Dietary Potassium Intake and Risk of Stroke
A Dose–Response Meta-Analysis of Prospective Studies

Susanna C. Larsson, PhD; Nicola Orsini, PhD; Alicja Wolk, DrMSc

Background and Purpose—Potassium intake has been inconsistently associated with risk of stroke. Our aim was to conduct a meta-analysis of prospective studies to assess the relation between potassium intake and stroke risk.

Methods—Pertinent studies were identified by a search of PubMed from January 1966 through March 2011 and by reviewing the reference lists of retrieved articles. We included prospective studies that reported relative risks with 95% CIs of stroke for ≥3 categories of potassium intake or for potassium intake analyzed as a continuous variable. Study-specific results were pooled using a random-effects model.

Results—Ten independent prospective studies, with a total of 8695 stroke cases and 268,276 participants, were included in the meta-analysis. We observed a statistically significant inverse association between potassium intake and risk of stroke. For every 1000-mg/day increase in potassium intake, the risk of stroke decreased by 11% (pooled relative risk, 0.89; 95% CI, 0.83 to 0.97). In the 5 studies that reported results for stroke subtypes, the pooled relative risks were 0.89 (95% CI, 0.81 to 0.97) for ischemic stroke, 0.95 (95% CI, 0.83 to 1.09) for intracerebral hemorrhage, and 1.08 (95% CI, 0.92 to 1.27) for subarachnoid hemorrhage.

Conclusions—Dietary potassium intake is inversely associated with risk of stroke, in particular ischemic stroke. (Stroke. 2011;42:2746-2750.)

Key Words: diet ■ epidemiology ■ minerals ■ population ■ potassium ■ prospective studies ■ stroke

Hypertension is an important modifiable risk factor for stroke.1 Several dietary factors can affect blood pressure and hence the risk of stroke. Well-established nutritional modifications that lower blood pressure are weight loss, reduced dietary intake of sodium chloride (salt), and moderation of alcohol consumption.2 Evidence also indicates that increased potassium intake may reduce blood pressure.2,3 Meta-analyses of randomized controlled trials indicate that supplementation with potassium alone or in combination with calcium and/or magnesium leads to a small reduction in blood pressure.3,5

A recent meta-analysis that combined the results from 9 observational studies of potassium intake and risk of stroke found a pooled relative risk of total stroke of 0.79 (95% CI, 0.68 to 0.90) for the highest versus lowest category of potassium intake (7 studies) or for an increase of potassium intake of 10 mmol/day (1 study) or 800 mg/day (1 study).6 Potassium intake in the highest and lowest categories differed substantially between studies, which makes it difficult to interpret the summary estimate based on results from study populations with different ranges of potassium intake. A more robust method to combine results from individual studies is to derive a summary relative risk for a standardized increase in potassium intake.

A dose–response meta-analysis provides a solution to the problem with different ranges of potassium intake in different populations and would better quantify the relationship between potassium intake and stroke. To quantify the potential association between potassium intake and stroke risk, we conducted a dose–response meta-analysis of prospective studies. Because the etiology of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage is known to differ,7 we performed a stratified analysis by stroke subtypes.

Methods

Literature Search and Selection

We followed standard criteria for conducting and reporting of meta-analyses of observational studies.8 We performed a literature search from January 1966 through March 2011 using the PubMed database with the key words potassium intake combined with stroke. The search was limited to studies in humans. Furthermore, the reference lists of retrieved articles were scrutinized to identify additional relevant studies. No language restrictions were imposed.

Studies were eligible for inclusion in this meta-analysis if they met the following inclusion criteria: (1) had a prospective design; (2) the exposure of interest was potassium intake; (3) the outcome was nonfatal and/or fatal stroke; and (4) they reported relative risks (RRs) and 95% CIs for at least 3 quantitative categories of potassium intake. The RRs had to be adjusted for at least age and sex (if applicable).

Data Extraction

The following data were extracted from each study: the first author’s last name, publication year, the name of the cohort study, study
Statistical Analysis

Because the range of potassium intake and the cut points for the categories differed between studies, we estimated for each study a RR with 95% CI for a 1000-mg/day increase of potassium intake. We used the method proposed by Greenland and Longnecker and Orsini et al. to compute the trend from the correlated log RR estimates across categories of potassium intake. For every study, the median or mean potassium intake for each category was assigned to each corresponding RR. When the median or mean intake per category was not provided in the article, we assigned the midpoint of the 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. When results for potassium intake were reported as a continuous variable (eg, for 1-SD increase in intake), we rescaled the RR to a 1000-mg/day increase in intake.

