Original Article

Calcium intake and the risk of stroke: an up-dated meta-analysis of prospective studies

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Background and Purpose: Calcium intake has been associated with stroke risk in a prior meta-analysis, however, newly published results are inconsistent. Dairy food benefits on stroke incidence may involve a calcium-related mechanism. We have therefore updated this meta-analysis with particular references to any possibility of a calcium-mediated dairy food risk reduction of stroke risk. **Methods:** We searched multiple databases and bibliographies for prospective cohort studies. Reports with multivariate-adjusted relative risk (RR) and corresponding 95% confidence intervals (CI) for the association of calcium intake with stroke incidence were considered. **Results:** Ten studies with 371,495 participants and 10,408 stroke events were analyzed. The pooled analysis showed no statistically significant association of the risk of total stroke (RR=0.96; 95% CI: 0.89-1.04) and stroke subtypes with the highest and lowest calcium intake quantiles. Nevertheless, high dairy calcium intake was significantly associated with an approximately 24% reduction of stroke risk. (RR=0.76; 95% CI: 0.66-0.86). Furthermore, a long-term follow-up (≥14 years) was helpful to reduce the risk of stroke (RR=0.67; 95% CI: 0.51-0.88). Additionally, a non-linear dose-response relationship was predicted between calcium intake and stroke risk. **Conclusions:** Dairy calcium intake is inversely associated with stroke incidence. There is a non-linear dose-response relationship between calcium intake and stroke risk. However, when the follow-up time is long enough, the inverse relationship is independent of dose. Additional large cohort studies are required to illustrate this relationship in detail.

Key Words: stroke, calcium intake, meta-analysis, prospective cohort studies, dose-response

INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity globally. Despite the advances achieved in recent years, stroke prevention remains a public health priority.[1] Dietary intakes of potassium, calcium, and magnesium have been proved to be associated with stroke risk in previous studies.[2] The mechanisms mainly involve regulation of blood cholesterol concentrations, blood pressure, insulin secretion and sensitivity, vasodilation, inflammation, thrombosis, and obesity.[3] Several randomized controlled studies have showed that calcium supplementation reduces blood pressure.[4] However, the association of calcium intake with risk of stroke remains controversial. Some studies suggested an inverse relation between the two,[5-7] while the others reported no association.[8-14]

Meta-analysis is a method to reduce the likelihood of false-positive or false-negative results by increasing the sample size, it is thought to be a valuable tool for studying unintended treatment effects.[15] Although, previous meta-analyses of randomized controlled trials suggested that there was no association between calcium intake and stroke risk, the follow-up period in these studies was considerably short.[16,17] In contrast, a meta-analysis of observational prospective studies demonstrated a U-shaped association between calcium intake and stroke risk.[18] However, one recently published study did not find the same association.[13] We conducted a detailed meta-analysis of prospective studies to investigate the relationship between levels of dietary calcium intake and stroke incidence.

METHODS

Data sources and searches

The search was conducted according to the recommenda-

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tions of MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines.[19] A systematical search of the electronic databases included Pubmed, Embase, Web of Science and the Cochrane Library using no language restrictions was performed for articles published between 1966 and 2014 July. The search terms used were: ("stroke" OR "cerebrovascular disease" OR "cerebrovascular accident" OR "intracranial hemorrhage" OR "subarachnoid hemorrhage" OR "CVD" OR "cerebral infarction") AND ("calcium intake" OR "calcium consumption" OR "calcium supplement" OR "dietary calcium").

The titles and abstracts of studies identified in the search were scanned to exclude any that were clearly irrelevant. The full texts of the remaining articles were read to determine whether they met the inclusion criteria. The reference lists of articles with information on the topic were also reviewed to identify additional pertinent studies.

The study design was approved by the ethical committee of the 1st Affiliated Hospital of Zhengzhou University.

