Dietary calcium intake and risk of stroke: a dose-response meta-analysis1–3

Susanna C Larsson, Nicola Orsini, and Alicja Wolk

ABSTRACT
Background: The findings from epidemiologic studies of calcium intake and risk of stroke have been conflicting.

Objective: The objective was to conduct a dose-response meta-analysis of prospective studies to assess the association between dietary calcium intake and stroke risk.

Design: Relevant studies were identified by searching PubMed and EMBASE databases until 11 December 2012 and by reviewing the reference lists of relevant articles. Observational prospective studies that reported RRs and 95% CIs for the association of calcium intake with stroke incidence or mortality were eligible. Study-specific RRs were combined by using a random-effects model.

Results: Eleven prospective studies, including 9095 cases of stroke, were included in the meta-analysis. Evidence of a nonlinear association between dietary calcium intake and risk of stroke was found. In a stratified analysis, calcium intake was inversely associated with risk of stroke in populations with a low to moderate average calcium intake (<700 mg/d; RR for a 300-mg/d increase in calcium intake: 0.82; 95% CI: 0.76, 0.88) but was weakly positively associated with risk in populations with a high calcium intake (≥700 mg/d; corresponding RR: 1.03; 95% CI: 1.01, 1.06). An inverse association between calcium intake and risk of stroke was observed only in Asian populations (n = 4; RR for a 300-mg/d increase in calcium intake: 0.78; 95% CI: 0.71, 0.87).

Conclusion: These findings suggest that dietary calcium intake may be inversely associated with stroke in populations with low to moderate calcium intakes and in Asian populations. Am J Clin Nutr 2013;97:951–7.

INTRODUCTION
Evidence from experimental studies in vitro and in vivo indicates that calcium may lower the risk of cardiovascular disease via multiple mechanisms, eg, through effects on blood cholesterol concentrations, blood pressure, insulin secretion and sensitivity, vasodilation, inflammation, thrombosis, and obesity (1). However, results from observational prospective studies and randomized controlled trials of calcium intake and calcium supplementation, respectively, and stroke risk have been conflicting. An inverse association between dietary calcium intake and risk of stroke has been observed in some but not all prospective studies (1). In contrast, a recent meta-analysis of 9 randomized controlled trials of calcium supplementation, with or without vitamin D, showed a borderline significant increased risk of stroke in individuals allocated to calcium supplementation (RR: 1.15; 95% CI: 1.00, 1.32) (2). One of the differences between the observational studies and randomized trials is the dose of calcium intake (higher in the trials).

To examine whether the association between calcium intake and risk of stroke varies by levels of calcium intake, we performed a dose-response meta-analysis of prospective studies. We also assessed whether the association varied by population because calcium intake is generally low in Asia, moderate to high in North America, and high to very high in Europe. In addition, we examined whether the relation differed by stroke types and source of calcium.

MATERIALS AND METHODS

Literature search and selection
We followed standard criteria for performing and reporting of meta-analyses of observational studies (3). A systematic review of the literature (through 11 December 2012) was performed by using electronic databases including PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.embase.com/home). We used the following search strategy and keywords: (calcium intake OR calcium supplements OR calcium supplementation) AND (stroke OR cerebral infarction OR cerebrovascular disease OR hemorrhage). No restrictions were imposed. Furthermore, we searched the reference lists of pertinent articles for more studies. We included observational prospective studies that reported RRs with 95% CIs for the association between dietary calcium intake and stroke incidence and/or stroke mortality. We did not include randomized trials because results from randomized trials of the effect of supplemental calcium on stroke risk were recently summarized in a meta-analysis (2). We followed the Meta-analysis Of Observational Studies in Epidemiology guidelines for conducting and reporting meta-analyses (3).