To examine a potential nonlinear relationship between potassium intake and stroke risk, we performed a 2-stage random-effects dose–response meta-analysis. This was done by modeling potassium intake using restricted cubic splines with 3 knots at fixed percentiles 10%, 50%, and 90% of the distribution. At the first stage, a restricted cubic spline model was estimated using generalized least square regression taking into account the correlation within each set of published RRs as described by Orsini et al. At the second stage, we combined the study-specific estimates using the restricted maximum likelihood method in a multivariate random-effects meta-analysis. A probability value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0.

Statistical heterogeneity among studies was assessed using the I^2 statistic. Two cut points of these I^2 values were considered: <30% (no or marginal between-study heterogeneity), 30% to 75% (mild heterogeneity), and >75% (notable heterogeneity). We conducted analyses stratified by study location, sex, follow-up time, and stroke subtypes. Publication bias was evaluated with the Egger regression test. All statistical analyses were conducted with Stata (StataCorp, College Station, TX). Probability values <.05 were considered statistically significant.

Results

Study Characteristics

Our literature search identified 107 articles in humans of which 94 were excluded after review of title or abstract (Figure 1). Thirteen full-text articles were reviewed. We excluded 1 study because a RR was reported only for the highest versus the lowest tertile of potassium intake. Another study was excluded because no RRs were reported. We further excluded 1 study that assessed the association between urinary potassium excretion and risk of total cardiovascular disease. Thus, the meta-analysis included 10 independent prospective studies published between 1987 and 2011 (Table). Combined, these studies had a total of 8695 stroke cases and 268 276 study participants. Five studies were conducted in the United States, 3 in Europe, 1 in Japan, and 1 in Taiwan. Most studies provided RRs that were adjusted for age (all 10 studies), smoking (9 studies), alcohol consumption (8 studies), body mass index (8 studies), history of diabetes (8 studies), history of hypertension or measured blood pressure (8 studies), physical activity (7 studies), and other nutrients (6 studies).

Potassium Intake and Stroke

We found no evidence of a nonlinear relationship between potassium intake and risk of stroke (P for nonlinearity=0.35). The estimated RRs of total stroke for an increment in potassium intake of 1000 mg/day for each study and the pooled RR are shown in Figure 2. The pooled RR of total stroke for each 1000-mg/day increase in potassium intake was 0.89 (95% CI, 0.83 to 0.97) with mild heterogeneity among studies (P=0.03, I^2=50.8%). In a sensitivity analysis, we found that the study by Khaw et al accounted for the observed heterogeneity. When that study was omitted, the pooled RR was 0.91 (95% CI, 0.86 to 0.96) with marginal between-study heterogeneity (P=0.25, I^2=20.7%). The dose–response relation between potassium intake and risk of stroke is presented in Figure 3. In this analysis, the 2 studies that provided a RR for potassium intake analyzed as a continuous variable could not be included. Egger regression test showed no significant asymmetry of the funnel plot (P=0.14), indicating no evidence of substantial publication bias.

When we restricted the analysis to the 6 studies that adjusted for other nutrients, the pooled RR of total stroke for each 1000-mg/day increase in potassium intake was 0.90 (95% CI, 0.83 to 0.97). The association between potassium intake and risk of stroke was similar in men (RR, 0.87; 95% CI, 0.73 to 1.05), women (RR, 0.81; 95% CI, 0.58 to 1.14), and in studies of men and women combined (RR, 0.90; 95% CI, 0.80 to 1.01). The pooled RRs of stroke for a 1000-mg/day increment in potassium intake were 0.88 (95% CI, 0.77 to 1.02) in studies conducted in the United States, 0.93 (95% CI, 0.88 to 0.98) in European studies, and 0.77 (95% CI, 0.57 to 1.06) in Asian studies. The association between potassium intake and stroke was similar in studies with <10 years of follow-up (RR, 0.86; 95% CI, 0.72 to 1.03).
## Table. Prospective Studies of Potassium Intake and Risk of Stroke

