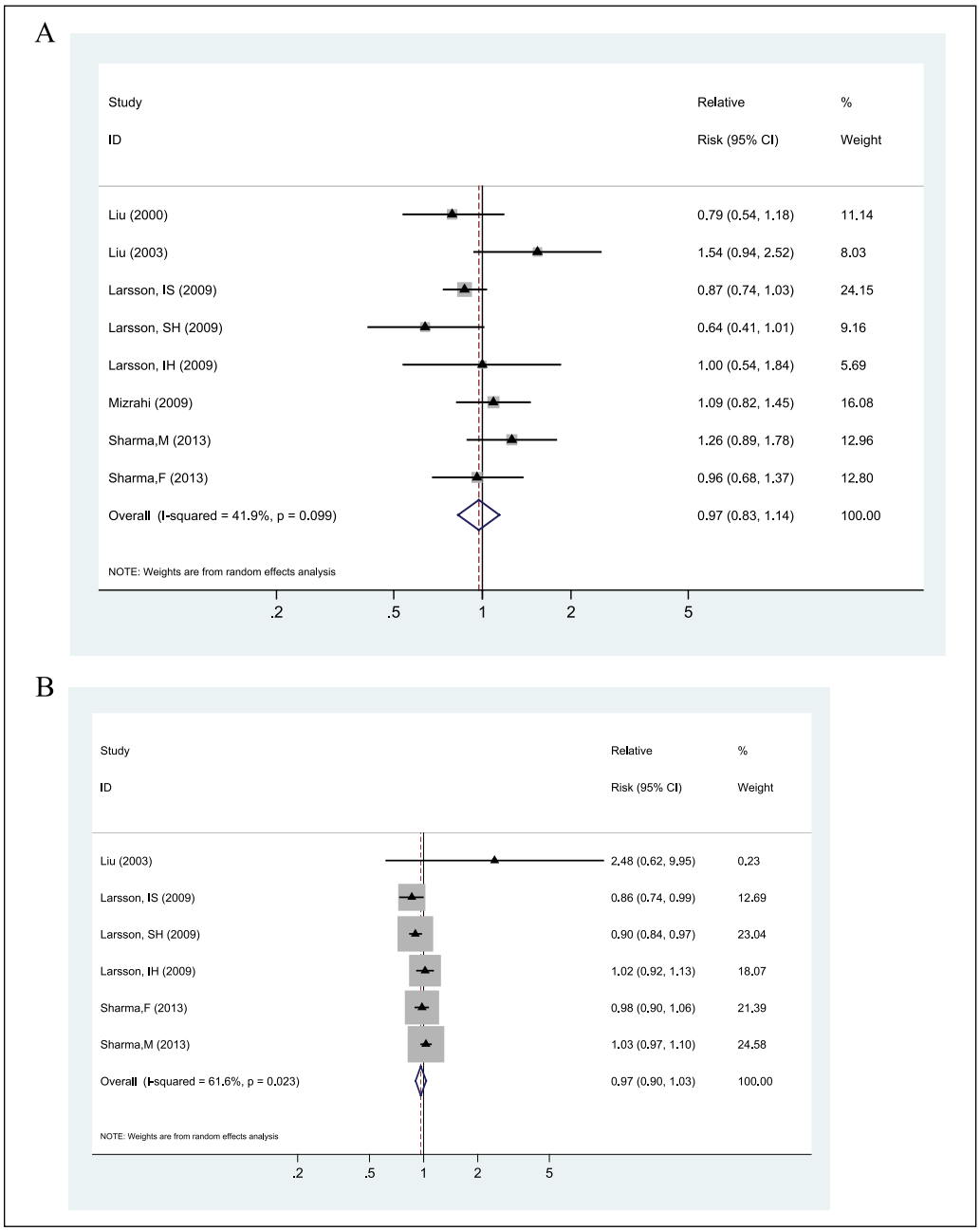

Figure 1. The summary risk association between intake of total grains and stroke risk for (A) high versus low analysis; (B) linear dose-response analysis per 3 servings/day.