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Data extraction

We extracted the first author’s last name, year of publication, study location, sex, age, sample size (number of stroke cases and number of participants), duration of follow-up, methods used to assess calcium intake (including validity of the method) and ascertain stroke cases, RRs with 95% CIs for each category of calcium intake, and covariates adjusted for in the multivariable model. Study quality was evaluated by using the 9-star Newcastle-Ottawa Scale (4). The risk estimates from the most fully adjusted multivariable model were extracted. Two researchers (SCL and NO) independently reviewed articles and extracted information.

Statistical analysis

We estimated for every study an RR with 95% CI for a 300-mg/d increase in calcium intake. The method proposed by Greenland and Longnecker (5) and Orsini et al (6) was used to compute the trend from the correlated log RRs across categories of calcium intake. We assigned the median or mean calcium intake for each category to the corresponding RR. When the median or mean intake was not provided in the article, we assigned the midpoint of the upper and lower boundaries in each category as the average intake. For the lowest and highest categories, we assumed that the boundary had the same amplitude as the closest category.

We tested for a potential nonlinear relation between calcium intake and stroke risk using a 2-stage random-effects dose-response meta-analysis. This was done by modeling calcium intake with the use of restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (7). First, a restricted cubic spline model was estimated with a generalized least-squares regression taking into account the correlation within each set of published RRs as described by Orsini et al (6). At a second stage, we combined the study-specific estimates using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (8). A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. We performed a sensitivity analysis using other percentiles of the distribution as knots and obtained similar results.

To examine heterogeneity among studies, we used the Q and I^2 statistics (9). We conducted the analyses stratified by median calcium intake in the populations (below and above the median of ~700 mg/d), population (Asian, American, or European), study quality, and stroke types. We also investigated the association between source of calcium intake (dairy compared with nondairy) and stroke risk. Small study bias (eg, publication bias) was assessed through visual inspection of funnel plots and Egger’s test (10). All statistical analyses were performed with Stata (StataCorp), version 12. P values <0.05 were considered statistically significant.

RESULTS

Study characteristics

Our literature search identified 1099 articles (nonduplicates), of which 1088 were excluded after review of the title or abstract (Figure 1). The remaining 11 articles were based on data from prospective studies (11–21) and were eligible for inclusion in the meta-analysis. The studies were published between 1996 and 2012 (Table 1). Combined, these studies included 9095 stroke cases. Five studies were conducted in European populations, 4 in Asian populations, and 2 in American populations. One study included calcium from multivitamin supplements in the calculation of total calcium intake (12). Another study reported results for calcium intake from foods and dietary supplements combined and for calcium from foods only (13). For that study, we used the results for calcium from foods. The other 9 studies reported results for calcium intake from foods only. All studies provided RR estimates that were adjusted for age and smoking. Most of the studies also controlled for alcohol consumption (n = 10), BMI (n = 9), physical activity (n = 8), history of diabetes (n = 8), history of hypertension or measured blood pressure (n = 8), and other nutrients (n = 8). For further information about the included studies, see Table 1 under “Supplemental data” in the online issue.

Dietary calcium intake and stroke

We first assessed the dose-response relation between total dietary calcium intake and risk of stroke. We found evidence of a nonlinear association (P-nonlinearity = 0.03), with an inverse relation between calcium intake and stroke at low to moderate calcium intakes and no association or a tendency of a weak positive association at high intakes (Figure 2).

There was a statistically significant heterogeneity among all studies (P < 0.001, I^2 = 70.3%). We therefore stratified the analysis by average calcium intake in the study population (<700 compared with ≥700 mg/d). A statistically significant inverse association was found between calcium intake and risk of stroke in populations with low calcium intakes and a weak but statistically significant positive association in populations