<table>
<thead>
<tr>
<th>Source, Cohort Study (Country)</th>
<th>No. of Cases (Cohort Size)</th>
<th>Follow-up, y</th>
<th>Sex and Age, y</th>
<th>RR (95% CI) for Highest vs Lowest Category of Potassium Intake, mg/d</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khaw et al, 1987,15 NA (USA)</td>
<td>24 total strokes (deaths) (859)</td>
<td>12</td>
<td>Men and women 50–79</td>
<td>390-mg/d increase in intake: RR, 0.65 (95% CI, 0.41–1.00) in men and RR, 0.56 (95% CI, 0.38–0.82) in women</td>
<td>Age, systolic blood pressure, serum cholesterol, fasting plasma glucose, obesity, smoking</td>
</tr>
<tr>
<td>Ascherio et al, 1998,17 Health Professionals Follow-up Study (USA)</td>
<td>328 total strokes (43 738)</td>
<td>8</td>
<td>Men 40–75</td>
<td>4300 vs 2400 (median intake): RR, 0.69 (95% CI, 0.45–1.07)</td>
<td>Age, smoking, profession, histories of hypertension and hypercholesterolemia, family history of MI, BMI, physical activity, intake of alcohol, dietary fiber, magnesium, and total energy</td>
</tr>
<tr>
<td>Iso et al, 1999,18 Nurses’ Health Study (USA)</td>
<td>690 total strokes, 386 IS, 74 ICH, 129 SH (85 764)</td>
<td>14</td>
<td>Women 34–59</td>
<td>3555 vs 2017 (median intake): RR, 0.87 (95% CI, 0.58–1.30)</td>
<td>Age, smoking, menopausal status, postmenopausal hormone use, BMI, exercise, histories of diabetes and high cholesterol, aspirin use, multivitamin use, vitamin E use, intake of alcohol, omega-3 fatty acids, and calcium</td>
</tr>
<tr>
<td>Bazzano et al, 2001,20 NHANES I Epidemiologic Follow-Up Study (USA)</td>
<td>927 total strokes (9805)</td>
<td>19</td>
<td>Men and women 25–74</td>
<td>3030 vs 1053* (median intake): RR, 0.76 (95% CI, 0.58–1.01)</td>
<td>Age, race, sex, education, smoking, serum cholesterol, systolic BP, BMI, diabetes, physical activity, vitamin supplement use, intake of alcohol, saturated fat, cholesterol, sodium, calcium, dietary fiber, vitamin C, and vitamin A</td>
</tr>
<tr>
<td>Green et al, 2002,21 Cardiovascular Health Study (USA)</td>
<td>473 total strokes (4934)</td>
<td>4–8</td>
<td>Men and women &gt;65</td>
<td>4510 vs 2060 (median intake): nonusers of diuretics, RR, 0.57 (95% CI, 0.39–0.83); users of diuretics, RR, 1.15 (95% CI, 0.71–1.85)</td>
<td>Age, sex, history of diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, systolic BP, serum creatinine, and potassium supplement use</td>
</tr>
<tr>
<td>Geleijnse et al, 2007,22 Rotterdam Study (The Netherlands)</td>
<td>181 total strokes (1448)</td>
<td>5</td>
<td>Men and women ≥50</td>
<td>800-mg/d increase in intake: RR, 1.02 (95% CI, 0.71–1.46)</td>
<td>Age, sex, education, smoking, BMI, diabetes, use of diuretics, intake of total energy, alcohol, calcium, saturated fat, and 24-h urinary sodium excretion</td>
</tr>
<tr>
<td>Larsson et al, 2008,23 Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Finland)</td>
<td>2702 IS, 383 ICH, 196 SH (26 556)</td>
<td>13.6</td>
<td>Men 50–69</td>
<td>5859 mg/d vs 3912 mg/d (median intake): IS, RR, 0.92 (95% CI, 0.81–1.04); ICH, RR, 0.87 (95% CI, 0.62–1.21); SH, RR, 1.35 (95% CI, 0.86–2.11)</td>
<td>Age, supplementation group, cigarettes smoked daily, BMI, systolic and diastolic BP, serum total and HDL cholesterol, histories of diabetes and coronary heart disease, physical activity, intake of alcohol, and total energy</td>
</tr>
<tr>
<td>Umesawa et al, 2008,24 Japan Collaborative Cohort Study (Japan)</td>
<td>986 total strokes (deaths), 510 IS, 227 ICH, and 153 SH (58 730)</td>
<td>12.7</td>
<td>Men and women 40–79</td>
<td>2652 vs 1365* (median intake): RR, 0.83 (95% CI, 0.60–1.14)</td>
<td>Age, sex, education, BMI, smoking, histories of hypertension and diabetes, menopause, hormone replacement therapy, sports activity, walking, perceived mental stress, intake of alcohol, calcium, and sodium</td>
</tr>
<tr>
<td>Weng et al, 2008,25 CardioVascular Disease risk FACTor Two-township Study (Taiwan)</td>
<td>132 IS (1772)</td>
<td>10.6</td>
<td>Men and women ≥40</td>
<td>&gt;3150 vs &lt;2555, RR, 0.59 (95% CI, 0.39–0.89)</td>
<td>Age, sex, age<em>sex, area, hypertension, use of anthypertensive drugs, diabetes mellitus, central obesity, BMI, alcohol, smoking, sex</em>smoking, self-report heart disease, hypercholesterolemia, hypertriglyceridemia, physical activity, fibrinogen, apolipoprotein B, and plasminogen</td>
</tr>
<tr>
<td>Larsson et al, 2011,27 Swedish Mammography Cohort Study (Sweden)</td>
<td>1680 total strokes, 1310 IS, 154 ICH, and 79 SH (34 670)</td>
<td>10.4</td>
<td>Women 49–83</td>
<td>3744 mg/d vs 2419 mg/d (median intake): RR, 0.89 (95% CI, 0.72–1.10)</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>
</table>

