Alcohol Consumption and Risk of Stroke
A Meta-analysis

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STROKE IS THE THIRD LEADING cause of death and a major cause of disability in the United States.1,2 In 1999, 167,366 deaths in the United States resulted from stroke.1 Approximately 30% of stroke survivors are permanently disabled and 20% require institutionalized care. Stroke is also a huge financial burden for patients, their families, and the health care system. The cost of stroke in the United States in 2002 is estimated to be $49.4 billion, which includes direct health expenditures and lost productivity resulting from morbidity and mortality.1

Alcoholic beverages are consumed widely throughout the world, and an association between alcohol consumption and stroke could have considerable public health and clinical implications. Over the past 2 decades, many observational epidemiologic studies3-37 have examined the role of alcohol as both a risk factor and a potential protective factor for stroke. Heavy alcohol consumption has been linked to an increased risk of total stroke,23,32 ischemic stroke,29,33 and hemorrhagic stroke.3,7,35 However, studies investigating the association between moderate alcohol consumption and stroke have reported conflicting results. Some studies have reported that moderate alcohol consumption is inversely related to risk of total stroke,31 ischemic stroke,27,31,32 and hemorrhagic stroke,27,31 while others found that moderate alcohol consumption is positively related to risk of stroke.3,25

We performed a meta-analysis of epidemiologic studies to examine the relative risk of stroke at various levels of alcohol consumption.

METHODS

Study Selection

A literature search of the MEDLINE database (from January 1966 through April 2002) using the Medical Subject Headings alcohol drinking, ethanol, cerebrovascular accident, cerebrovascular disorders, and intracranial embolism and thrombosis and the key word stroke; Dissertation Abstracts Online using the keywords stroke and alcohol; and bibliographies of retrieved articles.

Data Sources

Studies published in English-language journals were retrieved by searching MEDLINE (1966–April 2002) using Medical Subject Headings alcohol drinking, ethanol, cerebrovascular accident, cerebrovascular disorders, and intracranial embolism and thrombosis and the key word stroke; Dissertation Abstracts Online using the keywords stroke and alcohol; and bibliographies of retrieved articles.

Data Synthesis

A random-effects model and meta-regression analysis were used to pool data from individual studies. Compared with abstainers, consumption of more than 60 g of alcohol per day was associated with an increased relative risk of total stroke, 1.64 (95% confidence interval [CI], 1.39-1.93); ischemic stroke, 1.69 (95% CI, 1.34-2.15); and hemorrhagic stroke, 2.18 (95% CI, 1.48-3.20), while consumption of less than 12 g/d was associated with a reduced relative risk of total stroke, 0.83 (95% CI, 0.75-0.91) and ischemic stroke, 0.80 (95% CI, 0.67-0.96), and consumption of 12 to 24 g/d was associated with a reduced relative risk of ischemic stroke, 0.72 (95% CI, 0.57-0.91). The meta-regression analysis revealed a significant nonlinear relationship between alcohol consumption and total and ischemic stroke and a linear relationship between alcohol consumption and hemorrhagic stroke.

Conclusions

These results indicate that heavy alcohol consumption increases the relative risk of stroke while light or moderate alcohol consumption may be protective against total and ischemic stroke.
studies published in English-language journals and conducted in human subjects. We also conducted a search of abstracts listed in Dissertation Abstracts Online using the keywords ‘stroke’ and ‘alcohol,’ and we performed a manual search of references cited in published original study and relevant review articles. The contents of 122 abstracts or full-text manuscripts identified during the literature search were reviewed independently by 2 investigators in duplicate to determine whether they met the criteria for inclusion. When there were discrepancies between investigators for inclusion or exclusion, other investigators conducted additional evaluation of the study and discrepancies were resolved in conference. To be included in our meta-analysis, a published study had to meet the following criteria: (1) observational cohort or case-control study in which total stroke, ischemic stroke, or hemorrhagic (intracerebral or total) stroke was an end point; (2) relative risk or relative odds and their variance (or data to calculate them) of stroke associated with alcohol consumption were reported; (3) alcohol consumption was quantified; and (4) abstainers were used as the reference group.