Study selection and data abstraction

Retrieved citations were reviewed independently by two authors at the title and abstract level. The inclusion criteria were set as follows: (1) the study design was prospective cohort-based; (2) the general population was studied; (3) the exposure of interest was calcium intake; (4) the outcome of interest was stroke incidence; (5) relative risk (RR), hazard ratio (HR) and the corresponding 95% confidence interval (CI) (or the data required to calculate them) were reported. We also extracted study characteristics for each trial.

Statistical methods

We conducted meta-analyses combining risk ratios and hazard ratios for stroke. Relative risk (RR) was pooled. The I^2 statistic, a quantitative measure of inconsistency across studies, was also calculated. If $p<0.10$, the between-study heterogeneity was considered statistically significant, and we chose the random-effects model to calculate the pooled RR. Conversely, if $p>0.10$, the between-study heterogeneity was not considered significant, the fixed-effects model was applied. Mantel-Haenszel's fixed effects method and Der-Simonian and Laird's random effects method were used in STATA 12 software.

The range of calcium intake and the cutoffs for the categories varied between studies. Therefore, a dose-response relationship between calcium intake and risk of stroke was examined, using a method proposed by Greenland and Orsini.[20,21] For all studies, the median or mean level of calcium for each category was assigned to each corresponding RR estimate. In studies that did not provide the number of cases and person-years in each exposure category, the variance-weighted least square regression model was used to estimate the slopes.

As characteristics of populations, ascertainment of stroke, and adjustments for confounding factors were not consistent between studies, we performed a sensitivity analysis to further explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the overall result, we investigated the influence of a single study on the overall risk estimate by omitting one study in each turn. Publication bias was quantified by Begg's and the Egger's tests.

RESULTS

Literature search and study characteristics

A total of 798 unique citations (non-duplicates) were retrieved from the PubMed, Embase, Web of Science and Cochrane Library Database. Most of these were excluded after the first screening based on abstracts or titles. After a full-text review, ten prospective cohort studies were identified that met the predefined inclusion criteria.

These ten studies included 371,495 participants and were published between 1996 and 2014. Four had been conducted in the United States,[5,8,9,14] one in Taiwan,[6] one in Finland,[10] one in Japan,[7] one in Sweden,[11] one in Germany[12] and one in The Netherlands.[13] Dietary calcium intake was assessed by validated food frequency questionnaire (FFQ) in most studies and a 24-hour recall method in one study.[8] The characteristics of included studies are listed in Table 1.

Five of the ten studies directly evaluated the relationship of calcium intake and risk of total stroke and different stroke subtypes,[7-9,11,12] while three studies only focused only on specific stroke subtypes.[5,6,10] Of these three studies, one study evaluated calcium intake and risk of ischemic stroke, intraparenchymal hemorrhage and subarachnoid hemorrhage, but not total stroke[10] and two studies focused only on calcium intake and risk of ischemic stroke.[5,6] The remaining studies evaluated only the risk of total stroke.[13,14] Five of the ten studies also reported dairy calcium intake and risk of stroke.[5,7-9,12]

Meta-analysis of stroke risk with dietary calcium intake

The heterogeneity was significant among the results of included studies ($p=0.003$, $I^2=66.3\%$), Hence, a random-effects model was used for the analysis. The results showed that high calcium intake was not associated with the risk of total stroke (RR=0.96; 95% CI: 0.89-1.04) (Figure 1).

Further, a subgroup analysis for different stroke subtypes indicated that highest or lowest calcium intake quartile has no protective effect in ischemic stroke (RR=0.83; 95% CI: 0.66-1.03), intraparenchymal hemorrhage (RR=1.04; 95% CI: 0.63-1.71) or subarachnoid hemorrhage (RR=1.13; 95% CI: 0.77-1.64). We further explored the influence of gender and years of follow-up. No significant association was observed in either gender: male (RR=1.05; 95% CI: 0.94-1.18) or female (RR=0.98; 95% CI: 0.85-1.13). Interestingly, long-term calcium intake was observed to be significantly associated with stroke incidence. (14 years and above: RR=0.67; 95% CI: 0.51-0.88; less than 14 years: RR=0.99; 95% CI: 0.91-1.08) (Figure 2).