Total Grains

High Versus Low Grain Consumption Analysis. Five studies[13,14,17-19] presented results for the association between total grain consumption and stroke risk, with an SRR of 0.97 (95% CI = 0.83-1.14; $P_{\text{heterogeneity}} = .099$, $I^2 = 41.9\%$; Figure 1A) for the high versus low grain consumption analysis.

Table 1. Characteristics of 7 Prospective Cohort Studies Evaluating the Association Between Whole and Refined Grain Consumption and Stroke Risk.

Author/ Publication Year/ Country	Study Characteristics	Dietary Assessment	Outcome Ascertainment and Cases, n	Contrast	RR (95% CI), Highest Versus Lowest	Adjustments
Liu/2000/USA	NHS: n = 75 521; females; 38-63 years of age; length of follow-up: 11.4 years	Validated FFQ-126; self-administered	Medical records; 352 IS	Total grains: Q5 versus Q1	0.79 (0.54-1.18)	Age; cigarette smoking; alcohol consumption; physical activity; BMI; history of type 2 diabetes, high cholesterol, and hypertension; use of multivitamins
				Whole grains:2.7 versus 0.13 servings/day	0.69 (0.50-0.98)	
				Refined grains: Q5 versus Q1	0.97 (0.67-1.42)	
Liu/2003/USA	PHS: n = 86 190; males; length of follow-up: 5.5 years	Validated FFQ-126; self-administered	Death registry; 146 fatal stroke	Total breakfast cereals ≥1 serving/day versus rarely	1.54 (0.94-2.52)	Age; cigarette smoking; alcohol consumption; physical activity; BMI; history of type 2 diabetes, high cholesterol, and hypertension; use of multivitamins
				Whole-grain breakfast cereals ≥1 serving/day versus rarely	1.41 (0.85-2.34)	
				Refined-grain breakfast cereals ≥1 serving/day versus rarely	1.22 (0.71-2.11)	
Steffen/2003/ USA	ARIC: n = 11 940; males and females; 45-64 years of age; length of follow-up: 11 years	Validated FFQ-61; interviewer	Medical record; 214 incident IS	Whole grains: 3.0 versus 0.1 serving/day	0.75 (0.46-1.22)	Age, race, sex, dietary energy intake education, smoking status, physical activity, alcohol consumption, hormone replacement, BMI, waist-to-hip ratio, systolic blood pressure, use of antihypertensive medications
				Refined grains: 5.0 versus 0.5 serving/day	0.82 (0.48-1.40)	
Jacobs/2007/ USA	IWHS: n = 27 312; females; 55-69 years of age; length of follow-up: 17 years	Validated FFQ-127	Medical records; 414 fatal stroke	Whole grains: >19 versus <3.5 servings/week	0.85 (0.60-1.21) total; 1.28 (0.64-2.56) HS; 0.88 (0.57-1.36) IS	Age, energy intake, BMI, waist-to-hip ratio, smoking, education, physical activity, estrogen use, use of multivitamins, alcohol consumption, refined grain, coffee, red meat, fish and seafood, total fruits and vegetables

(continued)

Table 1. (continued)

