Dietary Potassium Intake and Risk of Stroke in US Men and Women
National Health and Nutrition Examination Survey I
Epidemiologic Follow-Up Study

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Background and Purpose—The few prospective studies that have explored the association between dietary intake of potassium and risk of stroke have reported inconsistent findings. This study examines the relationship between dietary potassium intake and the risk of stroke in a representative sample of the US general population.

Methods—Study participants included 9805 US men and women who participated in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-Up Study. Dietary potassium and total energy intake were estimated at baseline by using a 24-hour dietary recall. Incidence data for stroke and coronary heart disease were obtained from medical records and death certificates.

Results—Over an average of 19 years of follow up, 927 stroke events and 1847 coronary heart disease events were documented. Overall, stroke hazard was significantly different among quartiles of potassium intake (likelihood ratio \( P = 0.03 \)); however, a test of linear trend across quartiles did not reach a customary level of statistical significance \((P = 0.14)\). Participants consuming a low potassium diet at baseline (<34.6 mmol potassium per day) experienced a 28% higher hazard of stroke (hazard ratio 1.28, 95% CI 1.11 to 1.47; \( P < 0.001 \)) than other participants, after adjustment for established cardiovascular disease risk factors.

Conclusions—These findings suggest that low dietary potassium intake is associated with an increased risk of stroke. However, the possibility that the association is due to residual confounding cannot be entirely ruled out in this observational study. (\textit{Stroke}. 2001;32:1473-1480.)

Key Words: cardiovascular diseases ■ cerebrovascular disorders ■ potassium, dietary ■ prospective study

Observational epidemiological studies have identified an inverse association between dietary intake of potassium and blood pressure level within and across populations.\(^1\) In addition, randomized controlled trials have documented that potassium supplementation lowers blood pressure in both hypertensive and normotensive persons.\(^2\) Some studies have indicated that potassium supplementation to lower blood pressure may be more effective in persons consuming a low potassium diet.\(^3\) Clinical trials have also shown that a low dietary potassium intake increases blood pressure.\(^4\) Given that blood pressure level is a strong risk factor for cardiovascular disease, particularly stroke, dietary potassium intake may be inversely related to the risk of cardiovascular disease via blood pressure.

To date, the relationship between dietary potassium and risk of stroke has been examined in only a few prospective studies. In a population of 859 male and female retirees in Southern California, Khaw and Barrett-Conner\(^5\) identified an inverse association between potassium intake and stroke mortality. Ascherio et al\(^6\) documented an inverse relationship between the risk of stroke and dietary potassium intake in a cohort of 43,738 male health professionals. However, data from the Honolulu Heart Study did not support an inverse association between dietary potassium intake and the risk of stroke.\(^7\) On the other hand, animal experiments tend to support the independent role of potassium in reducing the risk of stroke.\(^8\)

We took advantage of the large sample size, prolonged follow-up, and national representation of the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study (NHEFS) to examine the relationship between a low dietary potassium intake and the risk of stroke and coronary heart disease.
Subjects and Methods

Study Population

The first National Health and Nutrition Examination Survey (NHANES I) used a multistage, stratified, probability sampling design to select a representative sample of the US civilian noninstitutionalized population aged 1 to 74 years.9–10 Certain population subgroups, including those with a low income, women of childbearing age (25 to 44 years), and elderly persons (aged ≥65 years) were oversampled. The NHANES is a prospective cohort study of NHANES I participants who were aged 25 to 74 years at their baseline examinations between 1971 and 1975. Of the 14 407 persons in this age range at baseline, we excluded 1353 who had a self-reported history of heart attack, heart failure, or stroke at baseline or had used medication for heart disease during the 6 months preceding their baseline examinations, and we also excluded 2849 NHANES I Augmentation Survey participants for whom the study protocol did not include the administration of a 24-hour dietary recall. Among the remaining participants, 400 (3.9%) were lost to follow-up, leaving a total of 9805 participants who contributed 161 971 person-years of experience to this analysis.