RR indicates relative risk; NA, not available; NHANES, National Health and Nutrition Examination Survey; IS, ischemic stroke; ICH, intracerebral hemorrhage; SH, subarachnoid hemorrhage; MI, myocardial infarction; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; CI, confidence interval.

*Potassium intake in mg/d was calculated by multiplying the reported daily intake in mmol by 39.

0.69 to 1.08) and in studies with ≥10 years of follow-up (RR, 0.92; 95% CI, 0.88 to 0.96).

Five studies provided results for stroke subtypes,18,23,24,26,27 For those studies, the pooled RRs for a 1000-mg/day increase in potassium intake were 0.89 (95% CI, 0.81 to 0.97) for ischemic stroke, 0.95 (95% CI, 0.83 to 1.09) for intracerebral hemorrhage, and 1.08 (95% CI, 0.92 to 1.27) for subarachnoid hemorrhage.

**Discussion**

Findings from this meta-analysis of 10 prospective studies indicate a statistically significant inverse association between
potassium intake and risk of stroke. An increment of 1000 mg/day in potassium intake was associated with an 11% decreased risk of total stroke and ischemic stroke. Potassium intake was not associated with hemorrhagic strokes. The association was similar in studies conducted in the United States, Europe, and Asia.

Rich food sources of potassium include fruits, vegetables, root vegetables, legumes, and dairy foods. The US recommended daily allowance of potassium for adults is 4700 mg/day.28 The approximate potassium content of some foods are 420 mg in 1 medium banana, 470 mg in 1 cup of orange juice, 800 mg in 1 cup of tomato sauce, 610 mg in 1 baked potato, 360 mg in 0.5 cups of cooked kidney beans, 380 mg in 1 cup of nonfat milk, and 580 mg in an 8-oz container of low-fat yogurt.28

The inverse association between potassium intake and stroke risk appeared to be limited to ischemic stroke. If the potential protective effect of potassium on stroke risk was mediated by a reduction in blood pressure, potassium intake would be expected to reduce the risk also of hemorrhagic stroke. Hence, it appears that the effect of potassium on ischemic stroke might be based at least in part on different mechanisms. Studies in animals have shown that high-potassium diets suppress the formation of free radicals29–31 and may have a protective effect against endothelial dysfunction.32 Furthermore, increased dietary potassium has been shown to inhibit vascular smooth muscle cell proliferation in vitro.33

A strength of this meta-analysis is the prospective design of included studies, which should eliminate selection bias and recall bias that could be of concern in retrospective case-control studies. There are also several potential limitations. First, because of the observational design, the possibility that other factors may account for the observed association cannot be ruled out. However, most studies in this meta-analysis adjusted for potential confounders, including age, smoking, body mass index, physical activity, histories of diabetes and hypertension, alcohol consumption, and other nutrients. Potassium-rich fruits and vegetables are also rich in other nutrients such as vitamin C, folate, magnesium, carotenoids, and dietary fiber that may have an effect on stroke risk. The inverse association between potassium intake and risk of stroke persisted when we restricted the analysis to studies that adjusted for other nutrients. One study that reported results for the association between potassium supplement use and stroke found that potassium supplement use was strongly inversely associated with stroke after adjustment for history of hypertension (RR, 0.55; 95% CI, 0.35 to 0.86).17 This finding provides further support for the fact that potassium intake and not other nutrients explains the observed finding in this meta-analysis. A second limitation is misclassification of potassium intake, which would most likely lead to an underestimation of the true association between potassium intake
and stroke risk. Third, in a meta-analysis of published studies, publication bias could be of concern. Nevertheless, we found no evidence of publication bias in the present meta-analysis.