$\text{FIGURE 1. Flow chart of study selection.}$

```plaintext
1195 articles found in database search
(PubMed, n=314; EMBASE, n = 881)

96 articles excluded due to duplicates

1099 nonduplicates

1088 articles excluded based on screening of titles or abstracts
1081 not relevant (animal studies, did not relate to the exposure or outcome, or other publication types)
5 other exposures or outcomes
2 case-control studies

11 full-text articles reviewed

11 observational prospective studies included in meta-analysis

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FIGURE 1. Flow chart of study selection.

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<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Study name (country)</th>
<th>Sample size, sex, and age</th>
<th>Cases (n)</th>
<th>Follow-up</th>
<th>Average calcium intake in highest and lowest categories</th>
<th>RR (95% CI) for highest compared with lowest category</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott et al, 1996 (11)</td>
<td>Honolulu Heart Program (USA)</td>
<td>3150 men (Japanese ancestry), 55–68 y</td>
<td>229 total strokes</td>
<td>22 y</td>
<td>Dietary calcium: 705 compared with 210 mg/d</td>
<td>0.56 (0.34, 0.91)</td>
<td>Age, smoking, physical activity, systolic blood pressure, total cholesterol, serum glucose, serum uric acid, hematocrit, and intakes of alcohol, dietary fiber, potassium, and sodium</td>
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<tr>
<td>Ascherio et al, 1998 (12)</td>
<td>Health Professionals Follow-Up Study (USA)</td>
<td>43,738 men, 40–75 y</td>
<td>328 total strokes</td>
<td>8 y</td>
<td>Total calcium: 1400 compared with 500 mg/d</td>
<td>1.05 (0.72, 1.53)</td>
<td>Age, smoking, profession, BMI, physical activity, histories of hypertension and hypercholesterolemia, family history of myocardial infarction, and intakes of total energy, alcohol, dietary fiber, and magnesium</td>
</tr>
<tr>
<td>Iso et al, 1999 (13)</td>
<td>Nurses’ Health Study (USA)</td>
<td>85,764 women, 34–59 y</td>
<td>386 ischemic strokes</td>
<td>14 y</td>
<td>Dietary calcium: 1128 compared with 393 mg/d</td>
<td>0.73 (0.53, 1.01)</td>
<td>Age; smoking; time interval; menopausal status; postmenopausal hormone use; BMI; exercise; histories of hypertension, diabetes, and high cholesterol; aspirin use; multivitamin use; vitamin E use; and intakes of alcohol and omega-3 fatty acids</td>
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<tr>
<td>Marniemi et al, 2005 (14)</td>
<td>Turku and Southwestern Finland (Finland)</td>
<td>755 men and women, 65–99 y</td>
<td>70 total strokes</td>
<td>10 y</td>
<td>Dietary calcium: 1673 compared with 1167 mg/d</td>
<td>1.34 (0.70, 2.55)</td>
<td>Age, sex, smoking, functional capacity, and weight-adjusted energy intake</td>
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<tr>
<td>Umesawa et al, 2006 (15)</td>
<td>Japan Collaborative Cohort study (Japan)</td>
<td>21,068 men and 32,319 women, 40–79 y</td>
<td>566 total stroke deaths</td>
<td>9.6 y</td>
<td>Dietary calcium (men): 665 compared with 250 mg/d</td>
<td>0.68 (0.37, 1.26)</td>
<td>Age, smoking, BMI, hypertension, diabetes, and intakes of total energy and alcohol</td>
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<td>Larsson et al, 2008 (16)</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Finland)</td>
<td>26,556 men, 50–69 y</td>
<td>3281 total strokes</td>
<td>13.6 y</td>
<td>Dietary calcium: 1916 compared with 876 mg/d</td>
<td>1.14 (1.01, 1.27)</td>
<td>Age, supplementation group, cigarettes smoked daily, BMI, physical activity, systolic and diastolic blood pressure, serum total and HDL cholesterol, histories of diabetes and coronary heart disease, and intakes of alcohol and total energy</td>
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(Continued)
<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Study name (country)</th>
<th>Sample size, sex, and age</th>
<th>Cases (n)</th>
<th>Follow-up</th>
<th>Average calcium intake in highest and lowest categories(^1)</th>
<th>RR (95% CI) for highest compared with lowest category</th>
<th>Adjustments</th>