Meta-analysis of stroke risk with dairy calcium intake

As dairy calcium intake was also reported by the included studies, we further performed the analysis of dairy calcium intake and risk of stroke. High dairy calcium intake was significantly associated with an approximately 24% reduction in the risk of total stroke (RR=0.76; 95% CI: 0.66-0.86), while non-dairy calcium intake showed no effect (RR=1.01; 95% CI: 0.82, 1.24) (Figure 3).

Table 1. Characteristics of included studies in our meta-analysis

Study	Study location	Total participants	Gender	Stroke cases	Follow up (years)	Exposure assessment	Dairy calcium reported	Comparison range/median (mg/day)	Adjustment
Abbott et al., 1996[5]	USA (Japanese ancestry)	3,150	Men	229[†]	22	24-hour recall	Yes	Quintile (IV vs I) (606-3109) vs (0-275)	Age, dietary potassium and sodium, alcohol, smoking, physical activity index, systolic blood pressure, total cholesterol, serum glucose, serum uric acid, hematocrit
Ascherio et al., 1998[8]	USA	43,738	Men	328	8.0	FFQ	Yes	Quintile (V vs I) 1400 vs 500	Age, total energy intake, smoking, alcohol consumption, history of hypertension, history of hypercholesterolemia, parental history of myocardial infarction before age 65 years, profession, quintiles of BMI, physical activity, potassium intake, fiber intake
Iso et al., 1999[9]	USA	85,764	Women	690	14.0	FFQ	Yes	Quintile (V vs I) 1145 vs 395	Age, smoking, time interval, and a history of hypertension, BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, vitamin E use, v-3 fatty acid intake, histories of diabetes, high cholesterol levels
Weng et al., 2008[6]	Taiwan	1,772	Both	132[†]	10.6	FFQ	No	Quintile (IV+III vs I) (>592) vs (<451)	Age, sex, hypertension, use of antihypertensive drugs, diabetes mellitus, area, central obesity, alcohol consumption, smoking, sex-smoking habit interaction, BMI, self-report heart disease, high cholesterol levels, physical activity, fibrinogen, apolipoprotein B, plasminogen
Larsson et al., 2008[10]	Finland	26,556	Men	3,281	13.6	FFQ	No	Quintile (V vs I) 1916 vs 876	Age, supplementation group, number of cigarettes smoked daily, BMI, systolic and diastolic blood pressures, serum total cholesterol, serum high-density lipoprotein cholesterol, histories of diabetes, coronary heart disease, leisure-time physical activity, and intake of alcohol, total energy
Umesawa et al., 2008[7]	Japan	41,526	Both	1,321	12.9	FFQ	Yes	Quintile (V vs I) 753 vs 233	Age, sex, BMI, history of diabetes, medication for hypercholesterolemia, menopause, smoking status, ethanol intake, sodium intake, potassium intake, n-3 fatty acid intake, public health center, history of hypertension
Larsson et al., 2011[11]	Sweden	34,670	Women	1,680	10.4	FFQ	No	Quintile (V vs I) 1422 vs 698	Age, smoking status, pack-years of smoking, educational level, body mass index, total physical activity level, history of diabetes, history of hypertension, aspirin use, family history of myocardial infarction, and intakes of total energy, alcohol, protein, cholesterol, total fiber, and folate

FFQ: food frequency questionnaire; BMI: body mass index.
[†]Only ischemic stroke number was available in this study.

Table 1. Characteristics of included studies in our meta-analysis (cont.)