Fifty-three studies were identified and abstracted. Four studies reported total hemorrhagic stroke as the outcome, which includes intracerebral and subarachnoid hemorrhage. None of the studies reported information on subdural hemorrhagic strokes. We have used the term hemorrhagic stroke throughout the article. Two reports consisted of the same case patients but different controls and were treated as 2 separate studies. From the 53 studies, 18 were further excluded for various reasons. Two studies were excluded because combined risk estimates were reported for men and women but levels of alcohol consumption were not the same for men as for women. We excluded 5 studies that examined only the effect of binge drinking or acute alcohol consumption (within 24 hours before stroke) because our study assessed habitual alcohol consumption and relative risk of stroke. Five studies that lacked sufficient data for calculation of relative risk estimates were excluded. The remaining 6 excluded reports did not use abstainers as the reference group. We included 19 cohort studies and 16 case-control studies in our final analysis.

Data Abstraction
All data were independently abstracted in triplicate by means of a standardized data-collection form. Discrepancies were resolved by discussion and referencing the original publication. We did not contact authors to request additional information. Study characteristics recorded were as follows: title, article’s first author’s name, year, and source of publication, country of origin, study design (cohort study or case-control study), characteristics of the study population (sample size; sampling methods; and distribution of age, sex, and race), measures of outcome and exposure, duration of follow-up (for prospective cohort studies), confounding factors controlled for by matching or adjustment, and the relative risk (or relative odds) of stroke associated with alcohol consumption and the corresponding confidence interval (or SE). Relative risks overall and in each subgroup, according to sex, subtype of stroke, level of alcohol consumption, and type of alcoholic beverage, were abstracted.

Statistical Analysis
Relative risk was used as a measure of the relation between alcohol consumption and risk of stroke. For case-control studies, relative odds were used as a surrogate measure of the corresponding relative risk. Because the absolute risk of stroke is low, the relative odds approximate the relative risk. Relative risks from individual studies for each level of alcohol consumption and the corresponding SEs were transformed to their natural logarithms to stabilize the variances and to normalize the distributions. The SEs were derived from the confidence intervals provided in each study.

The studies included in our meta-analysis often differed in the measurement units of alcohol consumption (eg, grams, milliliters, ounces, or drinks consumed every day, week, or month). Therefore, we first converted these different units of alcohol consumption to grams per day. Among the 35 studies included in our meta-analysis, 20 reported alcohol consumption as grams. We used the following conversion factors for the 4 studies that reported alcohol data as milliliters or ounces: 1 mL, 0.785 g; 1 fl oz, 28.41 mL (United Kingdom); and 1 fl oz, 29.58 mL (United States). Two of the 11 studies that reported alcohol data as drinks provided conversion factors in their articles. The other 9 used common conversion factors. In the latter, a drink was defined as 12 g in the United States, 10 g in Australia and Europe, and 21.2 g in Japan, which is the standard drink volume in Japan.

Alcohol consumption was reported as categorical data with a range in all studies. We assigned the mean of the upper and lower bounds in each category as the average alcohol consumption. An upper bound was not reported in many studies for the category of highest consumption, so we assumed it to be the same amplitude as the preceding category for calculation of average alcohol consumption in this category. In our meta-analysis, alcohol consumption was categorized into 5 groups: none (reference), less than 12, 12 to 23, 24 to 60, and more than 60 g/d. We assigned the level of alcohol consumption from each study to these groups based on the calculated average consumption of alcohol. In some studies, the average alcohol consumption from more than 1 category fell into the same group of alcohol consumption in our meta-analysis. When this occurred, we pooled the relative risks within each category for each study and then we pooled across all studies.

Both fixed-effects and DerSimonian and Laird random-effects models were used to calculate the pooled relative risk across levels of alcohol consumption. Although both models yielded similar findings, results from the random-effects model are presented herein because...
Table 1. Characteristics of 19 Cohort Studies of Alcohol Consumption and Risk of Stroke

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Participants</th>
<th>Exposure Assessment</th>
<th>Duration of Follow-up, y</th>
<th>Follow-up Process</th>
<th>Outcome Assessment</th>
<th>No. of Stroke Cases</th>
<th>Controlled Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donahue et al, 1986</td>
<td>7878 Men aged 45-69 y in Hawaii</td>
<td>In-person interview</td>
<td>12</td>
<td>Clinical examinations at years 2 and 6 and continued surveillance</td>
<td>Hospital discharge diagnosis, clinical diagnosis, death certificate, or autopsy record</td>
<td>290</td>
<td>Age, BMI, cigarette smoking, hypertension, serum cholesterol, uric acid, glucose level, hematocrit</td>
</tr>
<tr>
<td>Kono et al, 1986</td>
<td>5135 Men in Japan</td>
<td>Self-administered questionnaire</td>
<td>19</td>
<td>Vital status ascertainment by medical association</td>
<td>Death certificate</td>
<td>230</td>
<td>Age, cigarette smoking</td>
</tr>
<tr>
<td>Gordon and Doyle, 1987</td>
<td>1910 Men aged 38-55 y in New York</td>
<td>Self-administered questionnaire</td>
<td>29</td>
<td>Vital statistics records, newspapers, or reports from proxies</td>
<td>Proxy reports or death certificate</td>
<td>33</td>
<td>None</td>
</tr>
<tr>
<td>Stampfer et al, 1988</td>
<td>87 526 US women aged 34-69 y</td>
<td>Self-administered questionnaire</td>
<td>4</td>
<td>Biennial questionnaires</td>
<td>Medical records</td>
<td>120</td>
<td>Age, cigarette smoking, hypertension, DM, serum cholesterol level, obesity, exercise, cholesterol intake, saturated and polyunsaturated fat intake, parental history of MI before age 60 y, menopausal status, hormone use, study period</td>
</tr>
<tr>
<td>Klatsky et al, 1989</td>
<td>107 137 US men and women aged &lt;50 y</td>
<td>Self-administered questionnaire</td>
<td>6</td>
<td>Surveillance of hospital discharges</td>
<td>Clinical diagnosis</td>
<td>674</td>
<td>Age, sex, race, cigarette smoking, SBP, coffee consumption, BMI, baseline disease</td>
</tr>
<tr>
<td>Shaper et al, 1991</td>
<td>7735 UK men aged 40-59 y</td>
<td>In-person interview</td>
<td>8</td>
<td>Death register</td>
<td>Clinical diagnosis or death certificate</td>
<td>110</td>
<td>Age, cigarette smoking, SBP</td>
</tr>
<tr>
<td>Goldberg et al, 1994</td>
<td>6069 Men aged 51-75 y in Hawaii</td>
<td>In-person interview</td>
<td>15</td>
<td>Clinical examinations at years 2 and 6 and continued surveillance</td>
<td>Hospital discharge diagnosis, clinical diagnosis, or death certificate</td>
<td>70</td>
<td>Age, cigarette smoking; SBP; serum cholesterol, serum triglyceride, and serum uric acid levels, coffee consumption, total caloric intake</td>
</tr>
<tr>
<td>Hansagi et al, 1995</td>
<td>15 077 Men and women aged ≥40 y in Sweden</td>
<td>Self-administered questionnaire</td>
<td>20</td>
<td>Death register</td>
<td>Death certificate</td>
<td>769</td>
<td>Age, cigarette smoking</td>
</tr>
<tr>
<td>Iso et al, 1995</td>
<td>2890 Men aged 40-69 y in Japan</td>
<td>In-person interview</td>
<td>10.5</td>
<td>Not specified</td>
<td>Clinical diagnosis and CT scan</td>
<td>178</td>
<td>Age, cigarette smoking, hypertension, serum total cholesterol level, DM</td>
</tr>
<tr>
<td>Kiyohara et al, 1995</td>
<td>1621 Men and women aged ≥40 y in Japan</td>
<td>In-person interview</td>
<td>26</td>
<td>Biennial examinations, mail, or telephone</td>
<td>Neurological examination, CT scan, angiography, lumbar puncture, or autopsy</td>
<td>304</td>
<td>Age, sex, hypertension</td>
</tr>
<tr>
<td>Palmer et al, 1995</td>
<td>6369 Men and women aged 18-90 y in England</td>
<td>In-person interview (1971-1976)</td>
<td>Self-administered questionnaire (after 1976)</td>
<td>22</td>
<td>Questionnaire every 1-2 y</td>
<td>Death certificate</td>
<td>159</td>
</tr>
<tr>
<td>Yuan et al, 1997</td>
<td>18 244 Men aged 45-64 y in China</td>
<td>In-person interview</td>
<td>9</td>
<td>Annual contact</td>
<td>Death certificate</td>
<td>269</td>
<td>Age, cigarette smoking, educational level</td>
</tr>
<tr>
<td>Maskarinec et al, 1998</td>
<td>27 678 Men and women aged ≥30 y in Hawaii</td>
<td>In-person interview</td>
<td>20</td>
<td>Passive follow-up</td>
<td>Death certificate</td>
<td>433</td>
<td>Age, BMI, cigarette smoking, ethnicity, educational level</td>
</tr>
<tr>
<td>Hart et al, 1999</td>
<td>5766 Men aged 35-64 y in Scotland</td>
<td>In-person interview</td>
<td>21</td>
<td>NHS death register</td>
<td>Death certificate</td>
<td>133</td>
<td>Age, BMI, cigarette smoking, DBP, serum cholesterol level, educational level, social class, father’s social class, car use, siblings, deprivation category, adjusted FEV, angina, ischemia on ECG, bronchitis</td>
</tr>
</tbody>
</table>

(continued)
significant heterogeneity was identified among studies. A weighted meta-regression analysis with no intercept term was performed to examine the association between alcohol consumption and the natural logarithm of the relative risk of stroke. We used the “pool-first” method proposed by Greenland and Longnecker. This method was chosen because several studies reported finding a nonlinear, J- or U-shaped relationship between alcohol consumption and relative risk of stroke. This method is advantageous because it can easily be extended to test nonlinearity and identify J- or U-shaped curves, or other relationships between exposure levels and relative risks. For each included study, we performed an initial fit of a quadratic curve. When a nonsignificant term was found in the initial model, a subsequent fit of a simpler model (linear or solitary square term) was conducted.

Pretested subgroup analyses were conducted by subtype of stroke and sex for the different levels of alcohol consumption. Subgroup analyses were not performed by type of alcoholic beverage due to the lack of such detailed information in most studies.

To assess the potential for publication bias, we constructed a funnel plot in which the log relative risks were plotted against their SEs. In addition, a rank correlation for the association between standardized log relative risks and their SEs was conducted using the Kendall τ correlation coefficient. The correlation between sample size and relative risk would be high if small studies with null results were less likely to be published. A significant correlation between sample size and relative risk would not exist in the absence of this type of publication bias.

### RESULTS

The characteristics of the study subjects and design of the cohort studies are presented in Table 1. Of the 19 cohort studies, 8 were conducted in the United States. The number of subjects in the cohort studies ranged from 1621 in the study by Kiyohara et al to 107 137 in the study by Klatsky et al. Among the 19 cohort studies, 15 reported total stroke as the outcome. In addition, 7 studies reported ischemic stroke, and 7 studies reported hemorrhagic stroke as the outcome. The follow-up period ranged from 4 to 30 years. The study population in 7 cohort studies consisted of men and women, 1 consisted entirely of women, and 11 consisted of only men.

Twelve of the 16 case-control studies were conducted outside the United States (Table 2). The number of case subjects enrolled in these studies ranged from 89 in the study by Henrich and Horwitz to 677 in the study by Sacco et al and the corresponding number of control subjects ranged from 153 in the study by Palomaki et al to 1139 in the study by Sacco et al. Total stroke was the study outcome in 9 studies, whereas 8 studies collected data on ischemic stroke and 5 collected data on hemorrhagic stroke. Fourteen of the 16 case-control studies were composed of both men and women, 1 case-control study consisted of only women, and 1 case-control study consisted of only men.
<table>
<thead>
<tr>
<th>Source, y</th>
<th>Stroke Cases</th>
<th>Controls</th>
<th>Case Assessment</th>
<th>Exposure Assessment</th>
<th>Controlled Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herman et al, 22 1983</td>
<td>132 Male and female patients with incident stroke event in 2 hospitals in the Netherlands</td>
<td>239 Patients from the same hospital</td>
<td>Clinical examination</td>
<td>In-person interview</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Gill et al, 23 1986</td>
<td>230 Male and female patients with stroke diagnosis in the district hospital in England</td>
<td>230 Hospital patients</td>
<td>Clinical examination, CT scan, angiography, and postmortem examinations, or lumbar puncture</td>
<td>In-person interview</td>
<td>Age, sex, race, cigarette smoking, treatment of hypertension, medication</td>
</tr>
<tr>
<td>Gill et al, 24 1988</td>
<td>230 Male and female patients with stroke diagnosis in the district hospital in England</td>
<td>577 Male and female industrial workers in the same community</td>
<td>Clinical examination, CT scan, angiography, and postmortem examinations, or lumbar puncture</td>
<td>In-person interview</td>
<td>Age, race, cigarette smoking, treatment of hypertension, social class, drug therapy</td>
</tr>
<tr>
<td>Gorelick et al, 25 1989</td>
<td>205 Male and female patients with incident ischemic stroke in 3 medical centers in Chicago</td>
<td>410 Outpatient clinic patients</td>
<td>Clinical diagnosis and CT scan</td>
<td>In-person interview</td>
<td>Age, sex, race, cigarette smoking, hypertension, method of hospital payment</td>
</tr>
<tr>
<td>Henrich and Horwitz, 26 1989</td>
<td>89 Male and female hospitalized patients with ischemic stroke in Connecticut</td>
<td>178 Patients discharged from the same hospital</td>
<td>Clinical examination and CT scan</td>
<td>Telephone interview</td>
<td>None</td>
</tr>
<tr>
<td>Gill et al, 27 1991</td>
<td>621 Male and female hospitalized patients with stroke diagnosis in 2 centers in England</td>
<td>573 Male and female industrial workers in the same community</td>
<td>Clinical examination, CT scan, angiography and postmortem examination, or lumbar puncture</td>
<td>In-person interview</td>
<td>Age, sex, race, cigarette smoking, hypertension, social class, medication</td>
</tr>
<tr>
<td>Ben-Shlomo et al, 28 1992</td>
<td>115 Male and female hospitalized patients with incident stroke in 3 hospitals in the United Kingdom</td>
<td>165 Generally matched, 115 selectively matched, and 752 community controls</td>
<td>Clinical examination, CT scan, or lumbar puncture</td>
<td>Cases, in-person taped interview Controls, self-administered questionnaire</td>
<td>General and selective controls: age, sex, cigarette smoking, hypertension, DM, heart disease Community controls: age, sex, cigarette smoking, hypertension, and social class</td>
</tr>
<tr>
<td>Palomäki et al, 29 1993</td>
<td>156 Male hospitalized patients with ischemic stroke in Finland</td>
<td>153 Hospital patients</td>
<td>Clinical diagnosis</td>
<td>In-person interview</td>
<td>Age, BMI, cigarette smoking, hypertension, DM, coronary heart disease, history of snoring</td>
</tr>
<tr>
<td>Shinton et al, 30 1993</td>
<td>125 Male and female patients with incident stroke in 11 general practice partnerships in England</td>
<td>198 Community controls</td>
<td>Clinical examination, CT scan, or autopsy</td>
<td>Alcohol diary</td>
<td>Age, sex, history of cardiovascular disease</td>
</tr>
<tr>
<td>Jamrozik et al, 31 1994</td>
<td>501 Male and female patients with stroke diagnosis in Australia</td>
<td>931 Community controls</td>
<td>Clinical examination, CT scan, MRI, or autopsy</td>
<td>In-person interview</td>
<td>Age, sex, cigarette smoking, hypertension, DM, previous stroke or TIA, previous MI, adding salt to food, consumption of fish &gt;2 times/mo, claudication, use of reduced fat or skim milk, consumption of meat &gt;4 times/wk</td>
</tr>
<tr>
<td>Beghi et al, 32 1995</td>
<td>200 Male and female hospitalized patients with stroke in Italy</td>
<td>170 Patients in the same hospital and 202 community controls</td>
<td>Clinical examination, CT scan, or neurological consultation</td>
<td>In-person interview</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Caicoya et al, 33 1999</td>
<td>467 Male and female patients with incident stroke in Spain</td>
<td>477 Residents of the same community</td>
<td>Clinical examination or CT scan</td>
<td>In-person interview</td>
<td>Age, sex, cigarette smoking, hypertension, DM, hypercholesterolemia, cardiac disease</td>
</tr>
</tbody>
</table>

(continued)
The results from the random-effects model and the meta-regression analysis test for trend are presented in Table 3. The overall results indicate a nonlinear association between alcohol consumption and relative risk of total stroke (P = .002 for nonlinear trend). Compared with the reference group of abstainers, alcohol consumption of less than 12 g/d, or less than 1 drink per day based on US conversions, was significantly associated with a decreased relative risk of total stroke, while alcohol consumption of more than 60 g/d, or more than 5 drinks per day, was significantly associated with an increased relative risk of total stroke. The association between alcohol consumption and relative risk of ischemic stroke was J-shaped with the lowest risk among those consuming less than 12 g/d, or less than 1 drink per day, or 12 to 24 g/d, or 1 to 2 drinks per day, and the highest risk among those consuming more than 60 g/d, or more than 5 drinks per day. (Figure 1). Relative risk of hemorrhagic stroke increased linearly with increasing alcohol consumption, and those consuming more than 60 g/d, or more than 5 drinks per day, had the highest relative risk.