In summary, this meta-analysis found a significant inverse association between potassium intake and risk of stroke. Future studies should attempt to assess whether this association is causal and whether the association differs by stroke subtypes.

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Disclosures

None.

References


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Abstract 1

кал럼 섭취와 뇌졸중 위험
전향적 연구들의 용량반응 메타분석

Dietary Potassium Intake and Risk of Stroke
A Dose–Response Meta-Analysis of Prospective Studies
Susanna C. Larsson, PhD; Nicola Orsini, PhD; Alicja Wolk, DrMSc
(Stroke. 2011;42:2746-2750.)

Key Words: diet ■ epidemiology ■ minerals ■ population ■ potassium ■ prospective studies ■ stroke

배경과 목적
칼륨(potassium) 섭취와 뇌졸중 위험의 관계성에 대한 연구가 많았다. 건강과 칼륨 섭취와 뇌졸중 위험과의 관계를 평가하기 위해 전향적 연구들에 대한 메타분석을 수행하였다.

방법
관련 연구는 1966년 1월부터 2011년 3월까지의 PubMed 검색과 검색된 논문들의 참조 목록을 검토하여 확인되었다. 3개 이상의 칼륨 섭취 병주 또는 연속 변수로 분석된 칼륨 섭취의 뇌졸중 상대위험도와 95% CI를 보고한 전향적 연구를 포함하였다. 연구 특정(study-specific) 결과는 무작위 효과 모형(random-effects model)을 사용하여 통합하였다.

결과
10개의 독립적인 전향적 연구에서 총 8,695건의 뇌졸중과 268,276명의 참여자가 메타분석에 포함되었다. 칼륨 섭취와 뇌졸중 위험 간에 통계적으로 유의한 역의 상관 관계가 있음을 관찰하였다. 하루 1,000 mg의 칼륨 섭취 증가당 뇌졸중 위험은 11% (동일 RR, 0.89: 95% CI, 0.83~0.97) 감소하였다. 뇌졸중 발생에 따른 결과를 보고한 5개의 연구에서 동일 RR은 허혈뇌졸중(ischemic stroke)에 대해 0.89 (95% CI, 0.81~0.97), 뇌내출혈(intracerebral hemorrhage)에 대해 0.95 (95% CI, 0.83~1.09), 거미막하출혈(subarachnoid hemorrhage)에 대해 1.08 (95% CI, 0.92~1.27)이었다.

결론
칼륨 섭취는 뇌졸중, 특히 허혈뇌졸중의 위험과 역의 관련성을 보였다.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Sex</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khaw</td>
<td>1987</td>
<td>MW</td>
<td>0.27 (0.12, 0.60)</td>
</tr>
<tr>
<td>Ascherio</td>
<td>1998</td>
<td>M</td>
<td>0.83 (0.67, 1.03)</td>
</tr>
<tr>
<td>Iso</td>
<td>1999</td>
<td>W</td>
<td>0.95 (0.75, 1.21)</td>
</tr>
<tr>
<td>Bazzano</td>
<td>2001</td>
<td>MW</td>
<td>0.89 (0.79, 1.01)</td>
</tr>
<tr>
<td>Green</td>
<td>2002</td>
<td>MW*</td>
<td>1.10 (0.92, 1.31)</td>
</tr>
<tr>
<td>Green</td>
<td>2002</td>
<td>MW</td>
<td>0.83 (0.72, 0.96)</td>
</tr>
<tr>
<td>Geleijnse</td>
<td>2007</td>
<td>MW</td>
<td>1.03 (0.85, 1.21)</td>
</tr>
<tr>
<td>Larsson</td>
<td>2008</td>
<td>M</td>
<td>0.93 (0.88, 0.99)</td>
</tr>
<tr>
<td>Wong</td>
<td>2008</td>
<td>MW</td>
<td>0.64 (0.45, 0.91)</td>
</tr>
<tr>
<td>Umesawa</td>
<td>2008</td>
<td>MW</td>
<td>0.89 (0.70, 1.11)</td>
</tr>
<tr>
<td>Larsson</td>
<td>2011</td>
<td>W</td>
<td>0.91 (0.78, 1.05)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.89 (0.83, 0.96)</td>
</tr>
</tbody>
</table>

Figure 2. Relative risks of total stroke for an increment of 1000 mg/day in potassium intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs. Tests for heterogeneity: Q=20.32; P=0.03; I²=50.8%. *The study by Green et al21 provided separate results for users of diuretics (first estimate) and for nonusers of diuretics (second estimate).