Measurements

Baseline data collection included a medical history, standardized medical examination, dietary assessment, laboratory tests, and anthropometric measurements.9,10 A single 24-hour dietary recall was conducted by trained NHANES I personnel with a minimum of a bachelor’s degree in nutrition; a standardized protocol and fifty-one 3D models to estimate portion size were used. The dietary recall questionnaires were coded by interviewers using nutrient information from the US Department of Agriculture Handbook No. 8 or other resources. Dietary intakes of saturated fat, cholesterol, sodium, potassium, calcium, vitamin C, vitamin A, and total energy were calculated for each participant by the National Center for Health Statistics. Dietary fiber intake was calculated by using food composition information from ESHA Food Processor software.11 Frozen sera were sent to the Centers for Disease Control and Prevention for measurement of total serum cholesterol levels. Blood pressure, body weight, and height were obtained by use of standard methods.9

Dietary potassium intake was calculated by using the Kaplan-Meier method,20 and differences in incidence of coronary heart disease by quartile of potassium intake was conducted by using orthogonal coefficients. The cumulative incidence of coronary heart disease by quartile of potassium intake was calculated by using the Kaplan-Meier method,20 and differences in cumulative rates were examined by using the log-rank test.21 Because the risk of stroke was similar among the upper 3 quartiles of potassium intake and significantly higher in the lowest quartile of potassium intake, the risk of stroke in the lowest quartile was compared with that in the upper 3 quartiles combined. Cox proportional hazards models were used to explore the relationship between dietary potassium intake and coronary heart disease risk.22 Age was used as the time scale for all time-to-event analyses.23 Data from the participants who had reached ≥85 years were censored because of the small number of participants surviving in each quartile at that age. All Cox proportional hazards models were stratified by birth cohort, with 10-year intervals used to control for calendar period and cohort effects. The proportional hazards assumption was verified by using time-dependent interaction terms.24 Methods to estimate variances that take into account the sample clustering and stratification of the NHANES I sample were used in all Cox proportional hazards models.25

Results

The baseline characteristics of study participants are presented by quartile of dietary potassium intake in Table 1. Participants in the lower 2 quartiles of potassium intake tended to be slightly older and were less often white or male than their counterparts with higher potassium intake. Additionally, compared with participants with greater dietary potassium intake, those with a lower potassium intake tended to have higher mean systolic and diastolic blood pressures, a higher prevalence of hypertension and hypercholesterolemia, and a higher mean body mass index. Compared with participants with higher potassium intake, those with lower intake were also less physically active and less likely to have completed high school, to drink regularly, or to smoke. On average, compared with persons in the lower quartiles of potassium intake, persons in the upper quartiles of potassium intake consumed more total energy, saturated fat, cholesterol, fiber, sodium, calcium, vitamin A, and vitamin C.

During 161 971 person-years of follow up from 1971 through 1992, 927 stroke events and 1847 coronary heart disease events were documented. Hazard ratios (HRs) and 95% CIs for stroke and coronary heart disease according to quartile of potassium intake are presented in Table 2. Overall, stroke hazard was significantly different among quartiles of potassium intake (likelihood ratio P=0.03); however, a test of linear trend across quartiles did not reach a customary level of statistical significance (P=0.14). Compared with persons consuming the lowest quartile of potassium intake (<34.6 mmol/d), persons consuming a higher potassium diet recorded by using an ICD-9 code of 410–414 or ≥1 hospital and/or nursing home stay in which the participant had a discharge diagnosis with 1 of these codes. The date of record for incident events was identified by the date of the first hospital admission with an established study event or date of death from a study event in the absence of hospital or nursing home documentation.