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<tbody>
<tr>
<td>Umesawa et al, 2008 (17)</td>
<td>Japan Public Health Center study (Japan)</td>
<td>41,526 men and women, 40–59 y</td>
<td>1321 total strokes</td>
<td>12.9 y</td>
<td>Dietary calcium: 753 compared with 233 mg/d</td>
<td>0.71 (0.56, 0.89)</td>
<td>Age, sex, public health center, smoking, menopause, BMI, diabetes, history of hypertension, medication for hypercholesterolemia, and intake of alcohol, omega-3 (n−3) fatty acids, and sodium</td>
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<td>Dairy calcium: 116 compared with 0 mg/d</td>
<td>0.70 (0.57, 0.86)</td>
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<td>Nondairy calcium: 652 compared with 214 mg/d</td>
<td>0.85 (0.66, 1.08)</td>
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<td>Weng et al, 2008 (18)</td>
<td>CardioVascular Disease risk FACtor Two-township Study (Taiwan)</td>
<td>1772 men and women, &gt;40 y</td>
<td>132 ischemic strokes</td>
<td>10.6 y</td>
<td>Dietary calcium: 661 compared with 381 mg/d</td>
<td>0.66 (0.43, 1.02)</td>
<td>Age, sex, area, smoking, BMI, central obesity, physical activity, diabetes, hypertension, use of antihypertensive drugs, self-reported heart disease, hypercholesterolemia, hypertriglyceridemia, fibrinogen, apolipoprotein B, plasminogen, alcohol</td>
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<tr>
<td>Goldbohm et al, 2011 (19)</td>
<td>Netherlands Cohort Study (Netherlands)</td>
<td>120,852 men and women, 55–69 y</td>
<td>842 total stroke deaths</td>
<td>10 y</td>
<td>Dietary calcium (men): 1387 compared with 549 mg/d</td>
<td>0.91 (0.58, 1.43)</td>
<td>Age, education, smoking, nonoccupational physical activity, BMI, multivitamin use, and intake of total energy, alcohol, PUFAs, vegetables, and fruit</td>
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<td>Dietary calcium (women): 1296 compared with 538 mg/d</td>
<td>0.73 (0.44, 1.22)</td>
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<tr>
<td>Larsson et al, 2011 (20)</td>
<td>Swedish Mammography Cohort (Sweden)</td>
<td>34,670 women 49–83 y</td>
<td>1680 total strokes</td>
<td>10.4 y</td>
<td>Dietary calcium: 1422 compared with 698 mg/d</td>
<td>1.08 (0.89, 1.31)</td>
<td>Age, education, smoking, BMI, total physical activity, history of diabetes, history of hypertension, aspirin use, family history of myocardial infarction, and intake of total energy, alcohol, protein, cholesterol, dietary fiber, and folate</td>
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<tr>
<td>Li et al, 2012 (21)</td>
<td>Heidelberg Cohort (Germany)</td>
<td>23,980 men and women, 35–64 y</td>
<td>260 total strokes</td>
<td>11 y</td>
<td>Dietary calcium: 1130 compared with 513 mg/d</td>
<td>1.12 (0.76, 1.65)</td>
<td>Age, sex, education, smoking, BMI, total physical activity, history of diabetes, use of calcium supplements, and intake of total energy, alcohol, vitamin D, SFAs, and total protein</td>
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<td>Dairy calcium: 780 compared with 188 mg/d</td>
<td>1.01 (0.70, 1.47)</td>
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<td>Nondairy calcium: 351 compared with 324 mg/d</td>
<td>1.26 (0.89, 1.77)</td>
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<td></td>
<td>Supplemental calcium: any use compared with nonusers</td>
<td>0.93 (0.66, 1.30)</td>
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</table>

\(^1\) Dietary calcium intake includes calcium from foods, both dairy and nondairy sources, but not from dietary supplements. One study (12) reported results for total calcium intake from foods and multivitamins.

\(^2\) The midpoint calcium intake in the lowest and highest tertiles was estimated as the mean intake (1420 mg/d) ± half of the SD (505 mg/d) among noncases.

\(^3\) RRs by calcium categories for stroke types were combined by using a fixed-effects model.
with high calcium intakes ($P$-heterogeneity by calcium intake <0.001) (Figure 3). We found evidence of publication bias among studies with a low average calcium intake (Egger’s test: $P = 0.05$) but not among studies with high calcium intakes ($P = 0.44$).

The association between calcium intake and stroke risk differed across populations ($P$-heterogeneity <0.001). A statistically significant inverse relation between calcium intake and stroke was observed in Asian populations (RR for a 300-mg/d increase in calcium intake: 0.78; 95% CI: 0.71, 0.87; heterogeneity test: $P = 0.69$, $I^2 = 0\%$), no association was observed in American populations (RR: 0.95; 95% CI: 0.81, 1.10; heterogeneity test: $P = 0.08$, $I^2 = 68.1\%$), and a weak positive relation was observed in European populations (RR: 1.03; 95% CI: 1.00, 1.06; heterogeneity test: $P = 0.40$, $I^2 = 2.4\%$). The observed positive relation between calcium intake and stroke in European studies was driven by the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (16). After this study was excluded, the RR of stroke for a 300-mg/d increment of calcium intake was 1.01 (95% CI: 0.94, 1.09) in European studies. The association between calcium intake and stroke did not differ substantially by study quality.

Dietary calcium intake and stroke types

Six studies provided results for stroke types (13, 15–18, 20). Among studies with a low average calcium intake (<700 mg/d; $n = 4$), the RRs for a 300-mg/d increase in calcium intake were 0.84 (95% CI: 0.77, 0.93) for ischemic stroke, 0.80 (95% CI: 0.68, 0.95) for intracerebral (intraparenchymal) hemorrhage, and 0.83 (95% CI: 0.55, 1.26) for subarachnoid hemorrhage. The corresponding RRs among studies with a high calcium intake ($\geq$700 mg/d; $n = 2$) were 1.03 (95% CI: 1.00, 1.06) for ischemic stroke, 1.37 (95% CI: 0.75, 2.50) for intracerebral hemorrhage, and 1.10 (95% CI: 0.98, 1.24) for subarachnoid hemorrhage.

Dairy compared with nondairy calcium

Of 4 studies that reported results for both dairy and nondairy calcium intakes (11, 13, 17, 21), the RRs of stroke for a 300-mg/d increase in calcium intake were 0.78 (95% CI: 0.62, 0.99) for dairy calcium and 0.98 (95% CI: 0.73, 1.30) for nondairy calcium. Addition of the study (15) that provided results for dairy but not for nondairy calcium did not change the results materially for dairy calcium (RR: 0.73; 95% CI: 0.59, 0.91).

Supplemental calcium intake

Three studies had examined the relation between supplemental calcium intake and stroke (12, 13, 21). None of the studies observed a statistically significant association (Table 1). The overall RR of stroke associated with calcium supplementation was 0.90 (95% CI: 0.74, 1.08).

DISCUSSION

This meta-analysis of 11 prospective studies indicates that calcium intake may be inversely associated with risk of stroke in populations with low to moderate calcium intakes as well as in Asian populations but not in American or European populations with high calcium intakes. In populations with low to moderate calcium intakes, a 300-mg/d increase in calcium intake was associated with an 18% reduction in stroke risk. In Asian populations, the risk of stroke decreased by 22% for each 300-mg/d increase in calcium intake. The association between calcium intake and stroke did not differ appreciably by stroke types.

Dietary calcium intake differed substantially between studies. In the Asian populations, calcium intake was much lower than in the European populations and somewhat lower than in the US studies. For example, in the Japan Public Health Center study, the median calcium intake in the highest category was lower than the median calcium intake in the lowest category in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish
men. The differences in calcium intake may explain the inconsistent findings across populations. In addition, the main dietary sources of calcium differed across populations. In European and American populations, dairy foods are the major sources of calcium whereas nondairy foods are the main contributors to calcium in Asian populations. It is likely that the conflicting results across populations is explained by confounding by other nutrients in dairy foods or nondairy food sources of calcium, leading to either an attenuation of the association or a spurious inverse association between calcium intake and stroke.

