Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies

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ABSTRACT
Background: Prospective studies of dietary magnesium intake in relation to risk of stroke have yielded inconsistent results.
Objective: We conducted a dose-response meta-analysis to summarize the evidence regarding the association between magnesium intake and stroke risk.
Design: Relevant studies were identified by searching PubMed and EMBASE from January 1966 through September 2011 and reviewing reference lists of retrieved articles. We included prospective studies that reported RRs with 95% CIs of stroke for ≥3 categories of magnesium intake. Results from individual studies were combined by using a random-effects model.
Results: Seven prospective studies, with 6477 cases of stroke and 241,378 participants, were eligible for inclusion in the meta-analysis. We observed a modest but statistically significant inverse association between magnesium intake and risk of stroke. An intake increment of 100 mg Mg/d was associated with an 8% reduction in risk of total stroke (combined RR: 0.92; 95% CI: 0.88, 0.97), without heterogeneity among studies (P = 0.66, I² = 0%). Magnesium intake was inversely associated with risk of ischemic stroke (RR: 0.91; 95% CI: 0.87, 0.96) but not intracerebral hemorrhage (RR: 0.96; 95% CI: 0.84, 1.10) or subarachnoid hemorrhage (RR: 1.01; 95% CI: 0.90, 1.14).

INTRODUCTION
Dietary magnesium intake has been inversely associated with risk factors for stroke such as hypertension (1, 2), metabolic syndrome (3), and type 2 diabetes (2, 4). Randomized clinical trials have shown that magnesium supplementation modestly reduces diastolic blood pressure (5) as well as fasting C-peptide and insulin concentrations (6). Furthermore, findings from animal studies have shown that high-magnesium diets have favorable effects on plasma glucose and blood lipid concentrations (7), and magnesium deficiency increases the susceptibility of lipoproteins to peroxidation (8). Hence, a high dietary magnesium intake may potentially reduce risk of stroke.

To our knowledge, the epidemiologic evidence on the relation between dietary magnesium intake and risk of stroke has not yet been summarized. Therefore, we performed a systematic review and dose-response meta-analysis to assess the association between magnesium intake and risk of total stroke and stroke subtypes.

METHODS

Literature search and selection
We followed standard criteria for conducting and reporting of meta-analyses of observational studies (9). We conducted a literature search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.embase.com) from January 1966 through September 2011 by using the key words “magnesium intake” combined with “stroke.” In addition, we reviewed reference lists of retrieved articles to identify additional relevant studies. No language restrictions were imposed.

Studies were included in this meta-analysis if they fulfilled the following criteria: 1) had a prospective design, 2) the exposure of interest was magnesium intake, 3) the outcome was stroke, and 4) the studies reported RRs with 95% CIs for ≥3 quantitative categories of magnesium intake. RRs had to at least be adjusted for age and sex (if applicable).

Data extraction
The following data were extracted from each study: first author’s last name, publication year, name of the cohort study, study location, years of follow-up, sex, age, sample size (number of cases and total number of participants), magnesium intake categories, covariates adjusted for in the multivariable analysis, and RRs with their 95% CIs for each category of magnesium intake. We extracted RRs that reflected the greatest degree of adjustment for potential confounders. Data extraction was conducted independently by 2 investigators (SCL and NO) with disagreements resolved by consensus.

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Statistical analysis

Because the range of magnesium intake and the cutoffs for the categories differed between studies, we estimated an RR with 95% CI for an increase in intake of 100 mg Mg/d for each study. We used the method proposed by Greenland and Longnecker (10) and Orsini et al (11) to compute the trend from the correlated log RR estimates across categories of magnesium intake. For each study, the median or mean magnesium intake for each category was assigned to each corresponding RR. When the median or mean intake per category was not provided, we assigned the midpoint of upper and lower boundaries in each category as the average intake. If the lower or upper boundary for the lowest and highest category, respectively, was not reported, we assumed that the boundary had the same amplitude as the closest category.

To examine a potential nonlinear association between magnesium intake and stroke risk, we performed a 2-stage, random-effects, dose-response meta-analysis. This was done by modeling magnesium intake by using restricted cubic splines with 3 knots at fixed percentiles 10%, 50%, and 90% of the distribution (12). First, a restricted cubic-spline model was estimated by using generalized least-square regression and taking into account the correlation within each set of published RRs as described by Orsini et al (11). Second, we combined the study-specific estimates by using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (13). A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. We showed no significant departure from a linear-response model (P-spline transformation = 0.15).