Statistical Analysis

Participants were divided into quartile groupings based on their potassium intake. For each baseline characteristic, the mean or percentage of study participants was calculated by quartile of potassium intake. The statistical significance of differences among quartiles was examined by using the F test from ANOVA (continuous variables) and the χ² test (categorical variables). Trend tests were conducted by using orthogonal coefficients. The cumulative incidence of coronary heart disease by quartile of potassium intake was calculated by using the Kaplan-Meier method,20 and differences in cumulative rates were examined by using the log-rank test.21 Because the risk of stroke was similar among the upper 3 quartiles of potassium intake and significantly higher in the lowest quartile of potassium intake, the risk of stroke in the lowest quartile was compared with that in the upper 3 quartiles combined. Cox proportional hazards models were used to explore the relationship between dietary potassium intake and coronary heart disease risk.22 Age was used as the time scale for all time-to-event analyses.23 Data from the participants who had reached ≥85 years were censored because of the small number of participants surviving in each quartile at that age. All Cox proportional hazards models were stratified by birth cohort, with 10-year intervals used to control for calendar period and cohort effects. The proportional hazards assumption was verified by using time-dependent interaction terms.24 Methods to estimate variances that take into account the sample clustering and stratification of the NHANES I sample were used in all Cox proportional hazards models.25

Follow-Up Procedures

Follow-up data were collected between 1982 and 1984 and in 1986, 1987, and 1992.13–16 Each follow-up examination included tracking a participant or his/her proxy to a current address, performing in-depth interviews with the participant or proxy, obtaining hospital and nursing home records, including pathology reports and ECGs, and, for decedents, acquiring a death certificate. Incident stroke and coronary heart disease events were based on documentation of an event that met prespecified study criteria and occurred during the period between the participant’s baseline examination and last follow-up interview. The validity of study outcome data from these sources has been documented.19

Incident stroke was based on a death certificate report in which the underlying cause of death was recorded by using the International Classification of Diseases, Ninth Revision (ICD-9) code of 430–434.9, 436, or 437.0–437.1 or ≥1 hospital and/or nursing home stay in which the participant had a discharge diagnosis with 1 of these codes. Incident coronary heart disease was based on a death certificate report in which the underlying cause of death was
(≥34.6 mmol/d) experienced a significantly lower hazard of stroke after adjustment for age, sex, race, and energy intake. The hazard of stroke for persons with a potassium intake in the second quartile (34.6 to 49.8 mmol/d) was 24% lower than that of their counterparts in the lowest quartile (HR 0.76, 95% CI 0.65 to 0.88; P<0.001). Similar estimates of relative hazard were obtained for persons in the third and fourth quartiles of potassium intake compared with those in the lowest. When additionally adjusted for systolic blood pressure, serum cholesterol, body mass index, history of diabetes, physical activity, education level, regular alcohol consumption, current cigarette smoking, vitamin supplement use, and other dietary factors, the relative hazard estimates for stroke remained the same. For instance, persons consuming 34.6 to 49.8 mmol/d of potassium experienced a 25% lower stroke hazard (HR 0.75, 95% CI 0.63 to 0.88; P=0.001) compared with those in the lowest quartile of intake (consuming <34.6 mmol/d). Again, relative hazard estimates were similar for the upper 3 quartiles of potassium intake. A linear trend test was not statistically significant. Given the findings of significantly lower hazard estimates of very similar magnitude at levels of potassium intake above the lowest quartile, persons with a potassium intake in the lowest quartile (<34.6 mmol/d) were compared with participants having a potassium intake in the upper 3 quartiles combined (≥34.6 mmol/d) in further analyses.