Study	Study location	Total participants	Gender	Stroke cases	Follow up (years)	Exposure assessment	Dairy calcium reported	Comparison range/median (mg/day)	Adjustment
Li et al., 2012[12]	German	23,980	Both	260	11	FFQ	Yes	Quintile (IV vs. I) 1130 vs 513	Age, sex, educational level, physical activity, BMI, smoking categories, lifetime alcohol intake, energy-adjusted dietary vitamin D, saturated fatty acid and total protein intake, total energy intake, self-reported diabetes mellitus at recruitment and use of calcium supplements
Sluijs et al., 2014[13]	Netherlands	36,094	Both	631	12	FFQ	No	Quintile (IV vs. I) 1316 vs 797	Age, sex, body mass index, education, physical activity, smoking status, intakes of alcohol, total energy, magnesium
Paik et al., 2014[14]	American	74,245	Women	1,856	24	FFQ	No	Quintile (V vs. I) >1000 vs 0	Diet calcium intake, total vitamin D intake, vitamin E intake, magnesium intake, multivitamin use, BMI, family history of heart disease, smoking status, alcohol intake, postmenopausal hormone use, physical activity, race, aspirin use, history of hypertension, diabetes, or high cholesterol, glycemic load, trans fat intake, polyunsaturated fat/saturated fat ratio, fiber intake, total energy intake, recent physical examination, and recent mammogram

FFQ: food frequency questionnaire; BMI: body mass index.
†Only ischemic stroke number was available in this study.

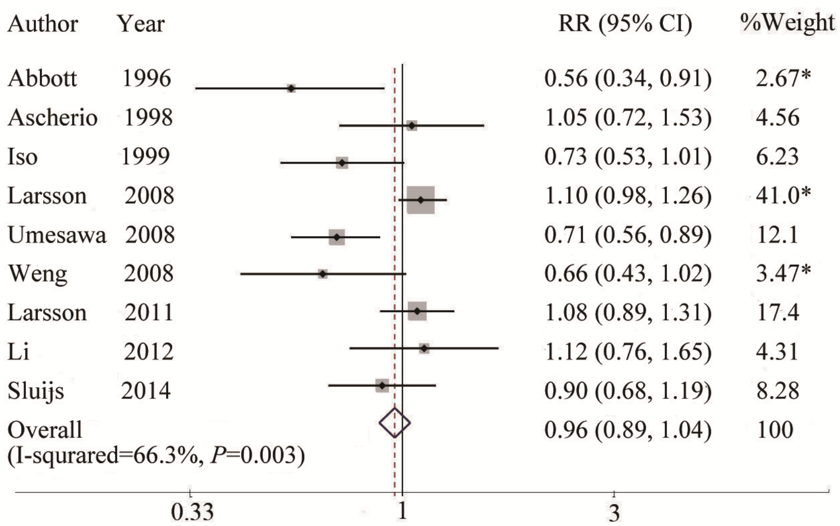

Figure 1. Meta-analysis of stroke risk with dietary calcium intake. * As data for total stroke was not available in the two studies, data for ischemic stroke was used.

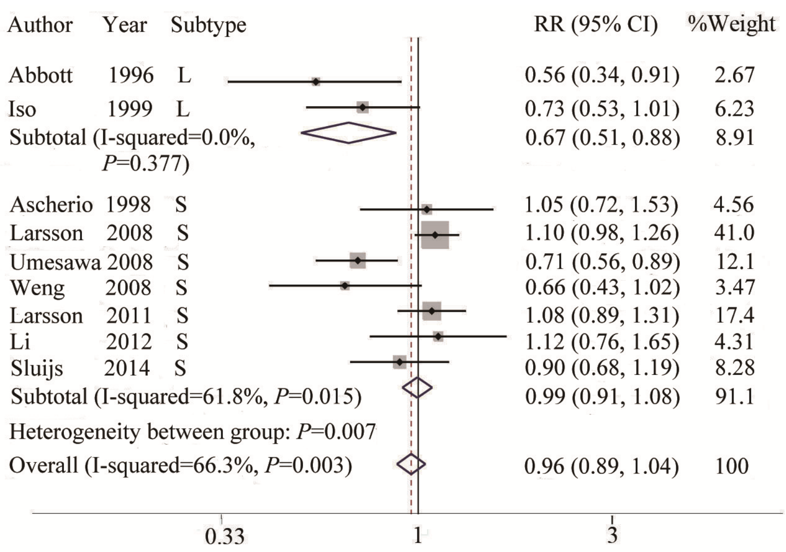

Figure 2. Subgroup analysis of stroke risk with dietary calcium intake (L: follow-up year ≥14 vs S: follow-up year <14)

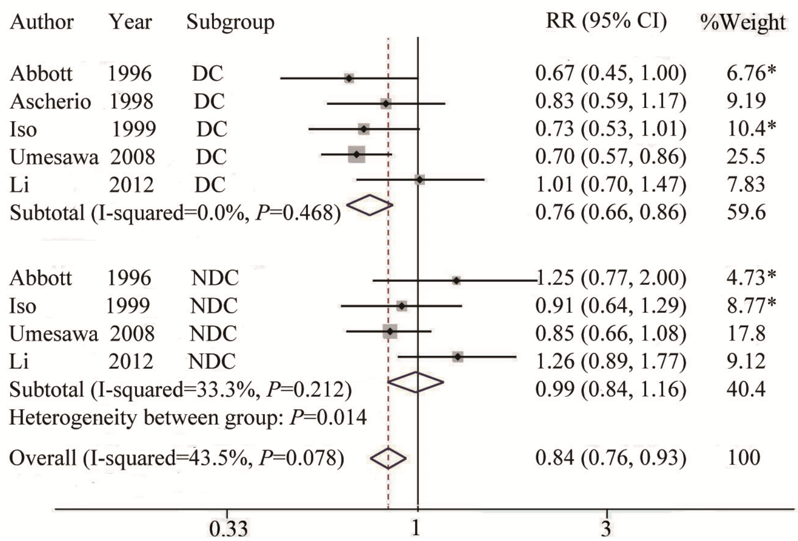

Figure 3. Meta-analysis of stroke risk with diary calcium intake. (DC: dairy calcium intake, NDC: nondairy calcium intake.) * As data for total stroke was not available in the two studies, data for ischemic stroke was used.

Meta-analysis of stroke risk with supplemental calcium intake

Four studies investigated the relationship between stroke risk and supplemental calcium, including one newly published article, however, no correlation was found (RR=0.97; 95% CI: 0.86-1.10).

Dose-response analysis

Two studies used "lowest vs. highest" quartile to evaluate the calcium intake and risk of stroke, so these results could not be combined with others,[5,6] Therefore, a dose-response analysis was performed in the other seven included studies.[8-13] The results showed a non-linear relationship between calcium intake and stroke risk.

Sensitivity analysis

Sensitivity analysis was conducted to explore potential sources of heterogeneity among included studies. Upon exclusion of a study that separately evaluated calcium intake and different subtypes,[10] the pooled RR become significant but still presented heterogeneity. Exclusion of any other single study did not alter the pooled RR significantly. The *p* values for the Begg's and the Egger's tests were both 0.175, suggesting a low probability of publication bias.

DISCUSSION

This meta-analysis of 10 prospective cohort studies involving 371,495 participants and 10,408 stroke events demonstrated no statistically significant difference in the risk of total stroke or stroke subtypes with calcium intake when the highest and lowest calcium intake quintiles were compared. Dose-response analysis also showed no inverse association between the two. Interestingly, a significant relationship was suggested when the follow-up period was longer than 14 years, however, more studies are required to confirm this conclusion. Furthermore, high dairy calcium intake was observed to be associated with a reduction of approximately 24% in the risk of total stroke.