Author/ Publication Year/ Country	Study Characteristics	Dietary Assessment	Outcome Ascertainment and Cases, n	Contrast	RR (95% CI), Highest Versus Lowest	Adjustments
				Refined grains: 22.5 versus 5.75 servings/week	1.30 (0.88-1.91) total; 1.10 (0.54-2.23) HS; 1.19 (0.72-1.97) IS	
Larsson/2009/ Finland	ATBC: n = 26 556; males; 50-69 years of age; length of follow-up: 13.6 years	Validated FFQ-276; self-administered	Discharge registry and death registry; 2702 IS and 579 HS	Cereals; 327.4 versus 116.4 g/day	0.87 (0.74-1.03) IS; 0.64 (0.41-1.01) SH; 1.00 (0.54-1.84) IH	Age, number of cigarettes smoked, BMI, systolic and diastolic blood pressure, serum total cholesterol, serum high-density lipoprotein cholesterol, history of diabetes and coronary heart disease, physical activity, alcohol consumption, total dietary energy
Mizrahi/2009/ Finland	Finnish Mobile Clinic Health Examination Survey: n = 3932; males and females; 40-74 years of age; follow-up: 24 years	Interview; 1-year dietary history	625 stroke	Cereals: 391-1535 versus 10-223 g/day	1.09 (0·82-1.45)	Age, sex, BMI, smoking, physical activity, serum cholesterol level, blood pressure, and total dietary energy
				Whole grains: 280-1321 versus 0-139 g/day	1.12 (0·87-1.45)	
				Refined grains: 125-567 versus 0-50 g/day	0.88 (0·69-1.14)	
Sharma/2013/ USA	The US Multiethnic Cohort Study: n = 215 000; males and females; length of follow-up: 8 years	Validated FFQ; self-administered	Death certificates; 860 fatal stroke	Grains ≥9.8 versus 0-6.3 servings/day (males)	1.26 (0.89-1.78), males	Age, years of education, energy intake, smoking, BMI, physical activity, diabetes, alcohol consumption, history of hormone replacement therapy
				Grains ≥8.1 versus 0-5.1 servings/day (females)	0.96 (0.68-1.37), females	

Abbreviations: PHS, Physicians' Health Study; IWHS, Iowa Women's Health Study; ARIC, Atherosclerosis Risk in Communities Study; ATBC, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; NHS, Nurses' Health Study; NHS-II, Nurses' Health Study II; HPFS, Health Professionals Follow-Up Study; SH, subarachnoid hemorrhage; HS, hemorrhagic stroke; IS, ischemic stroke; IH, intracerebral hemorrhage; BMI, body mass index; FFQ, Food Frequency Questionnaire.

Dose-Response Analysis. Three studies[14,17,19] reported total grain consumption in servings per day or week. As shown in Figure 1B, SRR for 3 servings/day was 0.97 (95% CI = 0.90-1.03; I^2 = 61.6%, $P_{\text{heterogeneity}}$ = .023).

Whole Grains

High Versus Low Grain Consumption Analysis. Five studies[13-16,18] presented results for the association between whole grain consumption and stroke risk, with an SRR of 0.92 (95% CI = 0.72-1.17; $P_{\text{heterogeneity}}$ = .076, I^2 = 52.8%; Figure 2A) for the high versus low grain consumption analysis.

Dose-Response Analysis. Five publications[13-16,18] were included in the dose-response analysis. As shown in Figure 2B, SRR for 3 servings/day was 0.88 (95% CI = 0.64-1.22), with evidence of high heterogeneity (I^2 = 79.6%, $P_{\text{heterogeneity}}$ = .001). Furthermore, a linear dose-response revealed that whole grain consumption had a preventive role in ischemic stroke (3 servings/day: SRR = 0.69, 95% CI = 0.55-0.87; 3 studies).

Refined Grains

High Versus Low Grain Consumption Analysis. Five studies[13-16,18] presented results for the association between refined grain consumption and stroke risk, with an SRR of 0.99 (95% CI = 0.84-1.16; $P_{\text{heterogeneity}}$ = .435, I^2 = 0; Figure 3A).

Dose-Response Analysis. As shown in Figure 3B, SRR for 3 servings/day was 0.95 (95% CI = 0.86-1.03), with no evidence of heterogeneity (I^2 = 0, $P_{\text{heterogeneity}}$ = .504).

Subgroup and Sensitivity Analyses

A stratified analysis by sex revealed no association between total or refined grain consumption and stroke risk. A significant association between whole grain consumption and stroke risk was observed in women (SRR = 0.76, 95% CI = 0.60-0.97; 2 studies). One study reported a null association in men.[14] A stratified analysis by stroke subtype resulted in an ischemic stroke SRR of 0.86 (95% CI = 0.74-0.99) for total grain consumption and of 0.75 (95% CI = 0.60-0.95) for whole grain consumption. No significant associations with hemorrhagic stroke risk were detected for total, whole, or refined grain consumption. Total and whole grain consumption were inversely related to the risk of incident stroke (total grains, SRR = 0.71, 95% CI = 0.54-0.94; whole grains, SRR = 0.71, 95% CI = 0.54-0.94), but not to the risk of fatal stroke. Restricting the data analysis to studies performed in the United States yielded an SRR of 1.08 (95% CI = 0.83-1.41) for total grains, 0.85 (95% CI = 0.65-1.12) for whole grains, and 1.08 (95% CI = 0.86-1.34) for refined grains.

To test the robustness of our results, we conducted sensitivity analyses. When we excluded one study[14] that examined the association between whole-grain breakfast cereals and stroke risk, SRR did not change (SRR = 0.86, 95% CI = 0.68-1.10). Further exclusions of any single study did not affect SRR (data not shown).

Publication Bias

Egger's funnel plots did not show any asymmetry in the studies (P = .40 for total grains, P = .96 for whole grains, and P = .48 for refined grains; Supplementary Figure 2, available online at http://aph.sagepub.com/supplemental). This assessment, however, was based on 5 prospective cohort studies.

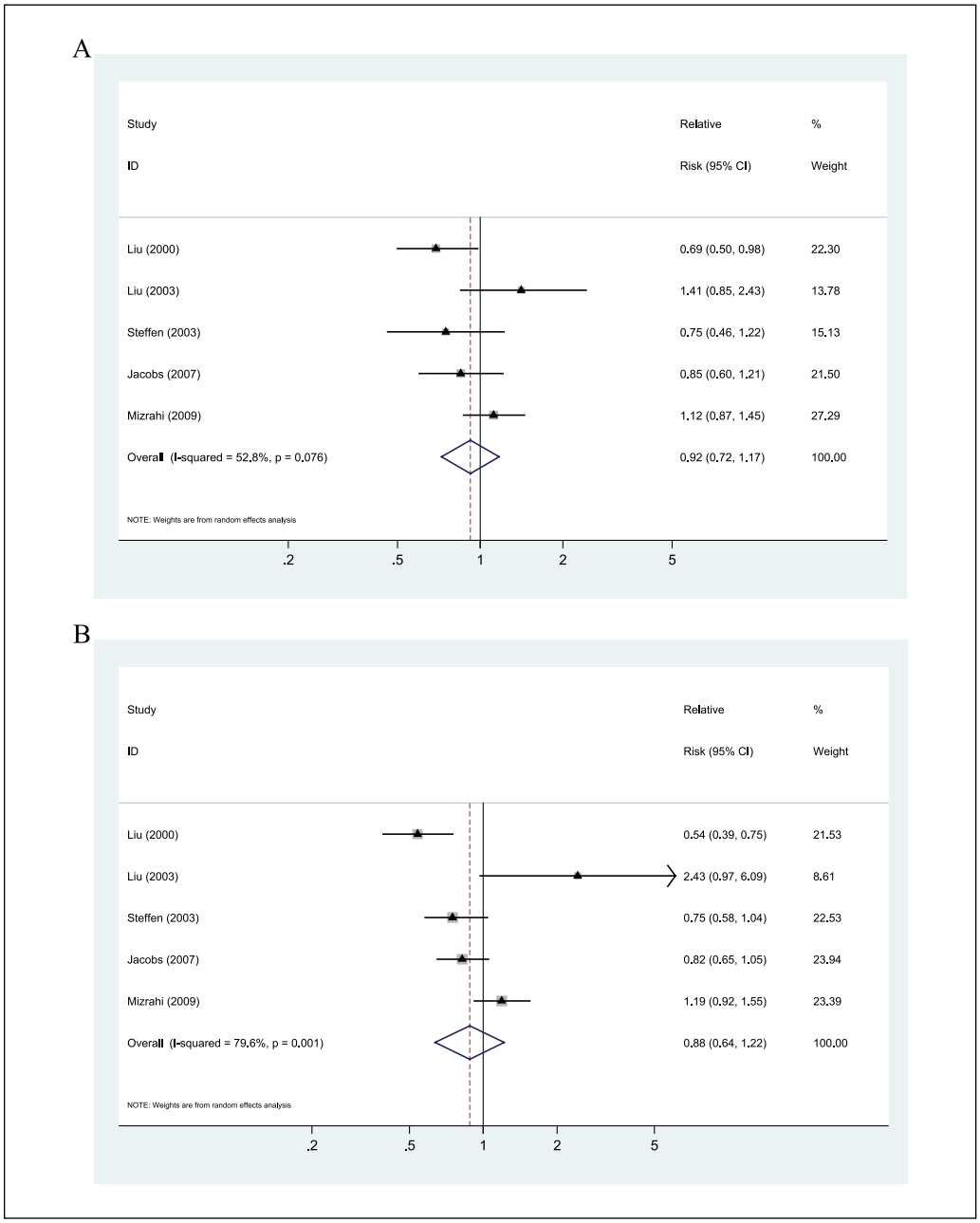

Figure 2. The summary risk association between intake of whole grains and stroke risk for (A) high versus low analysis; (B) linear dose-response analysis per 3 servings/day.

Discussion

Our meta-analysis examined the association between whole and refined grain consumption and the risk of stroke and its subtypes. Even though there were no significant associations between whole grain consumption and risk of total stroke, the stratification by stroke subtype revealed that diets rich in whole grains were inversely associated with risk of ischemic stroke and incident

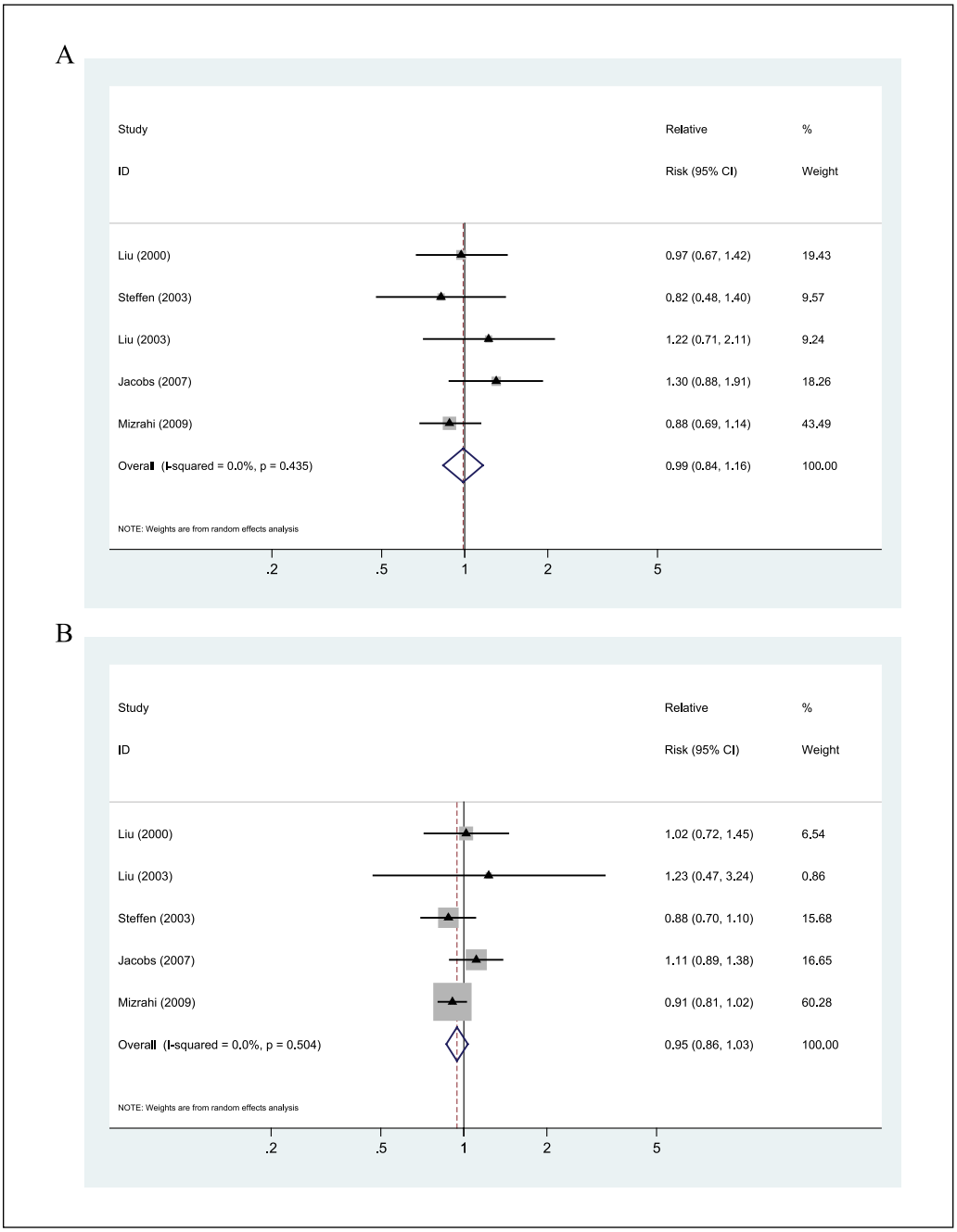

Figure 3. The summary risk association between intake of refined grains and stroke risk for (A) high versus low analysis; (B) linear dose-response analysis per 3 servings/day.

stroke, independent of a variety of cardiovascular disease risk factors (eg, smoking, alcohol consumption, body mass index, history of type 2 diabetes, hypertension, and dyslipidemia). We performed dose-response analyses, and similar results were observed. The consumption of refined grains was not associated with stroke risk.

Based on 6 prospective cohort studies, Fang et al[28] reported that the highest category of whole grain consumption was significantly associated with reduced stroke risk. While the authors failed to evaluate the risk association for stroke subtype and stroke outcome (incidence or mortality), they conducted subanalyses for sex, length of follow-up, and location. Two studies[16,31] analyzed by the authors were duplicates. In our meta-analysis, we included only the updated one.[16] Our meta-analysis quantitatively investigated whole and refined grain consumption and risk of stroke and its subtypes based on high versus low grain consumption and dose-response analyses. Our meta-analysis had adequate statistical power to detect moderate associations, because it included >0.4 million study participants and 5000 cases of stroke with a prolonged follow-up (median: 11.4 years; range: 5.5-24 years). Additionally, we carried out sensitivity analyses to investigate whether any particular study explained the results, but the findings were generally robust.

The majority of prospective studies have found no significant associations between whole grain consumption and total stroke risk.[14,31] Due to the distinct pathogenesis involved in hemorrhagic stroke and ischemic stroke,[32] the association between whole grain consumption and total stroke risk may in part be masked by combining both subtypes in the data analyses. Research findings from the Nurses' Health Study (NHS) revealed a 31% reduction in ischemic stroke risk in women consuming >1.77 servings of whole grains per day (RR = 0.69, 95% CI = 0.50-0.98).[13] Based on 3 prospective studies, we found a significant protective effect of whole grain consumption on ischemic stroke risk. This result was obtained from both high versus low consumption analysis and dose-response analysis. However, no inverse association was obtained for hemorrhagic stroke risk based on only one study.[16] The finding that whole grain consumption was not associated with hemorrhagic stroke risk indirectly emphasizes the interpretation that the inverse association between whole grain consumption and ischemic stroke may be mechanistic rather than due to chance or bias.[13] Nevertheless, this association should be interpreted with caution, because our findings were based on few studies and need further confirmation, especially for hemorrhagic stroke.

Results from our meta-analysis revealed an inverse association between whole grain consumption and ischemic stroke in women, but not in men. It has been reported that men experience more ischemic strokes than women,[33] which may be attributed to a higher prevalence of modifiable risk factors in men, such as smoking, coronary artery disease, and peripheral artery disease.[34] Furthermore, the protective effect of whole grains consumption was more significant on incident stroke than on fatal stroke, and there were significant differences between the 2 outcomes. Due to the small sample size in both subgroups, which could be subject to type I errors, and the observational nature of the studies included, this result should be interpreted with caution.

The association between high whole grain consumption and reduced risk of ischemic stroke is biologically plausible. Whole grains contain antioxidants, minerals (magnesium, potassium, and calcium), phytochemicals, and fiber in both the outer (bran) and inner (germ) layers. Results from observational studies and clinical trials have revealed that increased intakes of magnesium, potassium, and vitamin E are inversely associated with ischemic stroke or coronary events.[35,36] Furthermore, according to prospective cohort studies[37-39] and a recent meta-analysis,[40] cereal fiber consumption is associated with lower risk of total stroke. These nutrients present in whole grains may partially explain the protective effects observed on ischemic stroke. Furthermore, high whole grain consumption may reduce ischemic stroke risk by reducing concentrations of pro-inflammatory markers such as C-reactive protein and interleukin-6,[37-39] which increase stroke risk.[13] However, do the protective effects of whole grains on ischemic stroke risk go beyond these known components? Liu et al[13] reported an attenuated risk association between whole grain consumption and ischemic stroke risk after adjusting for known components in whole grains, which indicated that other components may confer additional protection.

Our meta-analysis had some limitations. First, the association between grain consumption and stroke risk may be due to other potential confounding factors. A high consumption of whole grains is correlated with a generally healthy lifestyle, for example, low prevalence of tobacco smoking and alcohol consumption, physical inactivity, obesity, hypercaloric diets, and/or high fat intakes.[40,41] Such unhealthy lifestyles and intermediate end points increase the risk of stroke.[13] However, most of the included studies had adjusted for major potential confounders including age, total energy intake, smoking, body mass index, alcohol consumption, and history of hypertension and diabetes. Furthermore, findings from the NHS[31] revealed that the protective effect of whole grain consumption on ischemic stroke was consistent among women who did not consume alcohol, did not report regular vigorous physical activity, did not use postmenopausal hormones, or were nonsmokers, which argues against the possibility of residual confounding factors. According to the Iowa Women's Health Study report,[16] high whole grain consumption is associated with a low incidence of diseases at baseline, including hypertension, diabetes, and coronary heart disease. In addition, intermediate end points that occurred during follow-up could have contributed to dietary modifications and may have, therefore, introduced confounding effects on these associations. Consequently, residual confounding factors should not be ruled out.

Second, measurement errors are important in the assessment of grain consumption because it is very difficult for subjects to accurately report their intakes. Among the studies, the NHS[13-16,19] had repeated dietary assessments (every 4 years) during the follow-up period, while in the other studies, the dietary assessment was only carried out at baseline. The studies used different units to quantify and classify grain consumption level: all but 2 studies used servings per day or per week,[17,18] and 1 study used grams per day.[42] Our meta-analysis included studies that evaluated grains classified as "all" or "total." Each type of whole or refined grains has a unique nutrient profile with potentially different health benefits. Therefore, the pooled consumption data may have masked the associations between specific whole grains and stroke risk. However, the assessment of whole grains was performed with a self-administered questionnaire, which had a relatively high validity (Spearman rank correlation coefficient of 0.70) compared to a 7-day dietary record.[43-45] Measurement errors in the exposure assessment are known to bias effect estimates toward the null and may partially explain the lack of an association between whole grain consumption and stroke risk.

Third, the number of stroke subtypes is relatively small, especially for hemorrhagic stroke. Consequently, the results for stroke subtypes should be interpreted with caution. More prospective studies for stroke subtypes should be performed to clarify the association for whole and refined grain consumption. Furthermore, our analysis was limited to data from only 2 countries (the United States and Finland). Future studies should focus on other populations to confirm our findings.

Fourth, in spite of the fact that there was no indication of asymmetry or major publication bias, we cannot completely rule out that unpublished null results exist.

In summary, our meta-analysis suggests that the consumption of whole grains is inversely associated with ischemic stroke risk. Consumption of refined grains is not associated with risk of stroke or its subtypes. To confirm our findings more thorough investigations, especially clinical trials, are required.

Authors' Note

Authors Jianguo Chen and Qingfeng Huang contributed equally to this work.

Declaration of Conflicting Interests

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