In Kaplan-Meier analyses, the cumulative hazard of stroke for persons in the lowest quartile of potassium intake compared with all others is presented in the Figure. At age 85, those in the lowest quartile of potassium intake experienced a 42.2% cumulative hazard of stroke, whereas participants with a higher intake of potassium experienced a 32.5% cumulative hazard of stroke (log rank P<0.0001). Table 3 presents HRs and 95% CIs for dietary potassium intake in the lowest quartile compared with potassium intake in the upper 3 quartiles combined. In age- and energy-adjusted analyses, persons consuming <34.6 mmol potassium per day experienced a 37% higher hazard of stroke than did persons

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;34.6</th>
<th>34.6–49.8</th>
<th>49.8–68.4</th>
<th>&gt;68.4</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>2452</td>
<td>2451</td>
<td>2450</td>
<td>2452</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.1±15.9</td>
<td>50.7±15.8</td>
<td>49.3±15.5</td>
<td>46.6±14.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>23.0</td>
<td>31.0</td>
<td>39.6</td>
<td>60.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Whites, %</td>
<td>68.5</td>
<td>84.9</td>
<td>89.6</td>
<td>92.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137.8±26.6</td>
<td>135.4±24.8</td>
<td>133.5±24.3</td>
<td>130.6±20.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>84.5±13.8</td>
<td>83.1±13.2</td>
<td>82.8±13.0</td>
<td>82.4±12.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>221.2±48.8</td>
<td>222.2±49.7</td>
<td>220.9±49.3</td>
<td>216.7±47.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>33.0</td>
<td>28.9</td>
<td>26.2</td>
<td>21.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>33.0</td>
<td>32.4</td>
<td>31.4</td>
<td>28.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>4.2</td>
<td>4.8</td>
<td>3.6</td>
<td>3.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4±5.8</td>
<td>25.8±5.2</td>
<td>25.2±4.8</td>
<td>25.1±4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Low recreational physical activity, %</td>
<td>54.8</td>
<td>48.1</td>
<td>43.3</td>
<td>38.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Less than high school education, %</td>
<td>60.1</td>
<td>49.5</td>
<td>40.9</td>
<td>36.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Current cigarette smoking, %</td>
<td>32.6</td>
<td>32.3</td>
<td>34.0</td>
<td>40.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Regular alcohol drinking, %</td>
<td>16.3</td>
<td>21.2</td>
<td>26.0</td>
<td>33.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin supplement use, %</td>
<td>27.1</td>
<td>31.3</td>
<td>35.5</td>
<td>36.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Saturated fat, g/24 h</td>
<td>15.7±8.9</td>
<td>22.0±10.9</td>
<td>27.7±14.1</td>
<td>40.6±23.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>262±226</td>
<td>334±251</td>
<td>390±267</td>
<td>514±338</td>
<td>0.001</td>
</tr>
<tr>
<td>Fiber, g/24 h</td>
<td>6.7±4.9</td>
<td>10.8±7.6</td>
<td>13.3±7.7</td>
<td>20.3±16.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Potassium, mmol/24 h</td>
<td>24.0±7.5</td>
<td>42.3±4.3</td>
<td>58.5±5.3</td>
<td>92.2±24.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Sodium, mmol/24 h</td>
<td>55.3±32.9</td>
<td>77.8±41.0</td>
<td>94.3±49.7</td>
<td>128.3±72.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium, mg/24 h</td>
<td>331±218</td>
<td>542±298</td>
<td>731±376</td>
<td>1109±648</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin A, IU/24 h</td>
<td>2631±4277</td>
<td>4045±5465</td>
<td>5576±9505</td>
<td>7685±12636</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin C, mg/24 h</td>
<td>37.5±50.9</td>
<td>67.5±60.1</td>
<td>91.6±75.0</td>
<td>130.6±100.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Dietary intake of energy, kcal/24 h</td>
<td>1118±469</td>
<td>1517±513</td>
<td>1844±606</td>
<td>2593±947</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SD or percentage of participants.
*Systolic BP ≥160 mm Hg and/or diastolic BP ≥95 mm Hg and/or use of antihypertensive medication.
†Serum cholesterol ≥240 mg/dL.
‡Vitamin supplement use includes both regular and irregular use of any vitamin supplement.
consuming more potassium per day (HR 1.37, 95% CI 1.20 to 1.54; P < 0.0001). Additional adjustment for established cardiovascular disease risk factors and dietary factors produced only slight attenuation of the relative hazard estimate. For instance, after adjustment for age, sex, race, systolic blood pressure, serum cholesterol, body mass index, history of diabetes, physical activity, education level, regular alcohol consumption, current cigarette smoking, vitamin supplement use, saturated fat intake, cholesterol intake, sodium intake, calcium intake, dietary fiber, vitamin C intake, and vitamin A intake (n = 9244).

### Discussion

The present study documents an independent association between low dietary potassium intake and increased hazard of stroke and suggests the possibility of a nonlinear (threshold) relationship. These findings are consistent with others suggesting that a low potassium intake may increase the risk of stroke.

Various lines of evidence suggest the possibility of a nonlinear relationship between dietary potassium intake and stroke risk. A low dietary potassium intake has been associated with elevated blood pressure levels. Krishna et al. conducted a randomized crossover trial of potassium depletion in normotensive men and found that feeding participants a low potassium diet (10 mmol/d) significantly increased mean arterial blood pressure (4 mm Hg increase, P < 0.05). Later, Krishna and Kapoor conducted a second randomized crossover trial examining dietary potassium depletion (from 96 to 16 mmol/d) in hypertensive subjects. Again they found significant increases in both systolic (7 mm Hg increase, P < 0.01) and diastolic (6 mm Hg increase, P < 0.04) blood pressures after feeding the subjects a low potassium diet. Furthermore, oral potassium supplementation to lower blood pressure is more effective in populations with a low potassium intake. In phase I of the Trials for Hypertension Prevention (TOHP), potassium supplementation of 60 mmol/d produced no significant reductions in blood pressure after 6 months. The TOHP participants’ baseline intake of potassium (78.3 mmol/d, assessed by dietary recall) may have been an important reason for the null results observed. In contrast, randomized trials of potassium supplementation in participants consuming a low potassium diet at baseline (32 to 35 mmol/d) tend to show large reductions in blood pressure.

Our findings of an independent relationship between low potassium intake and increased hazard of stroke were consis-
tent with those other prospective epidemiological studies, such as that of Khaw and Barrett-Connor and Ascherio et al. Khaw and Barrett-Connor found a relative risk of 0.60 (95% CI 0.44 to 0.82) for stroke mortality associated with a 10 mmol (377 mg) higher potassium intake after adjustment for age, systolic blood pressure, blood cholesterol level, obesity, cigarette smoking, fasting blood glucose level, and estrogen use (in women). Although important, this finding was based on a small sample (859 persons) with very few events (24 stroke deaths in 12 years). In contrast, the present study is based on evidence from 9805 participants who contributed 161 971 person-years of experience between 1971 and 1992 and among whom there were 927 stroke events. The study of Ascherio et al found a significant inverse relationship between dietary potassium intake and the risk of stroke in men (relative risk for fifth versus first quintile 0.62, 95% CI 0.43 to 0.88; \( P \text{ for trend}=0.007 \)), after adjustment for established cardiovascular disease risk factors. When relative risk estimates were additionally adjusted for dietary intakes of magnesium and fiber, the association failed to reach statistical significance (relative risk for extreme quintiles of potassium intake 0.69, 95% CI 0.45 to 1.07; \( P \text{ for trend}=0.11 \)). Their study was conducted among male health professionals, a highly select group with extensive education, generally high socioeconomic status, and a greater awareness of health-related issues than the general population. This population also had intakes well above the national average for potassium. A recent study of stroke mortality in the NHEFS cohort by Fang et al revealed an inverse association between hazard of stroke death and dietary potassium intake in hypertensive men and black men only. In the present study of stroke incidence, there was no significant difference in the relation of dietary potassium intake to hazard of stroke that was due to ethnicity or hypertensive status. The study by Fang et al examined stroke mortality only and did not include adjustment for dietary factors that might confound the relationship between potassium and stroke risk, such as dietary intake of fiber, calcium, or vitamin C.

The present study extends the findings of previous prospective studies by examining the effects of potassium intake on the risk of stroke and of coronary heart disease in a large representative sample of the noninstitutionalized US population with high event rates. Other strengths of the present study include the assessment of incident stroke and coronary heart disease over an average of 19 years of follow-up, with follow-up experience available for >96% of the study participants. Moreover, important dietary and nondietary cardiovascular disease risk factors were measured at baseline and controlled in the analysis to reduce the potential impact of confounding. For example, stroke risk has been inversely related to dietary intake of fiber, calcium, and vitamin C, whereas intake of potassium, fiber, calcium, and vitamin C are highly correlated in dietary studies. An additional concern is that persons consuming a diet with high levels of potassium may consume lower levels of saturated fat and cholesterol, important risk factors for stroke. We adjusted for all of the above-mentioned nutrients and total energy in a multivariate model. After this adjustment, the association between potassium intake and stroke hazard remained significant.

Data for coronary heart disease in the present study shows a nonsignificant association with dietary potassium intake. Experimental evidence, primarily in animals, suggests that potassium intake may reduce the progression of coronary artery disease. Most prospective cohort studies, except one, did not find significant association between potassium intake and risk of coronary heart disease. In a study conducted in 11 692 men and women in Scotland, a significant inverse association between urinary excretion of potassium and hazard of coronary heart disease was found in men but not in women. Those data should be interpreted with caution, because established cardiovascular disease risk factors, such as smoking, diabetes, and dietary nutrient intake, were not adjusted in the analysis.

One limitation of the present study is the estimation of potassium intake using a single 24-hour dietary recall. Estimates from a single day of intake may not be representative of the usual long-term intake of the participant and, thus, may result in misclassification of usual potassium consumption at the individual level. However, random errors of measurement in potassium intake would tend to bias any observed association toward the null rather than create a spurious association. Another limitation of the present study is that all outcome diagnoses were based on hospital and/or nursing home records or death certificates. Although it was possible to misdiagnose the subtype of stroke, the clinical diagnosis of complete stroke should be straightforward. We did not use stroke subtype in our analysis. Furthermore, there was no reason to believe that misdiagnosis would differ by baseline level of potassium intake.

Like all observational epidemiological studies, imperfect measurement of confounding variables and unmeasured po-

### TABLE 3. HR and 95% CI of Stroke and Coronary Heart Disease Incidence Associated With Low Dietary Potassium Intake in 9805 NHEFS Participants

<table>
<thead>
<tr>
<th>Model Adjustment</th>
<th>Stroke (HR 95% CI)</th>
<th>P</th>
<th>Coronary Heart Disease (HR 95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-, energy-adjusted</td>
<td>1.37 (1.20–1.54)</td>
<td>&lt;0.0001</td>
<td>1.04 (0.92–1.18)</td>
<td>0.54</td>
</tr>
<tr>
<td>Age-, race-, sex-, energy-adjusted</td>
<td>1.26 (1.11–1.45)</td>
<td>0.0007</td>
<td>1.04 (0.91–1.19)</td>
<td>0.53</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1.28 (1.11–1.47)</td>
<td>0.0001</td>
<td>1.00 (0.86–1.15)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Additionally adjusted for systolic BP, serum cholesterol, body mass index, history of diabetes, physical activity, education level, regular alcohol consumption, current cigarette smoking, vitamin supplement use, saturated fat intake, cholesterol intake, sodium intake, calcium intake, dietary fiber, vitamin C intake, and vitamin A intake (n=9244).
tential confounders may bias the study findings. For instance, a single measurement of blood pressure was obtained in NHANES I and used for adjustment, which may not have reflected long-term blood pressure levels for individuals. Furthermore, repeated measurements were not available for dietary potassium intake and potential confounding variables. Observational studies like ours provide evidence for an association between low potassium intake and increased risk of stroke. However, only randomized controlled trials can define the causality of this association.