Statistical heterogeneity among studies was evaluated by using $I^2$ statistics (14). Three cutoffs of these $I^2$ values were considered as follows: <30% (no or marginal between-study heterogeneity), 30–75% (mild heterogeneity), and >75% (notable heterogeneity). We performed analyses stratified by study location and stroke subtypes. Publication bias was assessed with Egger’s regression test (15). All statistical analyses were conducted with Stata software (version 10.1; StataCorp). $P < 0.05$ was considered statistically significant.

RESULTS

Study characteristics

Our literature search identified 7 independent prospective studies of dietary magnesium intake and stroke risk (Figure 1) (2, 3, 16–20). The studies were published between 1998 and 2011 and included a total of 6477 stroke cases and 241,378 participants (Table 1). Four studies were conducted in the United States, 2 studies were conducted in Europe, and one study was conducted in Taiwan. The median magnesium intake in the study populations ranged from 242 mg/d (in US men and women) to 471 mg/d (in Finnish men). All studies provided risk estimates that were adjusted for age, smoking, and BMI. Most studies also controlled for physical activity (6 studies), diabetes (6 studies), history of hypertension or measured blood pressure (6 studies), and alcohol consumption (6 studies); fewer studies adjusted for other nutrients (3 studies).

DISCUSSION

This meta-analysis of 7 prospective studies showed a significant inverse association between dietary magnesium intake and risk of stroke. An increase in intake of 100 mg Mg/d was associated with an 8% and 9% decreased risk of total stroke and ischemic stroke, respectively. Magnesium intake was not associated with hemorrhagic strokes. However, the number of cases was lower for hemorrhagic stroke than for ischemic and total strokes, which led to a lower statistical power to estimate the association between magnesium intake and risk of hemorrhagic stroke.

Rich food sources of magnesium are green leafy vegetables, nuts, beans, and whole grains. The US Recommended Dietary Allowance of magnesium for women and men 31–70 y of age is...
### TABLE 1
Prospective studies of magnesium intake and risk of stroke