Some potential explanations should be considered to illustrate the results of our meta-analysis. Firstly, it is possible that the inverse association between calcium intake and risk of stroke is stronger in specific subgroups of the population, such as patients with hypertension. The hypotensive effect of calcium has been well demonstrated by observational studies and large meta-analyses of randomized clinical trials.[22,23] Previous studies reported that calcium intake was inversely associated with not only the risk of hypertension development but also systolic blood pressure levels.[24] In one of our included studies, dairy calcium intake was also found to be inversely associated with a history of hypertension.[7] As hypertension is one of the risk factors for stroke, the potential anti-hypertensive effect of calcium may reduce stroke risk in individual with hypertension. However, according to the subgroup analysis of an included study,[11] calcium intake was not associated with risk of stroke among women with a history of hypertension. Since the history of hypertension or baseline blood pressure level had been adjusted in the other included studies, the relationship between calcium intake and risk of stroke among hypertensive individuals could not be further investigated. Additional evidence is needed to further support this hypothesis.

Secondly, the effect of dietary calcium intake may vary among different populations. In our analysis, calcium intake in the Japanese population was much lower than that of American or European populations, and interestingly, an inverse association with stroke risk was observed only in Japanese populations.[5-12] Currently, it remains unclear whether the reduction of stroke risk is related to a low dose or is population specific. Further studies of high-dose calcium and stroke risk in an Asian population can further illustrate this relationship. However, the possible protective effect of dietary calcium intake on stroke should not be neglected, especially in specific populations.

Thirdly, all but one of the included studies used FFQ as the evaluating instrument,[6-14] Hence, the calcium intake can be considered the "daily calcium intake" which represents habitual calcium intake. It may require a long time to exhibit effects on cardiovascular system. This indicates that long-term follow up is needed to observe the association between calcium intake and stroke risk. In our analysis, when follow-up time is longer than 14 years, an inverse association was predicted between the two, even when the dose of calcium intake was high.

An inverse association of stroke risk with calcium intake from dairy foods but not non-dairy sources was observed in our analysis. An earlier study conducted on a Chinese population cohort showed that dairy food intake reduced the mortality and stroke risk. Furthermore, calcium and vitamin-D intake contributed to the dairy-mortality association.[25] It is suggested that calcium plays an important role in combination with potassium and magnesium in achieving an appropriate metabolic balance that reduces blood pressure and stroke incidence.[26] It remains unclear how dairy calcium influences this process. One explanation is that the casein in milk and dairy foods enhances calcium absorption,[27,28] which may result in higher efficiency of calcium usage in the body, and thus contribute to a protective effect against stroke. However, other factors in dairy foods may also account for the observed association. In addition to calcium and other minerals, milk contains fats and bioactive peptides that inhibit the angiotensin-converting enzyme and thus reduce the risk of stroke.[25] Milk proteins have also been shown to delay stroke onset in stroke-prone spontaneously hypertensive rats model.[29] However, additional evidence is needed to further clarify this hypothesis.

A meta-analysis exploring calcium intake and cardiovascular disease-related death predicts an U-shaped association.[30] However, the author did not distinguish stroke incidence from mortality,[16] which might have influenced the results. In the current study, we set up stricter criteria to distinguish the incidence of stroke from mortality. In addition, our up-dated meta-analysis included two recent studies.[13,14] One of these studies predicted an inverse association between high calcium intake and stroke risk when only age and gender were adjusted. These findings are inconsistent with the result of the previous meta-analysis. The previous meta-analyses also suggested a weak positive association between high calcium intakes and stroke risk, but these were based on shorter follow-up periods. In the current study, additional aspects, such as the stroke subtype and years of follow-up were considered. Interestingly, when the follow-up time was sufficiently long, the individuals with high calcium intake were suggested to have reduced risk of stroke. Longitudinal studies with longer follow-up periods are required to verify our results.

There are certain limitations of this study. First, the analysis exhibited a significant heterogeneity among the studies in terms of sample size, duration of observation, number of events, and difference in dietary calcium intake between the groups being compared. As calcium intake is correlated with other healthy lifestyle and dietary factors, it is difficult to completely isolate the effect of calcium intake on stroke risk from other factors. This heterogeneity may lead to a reduced statistical power in detecting a possible association between dietary calcium and stroke. Second, misclassification bias may reduce the strength of the association.[31] Misclassification of dietary calcium intake is inevitable, because the assessment of these factors is based on self-administered questionnaires in most studies. Publication bias is also a concern because our review was based solely on published studies that reported stroke outcomes.[32] However, several reviewed studies reported null findings, suggesting that substantial selective reporting and publication of positive results was unlikely. Nevertheless, the Begg's and Egg's test indicates no evidence of substantial publication bias for the meta-analysis results.

Conclusion

In summary, the results of our meta-analysis indicated that while calcium intake had no apparent effect on stroke risk, dairy calcium intake was inversely associated with stroke risk. Additional large cohort studies particularly performed in special population such as people with hypertension are needed to further elucidate the potential role of calcium intake in the primary prevention of stroke.

AUTHOR DISCLOSURES

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REFERENCES

1. van der Worp HB, van Gijn J. Clinical practice. Acute ischemic stroke. N Engl J Med. 2007;357:572-9. doi: 10.1056/NEJMcp072057.
2. Sherzai A, Heim LT, Boothby C, Sherzai AD. Stroke, food groups, and dietary patterns: a systematic review. Nutr Rev. 2012;70:423-35. doi: 10.1111/j.1753-4887.2012.00490.x.
3. Wang L, Manson JE, Sesso HD. Calcium intake and risk of cardiovascular disease: a review of prospective studies and randomized clinical trials. Am J Cardiovasc Drugs. 2012; 12:105-16. doi: 10.2165/11595400-000000000-00000.
4. Van Leer EM, Seidell JC, Kromhout D. Dietary calcium, potassium, magnesium and blood pressure in the Netherlands. Int J Epidemiol. 1995;24:1117-23.
5. Abbott RD, Curb JD, Rodriguez BL, Sharp DS, Burchfiel CM, Yano K. Effect of dietary calcium and milk consumption on risk of thromboembolic stroke in older middle-aged men. The Honolulu Heart Program. Stroke. 1996;27:813-8.
6. Weng LC, Yeh WT, Bai CH, Chen HJ, Chuang SY, Chang HY, Lin BF, Chen KJ, Pan WH. Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? Stroke. 2008;39:3152-8. doi: 10.1161/strokeaha.108.524934.
7. Umesawa M, Iso H, Ishihara J, Saito I, Kokubo Y, Inoue M, Tsugane S. Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. Stroke. 2008;39:2449-56. doi: 10.1161/strokeaha.107.512236.
8. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation. 1998;98:1198-204.
9. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, Speizer FE, Willett WC. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke. 1999;30:1772-9.
10. Larsson SC, Virtanen MJ, Mars M, Mannisto S, Pietinen P, Albanes D, Virtamo J. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. Arch Intern Med. 2008;168:459-65. doi: 10.1001/archinte.168.5.459.
11. Larsson SC, Virtamo J, Wolk A. Potassium, calcium, and magnesium intakes and risk of stroke in women. Am J Epidemiol. 2011;174:35-43. doi: 10.1093/aje/kwr051.
12. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart. 2012;98:920-5. doi: 10.1136/heartjnl-2011-301345.
13. Sluijs I, Czernichow S, Beulens JW, Boer JM, van der Schouw YT, Verschuren WM, Grobbee DE. Intakes of potassium, magnesium, and calcium and risk of stroke. Stroke. 2014;45:1148-50. doi: 10.1161/strokeaha.113.004032.
14. Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, Taylor EN. Calcium supplement intake and risk of cardiovascular disease in women. Osteoporos Int. 2014; 25:2047-56. doi: 10.1007/s00198-014-2732-3.
15. Koretz RL. Methods of meta-analysis: an analysis. Curr Opin Clin Nutr Metab Care. 2002;5:467-74.
16. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691. doi: 10.1136/bmj.c3691.
17. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040. doi: 10.1136/bmj.d2040.
18. Larsson SC, Orsini N, Wolk A. Dietary calcium intake and risk of stroke: a dose-response meta-analysis. Am J Clin Nutr. 2013;97:951-7. doi: 10.3945/ajcn.112.052449.
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12.
20. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301-9.
21. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J. 2006;6:40-57.
22. Zemel MB. Calcium modulation of hypertension and obesity: mechanisms and implications. J Am Coll Nutr. 2001;20: 428S-35S; discussion 40S-2S.
23. van Mierlo LA, Arends LR, Streppel MT, Zeegers MP, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. J Hum Hypertens. 2006;20:571-80. doi: 10.1038/sj.jhh.1002038.
24. Houston MC, Harper KJ. Potassium, magnesium, and calcium: their role in both the cause and treatment of hypertension. J Clin Hypertens (Greenwich). 2008;10:3-11.
25. Huang LY, Wahlqvist ML, Huang YC, Lee MS. Optimal dairy intake is predicated on total, cardiovascular, and stroke mortalities in a Taiwanese cohort. J Am Coll Nutr. 2014;33:426-36. doi: 10.1080/07315724.2013.875328.
26. Massey LK. Dairy food consumption, blood pressure and stroke. J Nutr. 2001;131:1875-8.
27. Bennett T, Desmond A, Harrington M, McDonagh D, FitzGerald R, Flynn A, Cashman KD. The effect of high intakes of casein and casein phosphopeptide on calcium absorption in the rat. Br J Nutr. 2000;83:673-80.
28. Tsuchita H, Suzuki T, Kuwata T. The effect of casein phosphopeptides on calcium absorption from calcium-fortified milk in growing rats. Br J Nutr. 2001;85:5-10.
29. Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. Eur J Clin Nutr. 2004;58: 718-24. doi: 10.1038/sj.ejcn.1601869.
30. Wang X, Chen H, Ouyang Y, Liu J, Zhao G, Bao W, Yan M. Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies. BMC Med. 2014;12:158. doi: 10.1186/s12916-014-0158-6.
31. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. Am J Epidemiol. 1977;105:488-95.
32. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol. 2000;53:207-16.

Original Article

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钙的摄入与脑卒中风险：一项更新前瞻性研究的荟萃分析

背景与目的：尽管关于钙的摄入与脑卒中发生的关系已有 meta 分析研究，但新的研究结果与之前的分析结果并不一致。乳制品影响脑卒中发生可能与其中的钙摄入有关，因此，我们更新了现有的 meta 分析，以进一步研究摄入钙,尤其是含钙乳制品与脑卒中发生之间的关系。**方法：**利用计算机检索多个数据库中研究钙的摄入与脑卒中发生风险之间的关系的前瞻性队列研究，同时追索纳入文献的参考文献，检索文献自建库至 2014 年 6 月，按照纳入排除标准收集文献，根据 the Newcastle-Ottawa Scale，对纳入文献进行严格的质量评价， 应用 STATA 软件对符合标准的研究进行 meta 分析。**结果：**纳入 10 篇原始文献，共涉及 371495 例研究对象，其中 10408 例患者发生脑卒中。钙摄入的最高剂量范围与最低剂量范围相比，其脑卒中的发生并无显著性差异（RR=0.96; 95% CI: 0.89, 1.04），脑卒中类型的亚组分析结果同样无显著性差异。然而，乳制品中高的钙摄入量与脑卒中的发生风险降低有关（RR=0.76; 95% CI: 0.66, 0.86）。当随访时间大于 14 年时，钙的摄入与脑卒中呈显著负相关（RR=0.77; 95% CI: 0.63, 0.95），在进行剂量相关的 meta 分析时，发现钙摄入与脑卒中的发生风险有着非线性的剂量关系。**结论：**乳制品中的钙摄入较高可降低脑卒中的发生风险。当随访时间足够长时，钙的摄入对于脑卒中的发生是保护性因素，钙的摄入与脑卒中发生风险呈非线性剂量关系。此结果仍需大型队列研究进一步确认。

关键词：卒中、钙摄入、meta 分析、前瞻性队列研究、剂量反应关系