The inverse association between potassium and risk of stroke could result from a combination of factors. First, potassium supplementation tends to lower blood pressure, a major risk factor for stroke. It has been hypothesized that such reductions in blood pressure may be due to reduced renal vascular resistance and elevated glomerular filtration rate, in addition to the natriuresis and diuresis observed with potassium supplementation. One study in African American hypertensive men indicates that a low dietary potassium intake (30 mmol/d) may enhance adrenergically mediated vasoconstriction in response to stress. Second, high concentrations of potassium may slow the atherosclerotic process and clot formation by reducing free radical formation, smooth muscle proliferation, arterial thrombosis, and platelet aggregation. The latter effects have been observed only in tissue culture or animal experiments, so their relevance to humans is unknown.

Our findings of an independent relationship between low potassium intake and increased hazard of stroke in a representative sample of the US population have important clinical and public health implications. Stroke is the third leading cause of death and the leading basis for long-term disability in the United States. Given its severe health consequences, the prevention of stroke in the general population is of critical importance to reduce the public health burden of cardiovascular disease. Further prospective studies are needed to confirm the association and pattern of dietary potassium intake and risk of stroke. Depending on the results of such studies, randomized trials of potassium supplementation to reduce stroke may be warranted.

Acknowledgments

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References

Potassium, Stroke, and the Bounds of Epidemiological Studies

In the fall of 2000, Tropicana Products received approval from the US Food and Drug Administration to label orange juice with the claim, “Diets containing foods that are good sources of potassium and low in sodium may reduce the risk of high blood pressure and stroke.” A logo will appear on containers reading, “Promotes Cardiovascular Health.” The approval was based on a number of epidemiological and animal studies showing an association between higher intake of potassium and reduced stroke risk, but how strongly do these studies support a causative role? How strong is the evidence that increasing potassium intake will reduce the risk of stroke?

No randomized trial has been completed to show that increased potassium intake reduces stroke risk, so the direct association is supported solely by epidemiological studies, including the preceding article in this issue. In spite of its large sample and thoughtful implementation, the study illustrates the weakness of existing data on potassium and stroke and demonstrates the limitations of epidemiological, observational studies in general.

In an epidemiological study, an association does not prove causation. No matter how careful the study, it is always possible that the association of interest is due to an imbalance in underlying risk factors—that it is due to confounding. Confounding occurs when a factor is associated with the outcome and is also associated with the treatment. It can result in the illusion that an effect exists when none is present or can obscure a true causal effect. A randomized trial of adequate power is not subject to confounding because randomization assures balance of risk factors in the treatment groups. Randomization is expected to distribute risk factors evenly even if a factor is unknown or inaccurately measured. Epidemiological studies cannot assure such balance.

In the study by Bazzano et al, every measured variable was significantly associated with the treatment variable, potassium intake, except hypercholesterolemia. Some of these associations are not surprising given that those consuming more potassium are likely to consume more altogether, including total calories, sodium, fiber, and saturated fat.

Some of the factors associated with potassium intake are known stroke risk factors, such as diabetes, cigarette smoking, and low levels of physical activity, which makes them potential confounders. A simple univariate analysis of potassium and stroke risk ignores these associations, so that potassium becomes a marker for all the other factors that are associated with it. For example, an inverse association between potassium intake and stroke risk in a univariate analysis could represent higher levels of physical activity in those consuming more potassium (and more calories all together). In this instance, physical activity could be responsible for reduced stroke risk; then, potassium supplementation would have no effect.

Bazzano et al use multivariate modeling, a standard approach in epidemiological studies. By incorporating all known and identified risk factors into the model, the researcher attempts to adjust for existing imbalances. If every important risk factor for the outcome of interest is accurately measured and its form is correctly specified, multivariate models will lead to valid estimates of the treatment effect. However, multivariate models may produce biased results if confounding factors are not measured accurately. For example, those with low recreational activity have been identified, and a variable reflecting this can be entered into the multivariate model. Then, the association between potassium intake and stroke is said to be independent of recreational physical activity; this factor is said to be controlled. However, if this factor is inaccurately measured, control will be incomplete. If the definition of low recreational physical activity is too coarse, those who jog 5 miles each day may be placed in the same group as those who stroll around the block after dinner. Potassium intake could be a more accurate measure of physical activity, given its association with total energy intake, and its association with stroke risk could be through the more vigorous activity of those who take in more potassium. Then, the multivariable result could suggest that potassium intake is inversely associated with stroke risk after controlling for low recreational activity, but the association could still be due to physical activity. Including a potential

confounder in a multivariate model does not ensure that it is controlled if it is measured inaccurately or imprecisely.

Other confounding factors may not be measured, further weakening epidemiological studies. For example, those with greater potassium intake probably have healthier diets in general and may be more highly motivated to maintain health; they may be more adherent with medications, for example. Then, an inverse association between potassium intake and stroke risk could be due to differences in medication adherence. Such an association may be responsible for the apparent protective effect of hormone replacement therapy in results from epidemiological studies of cardiovascular disease risk, since recent randomized trials have shown a detrimental effect. Those who take hormone replacement therapy may have more healthy lifestyles in ways that have not been fully measured. Because the foods that contain large amounts of potassium, such as fruits and vegetables, are generally considered healthful, a similar association between potassium intake and healthy lifestyle could account for an association. If this is the case, potassium supplementation would not be beneficial.

Epidemiological studies are often more efficient than randomized trials, and because of this often have larger sample sizes, which can yield misleading results. In a randomized trial, a larger sample size increases the likelihood that a true causal effect will be demonstrated, if present, because a smaller treatment effect can reach statistical significance. Further, a larger sample size increases the likelihood that other confounding factors will be relatively balanced. However, in an epidemiological study, larger sample size increases the likelihood that a significant association is due to bias: a smaller treatment effect will reach statistical significance, but imbalances in confounding factors will not be reduced. For example, the 28% higher risk of stroke with P<0.001 in the large study by Bazzano et al is more likely to be due to confounding than a hypothetical 100% higher risk with P=0.01 in a smaller study. The larger sample size tempts one to attribute small associations to causal effects, but this may be the influence of confounders.

Epidemiological studies may also be weakened by post hoc definition of primary outcomes. Randomized trials commit to a single primary hypothesis, and epidemiological studies have not been held to the same standard. A 6 is more likely to show up in a game with more throws of the die. Similarly, changing the cut point for comparisons can increase the likelihood of finding a significant effect. For example, if a dose-response association between potassium intake and stroke risk, as seen in other epidemiological studies, is hypothesized a priori, then the test for trend in the multivariate model would be the primary test, which did not reach statistical significance in this study (P=0.14). Other studies of potassium and stroke have compared the highest to the lowest groups, which also did not reach statistical significance (confidence intervals of the relative risk include 1.0). Rather, the authors compared the lowest quartile to the other 3 (P<0.001). The prespecified comparison of stroke hazard among quartiles of potassium intake is a more realistic representation of the strength of the association (P=0.03). Regardless of how rational the comparisons seem in retrospect, unless a primary outcome measure has been selected a priori, the likelihood of finding a significant underlying association must be suspect—the probability value overestimates the true statistical significance.

In spite of the limitations of this careful study, the results provide additional support for a possible independent association between potassium intake and stroke risk. Also, prior randomized trials have shown a significant association between potassium supplementation and lower blood pressure in some groups, so a biological link to stroke risk is plausible. Although the limitations of epidemiological studies are important, such studies are essential to clinical research because randomized trials are expensive, slow to deliver results, often impractical, and occasionally unethical. However, when epidemiological studies find small treatment effects and confounding influences—measured and unmeasured—are likely, randomized trials are clearly indicated. Until a randomized trial is performed, the major indication for orange juice may be tastiness rather than reduction in stroke risk.

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