In an analysis of calcium sources, intake of dairy calcium but not of nondairy calcium was inversely associated with risk of stroke. This finding might suggest that it is not calcium per se that is beneficial but that the association is explained by other factors in dairy foods, such as other minerals (e.g., potassium), vitamins (e.g., vitamin D in fortified milk), SFAs, protein, or a combination of nutrients. Intakes of potassium (22) and protein (23, 24) have been inversely associated with risk of stroke in some studies. Moreover, SFA intake has been shown to be inversely associated with stroke risk in populations with a relatively low SFA intake, such as Japan (24, 25) and the United States (26). The different association for dairy and nondairy calcium intakes could also be due to different absorptions of calcium from dairy and nondairy foods. Calcium absorption from various dairy foods may also differ. For example, previous studies have suggested that calcium in low-fat dairy foods is better absorbed than calcium in high-fat dairy foods and that low-fat dairy foods but not high-fat dairy foods are inversely associated with risk of hypertension (27, 28).

A previous meta-analysis of milk consumption and risk of stroke showed a statistically nonsignificant inverse association, with an RR of 0.87 (95% CI: 0.72, 1.07) for each 200-mL/d increment of milk consumption (29). That meta-analysis included 6 prospective studies, of which 3 were conducted in Europe (2 in the United Kingdom and 1 in Finland), 2 in Japan, and 1 in the United States. The strongest inverse association between milk consumption and stroke was observed in the Japanese studies. A weak and nonsignificant inverse association was found in the US and UK studies, whereas no association was noted in the Finnish study. The results for milk agree with our findings on calcium, which showed an inverse association in Asian populations but not in European populations. In addition, we observed an inverse association between intake of dairy, but not of nondairy, calcium and risk of stroke. However, the strength of the association between dairy calcium and stroke was stronger than for milk and stroke.

A meta-analysis of observational studies inherits the limitation of the original studies. Because this meta-analysis was based on data from prospective studies, selection and recall bias was minimized. Although most studies adjusted for potential

![FIGURE 3. RRs of stroke for a 300-mg/d increase in dietary calcium intake, stratified by low compared with high average calcium intakes (in mg/d) in the study population. RRs were combined by using a random-effects model. Squares represent study-specific RR estimates (the size of the square reflects the study-specific statistical weight), horizontal lines represent 95% CIs; diamonds represent the combined RRs with 95% CIs. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention study; CVDFACTS, CardioVascular Disease risk FACTor Two-township Study; HC, Heidelberg Cohort; HHP, Honolulu Heart Program; HPFS, Health Professionals Follow-Up Study; JACC, Japan Collaborative Cohort study; JPHC, Japan Public Health Center study; NHS, Nurses' Health Study; NLCS, Netherlands Cohorts Study; SMC, Swedish Mammography Cohort; TSF, Turku Southwestern Finland (this study did not have a name).]
Our research shows that calcium intake and stroke risk may be inversely associated. In populations with low average calcium intake, there may be a lower risk of stroke. However, the effect may not be consistent across all populations. Dairy but not nondairy calcium intake was associated with stroke risk. When interpreting these results, we must consider the limitations of our study, such as the potential for residual confounding and the difficulty in accurately estimating calcium intake. Additionally, the use of self-reported dietary data may introduce measurement error. Our findings support the need for further research to better understand the relationship between calcium intake and stroke risk.