<table>
<thead>
<tr>
<th>Study, cohort study name (country)</th>
<th>No. of cases (cohort size)</th>
<th>Years of follow-up</th>
<th>Sex, age</th>
<th>Magnesium intake [RR (95% CI) for highest compared with lowest category of intake]</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascherio et al, 1998 (16), Health Professionals Follow-up Study (United States)</td>
<td>328 total strokes (43,738 nondiabetics)</td>
<td>8</td>
<td>M, 40–75 y</td>
<td>Median: 452 compared with 243 mg/d [0.92 (0.58, 1.46)]</td>
<td>Age, smoking, profession, histories of hypertension and hypercholesterolemia, family history of MI, BMI, physical activity, and intakes of alcohol, dietary fiber, potassium, and total energy</td>
</tr>
<tr>
<td>Iso et al, 1999 (17), Nurses’ Health Study (United States)</td>
<td>690 total strokes, 386 ISs, 74 ICHs, and 129 SHs (85,764)</td>
<td>14</td>
<td>F, 34–59 y</td>
<td>Median: 381 compared with 211 mg/d [0.80 (0.63, 1.01)]</td>
<td>Age, smoking, menopausal status, postmenopausal hormone use, BMI, exercise, histories of diabetes and high cholesterol, aspirin use, multivitamin use, vitamin E use, and intakes of alcohol, omega-3 fatty acids, and calcium</td>
</tr>
<tr>
<td>Song et al, 2005 (3), Women’s Health Study (United States)</td>
<td>368 total strokes (35,601)</td>
<td>10</td>
<td>F, 39–89 y</td>
<td>Median: 433 compared with 255 mg/d [0.90 (0.65, 1.26)]</td>
<td>Age, randomized treatment assignment, smoking, BMI, exercise, postmenopausal hormone use, multivitamin use, histories of diabetes, hypertension, and hypercholesterolemia, family history of MI, intake of alcohol, and total energy</td>
</tr>
<tr>
<td>Larsson et al, 2008 (18), Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Finland)</td>
<td>2702 ISs, 383 ICHs, and 196 SHs (26,556)</td>
<td>13.6</td>
<td>M, 50–69 y</td>
<td>Median: 575 compared with 382 mg/d [0.85 (0.76, 0.97)]</td>
<td>Age, supplementation group, cigarettes smoked daily, BMI, physical activity, systolic and diastolic BP, serum total and HDL cholesterol, histories of diabetes and ischemic heart disease, intake of alcohol, and total energy</td>
</tr>
<tr>
<td>Weng et al, 2008 (19), CardioVascular Disease risk FACtor Two-township Study (Taiwan)</td>
<td>132 ISs (1772)</td>
<td>10.6</td>
<td>M and F, ≥40 y</td>
<td>&gt;282.2 compared with ≤242.6 mg/d [0.68 (0.45, 1.04)]</td>
<td>Age, sex, age × sex, smoking, sex × smoking, area, central obesity, BMI, diabetes, physical activity, hypertension, use of antihypertensive drugs, self-reported heart disease, hypercholesterolemia, hypertriglyceridemia, fibrinogen, apolipoprotein B, plasminogen, and alcohol intake</td>
</tr>
<tr>
<td>Ohira et al, 2009 (2), Atherosclerosis Risk in Communities Study (United States)</td>
<td>577 ISs (13,277)</td>
<td>15</td>
<td>M and F, 45–64 y</td>
<td>&gt;307 compared with &lt;186 mg/d [0.80 (0.75, 1.13)]</td>
<td>Age, sex, center, education, smoking, BMI, diabetes, systolic blood pressure, use of antihypertensive medication, LDL and HDL cholesterol, fibrinogen, von Willebrand factor, and total energy intake</td>
</tr>
<tr>
<td>Larsson et al, 2011 (20), Swedish Mammography Cohort (Sweden)</td>
<td>1680 total strokes, 1310 ISs, 154 ICHs, and 79 SHs (34,670)</td>
<td>10.4</td>
<td>F, 49–83 y</td>
<td>Median: 373 compared with 267 mg/d [1.02 (0.82, 1.27)]</td>
<td>Age, education, smoking, BMI, physical activity, history of diabetes, history of hypertension, aspirin use, family history of myocardial infarction, and intakes of alcohol, protein, cholesterol, total fiber, folate, and total energy</td>
</tr>
</tbody>
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1 BP, blood pressure; ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction; SH, subarachnoid hemorrhage.
There are several potential mechanisms by which magnesium may reduce risk of ischemic stroke. The protective effect of magnesium against risk of stroke may in part be related to its blood pressure–lowering effect. Findings from a meta-analysis of 12 randomized clinical trials (median follow-up: 11 wk) showed that magnesium supplementation (mean dose: ~400 mg/d) may slightly decrease diastolic blood pressure by 2.2 mm Hg (5). Most studies included in this meta-analysis controlled for history of hypertension or blood pressure levels. There may have been overadjustment if the association between magnesium intake and stroke was mediated via a reduction in blood pressure. Magnesium intake has also been inversely associated with risk of type 2 diabetes (2, 4), which is a risk factor for ischemic stroke (23, 24). Therefore, it is possible that type 2 diabetes is a mediator of the association between magnesium intake and ischemic stroke. Moreover, a high-magnesium diet has been shown to have favorable effects on plasma glucose and blood lipid concentrations in rats with chronic diabetes (7). In addition, there are reports that showed that magnesium deficiency increased the susceptibility of lipoproteins to peroxidation in animals (8).

This meta-analysis had several strengths. First, our quantitative assessment was based on data from prospective studies, which eliminated recall and selection biases. Furthermore, by combining results from several studies, we had high statistical power to estimate the relation between magnesium intake and risk of stroke. Also, all studies were very consistent with no heterogeneity among study results. This meta-analysis also had several potential limitations. First, as a meta-analysis of observational studies, the possibility of confounding as a potential explanation for the observed inverse association between magnesium intake and stroke risk could not be excluded. Although the majority of studies adjusted for known risk factors for stroke, such as age, cigarette smoking, BMI, physical activity, histories of diabetes and hypertension, and alcohol consumption, the possibility for residual confounding remained. Moreover, it could not be excluded that other nutrients or dietary components that are correlated with dietary magnesium may have been responsible, partly or in whole, for the observed association. A second limitation was the misclassification of magnesium intake, which would most likely have led to an underestimation of the true relation between magnesium intake and stroke. Finally, in a meta-analysis of published studies, publication bias may be a problem. However, we showed no evidence of publication bias in this meta-analysis.

In conclusion, results from this meta-analysis indicate that dietary magnesium intake is inversely associated with risk of stroke. Although it is premature to recommend magnesium supplementation to reduce risk of stroke, increased consumption of magnesium-rich foods such as green leafy vegetables, beans, nuts, and whole-grain cereals appears to be prudent.

The authors’ responsibilities were as follows—SCL: provided study oversight and wrote and took primary responsibility for the final content of the manuscript; SCL and NO: undertook data collection and performed statistical analyses; and all authors: designed the research, assisted in the interpretation of analyses and revision of the manuscript, and read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES