Plasma levels of magnesium have been inversely associated with risk factors for stroke, such as hypertension\(^1,2\) and diabetes mellitus.\(^3,4\) Plasma magnesium has also been inversely associated with the risk of cardiovascular outcomes, including coronary heart disease\(^5,6\) and atrial fibrillation.\(^7\) Lower magnesium levels may lead to stroke by initiating an inflammatory cascade that triggers oxidative responses in endothelial cells leading to vasoconstriction and thrombus formation,\(^8\) or through effects on hypertension, diabetes mellitus, and atrial fibrillation.

The relationship between serum magnesium and risk of ischemic stroke has been examined in only 1 prospective cohort study.\(^9\) Low serum magnesium levels were associated with a higher risk of ischemic stroke among men and women in the Atherosclerosis Risk in Communities (ARIC) study; men and women in the lowest magnesium quartile had a 25% (95% confidence interval [CI], 5–41%) reduced risk of ischemic stroke in models adjusted for age, sex, and race; however, adjustment for hypertension and diabetes mellitus, which may possibly be biological mediators of the effects of magnesium, eliminated an association.\(^7\) To provide further evidence on this relationship, we prospectively examined the association between plasma magnesium and risk of ischemic stroke and ischemic stroke subtypes (thrombotic and embolic strokes) among women in the Nurses’ Health Study (NHS).

**Background and Purpose**—Lower plasma magnesium levels may be associated with higher blood pressure and endothelial dysfunction, but sparse prospective data are available for stroke.

**Methods**—Among 32,826 participants in the Nurses’ Health Study who provided blood samples in 1989 to 1990, incident ischemic strokes were identified and confirmed by medical records through 2006. We conducted a nested case–control analysis of 459 cases, matched 1:1 to controls on age, race/ethnicity, smoking status, date of blood draw, fasting status, menopausal status, and hormone use. We used conditional logistic regression models to estimate the multivariable adjusted association of plasma magnesium and the risk of ischemic stroke and ischemic stroke subtypes.

**Results**—Median magnesium levels did not differ between ischemic stroke cases and controls (median, 0.86 mmol/L for both; \(P=0.14\)). Conditional on matching factors, women in the lowest magnesium quintile had a relative risk of 1.34 (95% confidence interval, 0.86–2.10; \(P_{\text{trend}}=0.13\)) for total ischemic stroke compared with women in the highest quintile. Additional adjustment for risk factors and confounders did not substantially alter the risk estimates for total ischemic stroke. Women with magnesium levels <0.82 mmol/L had significantly greater risk of total ischemic stroke (multivariable relative risk, 1.57; 95% confidence interval, 1.09–2.27; \(P=0.01\)) and thrombotic stroke (multivariable relative risk, 1.66; 95% confidence interval, 1.03–2.65; \(P=0.03\)) compared with women with magnesium levels ≥0.82 mmol/L. No significant effect modification was observed by age, body mass index, hypertension, or diabetes mellitus.

**Conclusions**—Lower plasma magnesium levels may contribute to higher risk of ischemic stroke among women. (Stroke. 2014;45:2881-2886.)

**Key Words:** ischemic stroke ■ magnesium ■ plasma
We performed a nested case–control study of ischemic stroke among the 32 826 women who provided a blood sample. Cases and controls were both required to be free of cancer or prior cardiovascular disease at the time of blood collection. Incident ischemic stroke cases were matched 1:1 to controls who remained free of stroke before the case date, with matching by age (±2 years), race/ethnicity (white/black/Asian/Hispanic/other/unknown), smoking (never, past, and current), date of blood draw, fasting status, menopausal status, and hormone use (yes/no). This study was approved by the institutional review board at Brigham and Women’s Hospital, and informed consent was obtained from all participants.

**Ascertainment of Plasma Magnesium**

Matched ischemic stroke case–control pairs were shipped to the laboratory in the same batch. Magnesium was measured by colorimetric assay on a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN). The coefficient of variation (CV) for plasma magnesium was 4%, and the intraclass correlation between 2 blood samples collected from the same woman was 0.63 for samples obtained 2 to 3 years apart, and 0.39 for samples obtained 10 years apart. Total cholesterol (CV of 4%), low-density lipoprotein and high-density lipoprotein cholesterol (CV of 4%), C-reactive protein (CV of 2%), and glycosylated hemoglobin (CV of 4%) were measured in the Clinical and Epidemiological Research Laboratory at Children’s Hospital (Boston, MA) for all cases and controls.

**Ascertainment of Stroke**

Women who reported a nonfatal stroke on a follow-up questionnaire were asked for permission to review their medical records. Medical records were reviewed by physicians blinded to the exposure status. Fatal strokes were initially ascertained by reports from relatives or postal authorities and a search of the National Death Index and were then documented by medical records and death certificates.

Strokes were confirmed according to the criteria of the National Survey of Stroke, which requires a constellation of neurological deficits of sudden or rapid onset lasting ≥ 24 hours or until death. Strokes were regarded as incident if they occurred after the date of return of the 1980 questionnaire but before June 2006. Strokes were classified as ischemic because of thrombotic or embolic occlusion of a cerebral artery with imaging data from computed tomography or MRI. 97% of the cases had a computed tomography or MRI. Thrombotic strokes were defined as infarction involving the cortical artery regions in the cerebrum and the cerebellum (cortex and subcortical areas) or the foam, small, and deep areas such as the internal capsule, corona radiate, basal ganglia, and brain stem, without involvement of cortex. Strokes were defined as embolic if evidence of an embolic source was present in the medical record and if imaging studies or neurology consult supported the diagnosis.11 In the setting of incomplete evidence or competing causes where type could not be assigned, the strokes were considered unclassified ischemic stroke.

**Statistical Analyses**

A total of 459 confirmed ischemic stroke cases (303 thrombotic, 129 embolic, and 27 unclassified) and 459 controls had magnesium levels available for analyses. Quintiles of plasma magnesium were created based on the distribution of plasma magnesium among the controls and assigned cases to each quintile based on their plasma magnesium levels. Magnesium levels were also dichotomized (<0.82 versus ≥0.82 mmol/L) to approximate clinically low levels and compare the lowest quintile to all other quintiles. The means and proportions of baseline characteristics, cardiovascular risk factors, and biomarkers across quintiles of plasma magnesium were calculated among the cases and controls; we conducted tests of significance to compare the means and proportions between cases and controls using Mantel–Haenszel and Fisher exact tests.

Multivariable conditional logistic regression was used to examine the association between plasma magnesium and risk of ischemic stroke and ischemic stroke subtypes (thrombotic and embolic strokes). Three multivariable models were created: model 1 was conditional on matching factors only—age, race/ethnicity, smoking, date of blood draw, fasting status, menopausal status, and hormone use; model 2 was adjusted for lifestyle risk factors—alcohol, body mass index, physical activity, aspirin and thiazide diuretic use; model 3 was further adjusted for potential mediators—hemoglobin A1c, history of diabetes mellitus, hypertension, coronary heart disease, and total/high-density lipoprotein cholesterol. For each model, we derived relative risks (RRs) and 95% CIs. Effect modification by age, body mass index, hypertension, and diabetes mellitus was tested and significance of interactions assessed using the likelihood ratio tests. Sensitivity analyses were conducted to calculate adjusted RRs and 95% CIs for measurement error correction in plasma magnesium using samples collected ≥ 10 years apart. We also examined the possibly nonlinear relation between plasma magnesium and ischemic stroke with likelihood ratio tests, comparing the model with only the linear term to the model with the linear and cubic spline terms. All analyses were conducted with SAS for UNIX statistical software (version 9.2; SAS Institute).

**Results**

Among the 459 women who developed ischemic stroke, the mean age at baseline in 1990 was 60.8 years, whereas the

### Table 1. Baseline Characteristics by Case–Control Status in 1990

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=459)</th>
<th>Controls (n=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.8 (6.0)</td>
<td>60.7 (6.0)</td>
</tr>
<tr>
<td>Median magnesium, mmol/L</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9 (5.1)</td>
<td>25.4 (4.8)</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>96.0</td>
<td>97.0</td>
</tr>
<tr>
<td>Blacks, %</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Asian, %</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Other, %</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Smoking*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>42.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Past, %</td>
<td>41.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Current, %</td>
<td>18.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>5.9 (10.8)</td>
<td>5.3 (10.3)</td>
</tr>
<tr>
<td>Physical activity, METs/wk</td>
<td>15.1 (19.6)</td>
<td>16.2 (18.5)</td>
</tr>
<tr>
<td>History of heart disease, %</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>History of high cholesterol, %</td>
<td>48.0</td>
<td>46.0</td>
</tr>
<tr>
<td>History of high blood pressure, %</td>
<td>48.0</td>
<td>34.0</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Hemoglobin A1c ≥6, %</td>
<td>17.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonusers, %</td>
<td>53.0</td>
<td>49.0</td>
</tr>
<tr>
<td>1–5 tab/wk, %</td>
<td>25.0</td>
<td>31.0</td>
</tr>
<tr>
<td>≥6 tab/wk, %</td>
<td>22.0</td>
<td>19.0</td>
</tr>
<tr>
<td>CRP ≥28.5 nmol/L, %</td>
<td>39.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Postmenopausal hormone therapy use,* %</td>
<td>48.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Thiazide diuretics, %</td>
<td>24.0</td>
<td>17.0</td>
</tr>
</tbody>
</table>

Values are mean±SD (except where indicated) or % and are standardized to the age distribution of this study population. CRP indicates C-reactive protein; and MET, metabolic equivalent.

*Matching factors.
mean age at stroke diagnosis was 71 years. The differences between cases and controls in cardiovascular disease risk factors for ischemic stroke are shown in Table 1. Women in the lowest quintile of plasma magnesium were more likely to consume more alcohol, be current smokers, use thiazide diuretics and postmenopausal hormone therapy, and have hypertension and diabetes mellitus compared with women in the highest quintile (Table 2). The median magnesium levels in the lowest and highest quintiles, based on the distribution in controls, were 0.78 and 0.95 mmol/L, respectively. The median magnesium levels did not differ between ischemic stroke cases and controls (0.86 mmol/L in each; \( P=0.14 \)) in univariate analyses.

In models conditional on matching factors (Table 3), there was no significant association between plasma magnesium and risk of total ischemic stroke. The RR and 95% CI for the lowest quintile compared with the highest quintile was 1.34 (0.86–2.10; \( P \text{ trend}=0.13 \)). This risk was similar after adjusting for other lifestyle risk factors (RR, 1.24; 0.78–1.98; \( P \text{ trend}=0.29 \)), including alcohol intake, body mass index, physical activity, aspirin and thiazide diuretics use. When further adjusted for hemoglobin A1c, history of diabetes mellitus, history of hypertension, coronary heart disease, and total/high-density lipoprotein cholesterol, the risk estimates remained similar (RR, 1.34; 0.82–2.17; \( P \text{ trend}=0.19 \)). Next, we examined the association of plasma magnesium with thrombotic and embolic strokes; the RR and 95% CI for the lowest versus highest quintile was 1.63 (0.89–2.98; \( P \text{ trend}=0.09 \)) for thrombotic stroke and 1.12 (0.39–3.19; \( P \text{ trend}=0.72 \)) for embolic stroke in the fully adjusted models.

When magnesium levels were dichotomized comparing the lowest quintile to all other categories, the RR and 95% CI for magnesium levels <0.82 mmol/L compared with those \( \geq 0.82 \) mmol/L was 1.64 (1.17–2.31), conditional on matching factors only (Table 4). When we adjusted for confounding by other lifestyle risk factors, this risk estimate was not substantially altered. In the fully adjusted model (model 3), the RR and 95% CI for total stroke was 1.57 (1.09–2.27). The estimates were similar for thrombotic stroke (RR, 1.66; 95% CI, 1.03–2.65).

### Table 2. Baseline Characteristics by Magnesium Quintiles in 1990

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Range, mmol/L</th>
<th>Cases/controls</th>
<th>Age,* y</th>
<th>Magnesium, mmol/L</th>
<th>Body mass index, kg/m²</th>
<th>Race*</th>
<th>Smoking*</th>
<th>Alcohol, g/d</th>
<th>Physical activity, METs/wk</th>
<th>History of heart disease, %</th>
<th>History of high cholesterol, %</th>
<th>History of high blood pressure, %</th>
<th>History of diabetes mellitus, %</th>
<th>Hemoglobin A1c ≥6, %</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7 to &lt;0.82</td>
<td>106/71</td>
<td>61.4 (5.6)</td>
<td>0.74 (0)</td>
<td>25.9 (5.4)</td>
<td>98.3</td>
<td>41.0</td>
<td>7.8 (12.9)</td>
<td>15.1 (19.8)</td>
<td>5.0</td>
<td>50.0</td>
<td>52.0</td>
<td>13.0</td>
<td>16.0</td>
<td>Nonusers, %</td>
</tr>
<tr>
<td>2</td>
<td>0.82 to &lt;0.86</td>
<td>77/86</td>
<td>61.1 (5.8)</td>
<td>0.82 (0)</td>
<td>25.7 (5.3)</td>
<td>96.0</td>
<td>38.0</td>
<td>5.6 (9.9)</td>
<td>15.1 (16.9)</td>
<td>6.0</td>
<td>46.0</td>
<td>45.0</td>
<td>11.0</td>
<td>18.0</td>
<td>1–5 tab/wk, %</td>
</tr>
<tr>
<td>3</td>
<td>0.86 to &lt;0.90</td>
<td>96/113</td>
<td>60.6 (6.3)</td>
<td>0.86 (0)</td>
<td>25.5 (5.0)</td>
<td>96.1</td>
<td>43.0</td>
<td>4.3 (9.6)</td>
<td>17.1 (20.2)</td>
<td>5.0</td>
<td>44.0</td>
<td>34.0</td>
<td>9.0</td>
<td>11.0</td>
<td>≥6 tab/wk, %</td>
</tr>
<tr>
<td>4</td>
<td>0.90 to &lt;0.95</td>
<td>76/96</td>
<td>60.3 (5.7)</td>
<td>0.92 (0)</td>
<td>25.8 (4.4)</td>
<td>97.0</td>
<td>43.0</td>
<td>5.7 (11.0)</td>
<td>14.0 (16.0)</td>
<td>4.0</td>
<td>46.0</td>
<td>37.0</td>
<td>9.0</td>
<td>13.0</td>
<td>CRP ≥28.5 mmol/L, %</td>
</tr>
<tr>
<td>5</td>
<td>0.95 to 1.15</td>
<td>104/93</td>
<td>61.1 (6.1)</td>
<td>0.99 (0)</td>
<td>25.5 (4.5)</td>
<td>97.0</td>
<td>41.0</td>
<td>5.4 (10.1)</td>
<td>16.9 (21.5)</td>
<td>7.0</td>
<td>51.0</td>
<td>39.0</td>
<td>9.0</td>
<td>12.0</td>
<td>Postmenopausal hormone therapy use,* %</td>
</tr>
</tbody>
</table>

Values are mean±SD or % and are standardized to age distribution of this study population. CRP indicates C-reactive protein; and MET, metabolic equivalent. *Matching factors.
Additional analyses correcting for measurement error did not yield substantially different results. Potential effect modification of the association between plasma magnesium and risk of ischemic stroke by age, body mass index, hypertension, and diabetes mellitus was examined in stratified analysis. No significant effect modification was observed by any of these variables (P > 0.05), but power may be limited.

**Discussion**

In this prospective study, plasma magnesium levels were not associated with the risk of ischemic stroke in women across the full distribution of plasma magnesium. However, women with magnesium levels <0.82 mmol/L had a 57% (95% CI, 9–127%) higher risk of ischemic stroke, and this association remained unchanged after controlling for other factors associated with magnesium levels and stroke risk.

Several cross-sectional and retrospective case–control studies have observed that serum magnesium levels are lower in individuals with acute stroke compared with healthy controls. However, in these studies, magnesium was not measured before stroke diagnosis and thus hypomagnesemia may have been a consequence rather than a cause of stroke in these patients. Nonetheless, magnesium may influence stroke severity and outcome; individuals with lower magnesium levels had worse poststroke prognosis. Early data from a small randomized clinical trial suggested a benefit of intravenous magnesium on acute stroke prognosis and outcome, but results from the Intravenous Magnesium Efficacy in Stroke trial as well as preliminary results from the Field Administration of Stroke Therapy–Magnesium trial presented at the 2014 American Stroke Association’s International Stroke Conference failed to show any clinical benefit of intravenous magnesium infusion on stroke outcomes in the acute stroke setting.

To the best of our knowledge, only 1 other prospective study has examined magnesium levels and risk of ischemic stroke. In the ARIC study based on 577 ischemic stroke cases in men and women with 16 years of follow-up, serum magnesium levels were inversely associated with ischemic stroke incidence. However, adjustment for hypertension and diabetes mellitus attenuated risk ratios to nonsignificant levels (RR comparing high to low serum magnesium quartiles, 1.04; 95% CI, 0.82–1.32; P = 0.99), suggesting that these factors may have mediated the association. In our study, we found increased risk of ischemic stroke among women with lower magnesium levels, even after controlling for hypertension and diabetes mellitus. The difference between our findings and those of ARIC may be explained by differences in the populations. The ARIC study included white and black men and women who had a mean age of 54 years at baseline, whereas our study population consisted of only female nurses who were predominantly white with a mean age of ≈60 years at baseline.

Furthermore, our data are generally in accordance with the findings on dietary magnesium, although the correlation between dietary and plasma levels is poor (r = 0.02). In a meta-analysis of 7 prospective studies, dietary magnesium intake was inversely associated with the risk of stroke; an increase in intake of 100 mg per day was associated with a 9% significant reduction in risk of ischemic stroke. Magnesium-rich foods such as green leafy vegetables, whole grains, and coffee have also been associated with reduced risk of ischemic stroke in the NHS and other cohorts.

The best method of ascertaining magnesium status remains unclear. Plasma magnesium accounts for only 1% of...
whole-body magnesium concentration\textsuperscript{24} but has been shown to be fairly strongly correlated with intracellular free magnesium levels ($r=0.54$).\textsuperscript{23} Because magnesium is under tight homeostatic control, dietary magnesium may be a poor estimate of biologically active magnesium; thus, plasma magnesium may be a better exposure to estimate the true association between magnesium and stroke.

Several potential mechanisms may mediate a reduced risk of ischemic stroke by magnesium. Hypertension and diabetes mellitus, known risk factors for stroke, were inversely associated with plasma levels of magnesium.\textsuperscript{2} In experimental studies, increased plasma magnesium levels appeared to reduce blood pressure by blocking calcium channels, thus attenuating agonist-induced vasoconstriction, decreasing vascular resistance, and increasing the capacitance function of cerebral arteries.\textsuperscript{26–29} High magnesium levels have been shown to have beneficial effects on insulin resistance, glucose metabolism, and risk of type 2 diabetes mellitus.\textsuperscript{30} A small randomized clinical trial showed that magnesium supplementation (500 mg magnesium citrate daily for 4 weeks) was associated with reduced insulin concentrations.$^{31}$

In addition, magnesium has been shown to inhibit arterial thrombus formation in animal studies\textsuperscript{32,33}; thus, low plasma magnesium levels may be associated with the risk of thrombus formation in humans. In previous studies, serum magnesium levels were inversely associated with von Willebrand factor levels,\textsuperscript{3} and von Willebrand factor levels were positively associated with the incidence of ischemic stroke.\textsuperscript{34} Although low levels of serum magnesium have been associated with higher risk of atrial fibrillation,\textsuperscript{7,35} which is a potent risk factor for embolic stroke,\textsuperscript{8} our study was underpowered to evaluate the hypothesis of an antiarhythmic effect of magnesium as a potential pathway for reducing the risk of ischemic stroke.

This study has several strengths, including its nested case–control design, prospectively collected blood samples, and careful stroke outcome assessment based on medical records. However, the study is limited by using a single assessment of plasma magnesium at baseline to examine the relationship between plasma magnesium and ischemic stroke, and there may be substantial variation in levels over time; only a modest intraclass correlation between 2 plasma sample measurements 10 years apart was observed ($r=0.39$). Furthermore, we studied a population of women who were predominantly white; therefore, our results may not be generalizable to men or other racial and ethnic groups.

In conclusion, the results of this study suggest that low plasma magnesium may be associated with increased risk of ischemic stroke. If confirmed, our findings may have significant public health impact because magnesium deficiency is potentially modifiable.

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**Disclosures**

None.

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Plasma Magnesium and Risk of Ischemic Stroke Among Women
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