The association between alcohol consumption and relative risk of total stroke was similar in men and women (Table 3 and Figure 2) although the relative risk was somewhat lower in women consuming less than 12 g/d, or less than 1 drink per day, than in men. Likewise, the association was similar in case-control studies and cohort studies, with alcohol consumption of less than 12 g/d, or less than 1 drink per day, among cohort studies and alcohol consumption of less than 24 g/d, or less than 2 drinks per day, among case-control studies associated with a significant reduced relative risk while alcohol consumption of more than 60 g/d, or more than 5 drinks per day, was associated with an increased relative risk.

The findings from the sensitivity analyses that excluded studies based on different inclusion criteria are presented in Table 4. Risk estimates changed very little after the exclusion of outliers, studies without computed tomographic scans or other imaging measures, studies that did not adjust for important confounders, or studies that did not exclude prevalent stroke cases at baseline.

There was no evidence of publication bias in our study as indicated by a funnel plot (Figure 3) and the Kendall τ correlation coefficient. The Kendall τ correlation coefficient for the SE and the standardized log relative risk was −0.072 (P = .17) for all studies. When the outliers were excluded, the Kendall τ correlation coefficient for the SE and the standardized log relative risk became −0.053 (P = .32).

### COMMENT

Several large epidemiologic studies that have examined the effect of alcohol consumption on the risk of stroke have provided inconsistent findings. In our current meta-analysis, we found a J-shaped association between alcohol consumption and the relative risk of total and ischemic stroke and a linear association between alcohol consumption and the relative risk of hemorrhagic stroke. Moderate alcohol consumption was associated with a reduced relative risk of total and ischemic stroke while heavy...
alcohol consumption was associated with an increased relative risk of total, ischemic, and hemorrhagic stroke. The relationship between alcohol consumption and stroke is believed to involve various mechanisms including alcohol-induced hypertension, cardiomyopathy, coagulation disorders, atrial fibrillation, and reductions in cerebral blood flow.

Table 3. Overall Relative Risk (95% Confidence Interval) of Stroke Associated With Alcohol Consumption and Test for Trend

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Alcohol Intake, g/d</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12</td>
<td>12-24</td>
</tr>
<tr>
<td>Overall</td>
<td>35</td>
<td>0.83 (0.75-0.91)</td>
</tr>
<tr>
<td>Type of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>15</td>
<td>0.80 (0.67-0.96)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>12</td>
<td>0.79 (0.60-1.05)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>27</td>
<td>0.89 (0.79-1.01)</td>
</tr>
<tr>
<td>Women</td>
<td>16</td>
<td>0.66 (0.61-0.71)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>19</td>
<td>0.82 (0.73-0.92)</td>
</tr>
<tr>
<td>Case control</td>
<td>16</td>
<td>0.80 (0.67-0.97)</td>
</tr>
</tbody>
</table>

*Tests for linear associations were performed only when nonlinear associations were not statistically significant.

Figure 1. Scatterplot of Log Relative Risk and Meta-Regression Curve of Stroke Associated With Alcohol Consumption by Subtypes of Stroke

Most studies provided more than 1 relative risk estimate for multiple levels of alcohol consumption.

Figure 2. Scatterplot of Log Relative Risk and Meta-Regression Curve of Stroke Associated With Alcohol Consumption by Sex

Most studies provided more than 1 relative risk estimate for multiple levels of alcohol consumption.

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The anticoagulant effects of alcohol, although they appear to be beneficial for decreasing the risk of ischemic stroke, may play an important role in increasing the risk of hemorrhagic stroke.71,74

There are several potential limitations in our study. First, our study is a meta-analysis of observational studies. The quality of our study depends on data from original publications included in our analysis. Our study may inherit the problems of potential bias and confounding effects associated with observational studies. However, a randomized controlled trial of alcohol consumption and stroke has not been performed and is unlikely to be conducted in the future. Consequently, we must rely on data from observational studies to draw conclusions and make recommendations.

Second, computed tomographic scans and other imaging techniques were not available for some early studies. Furthermore, several studies only used death certificates or death register data for diagnosis of stroke outcome. However, our findings were unlikely due to misclassification of outcome because the relative risks of stroke associated with alcohol consumption did not change after exclusion of studies that did not use computed tomography or other imaging techniques for diagnosis. Our findings were also unlikely due to confounding effects because the relative risks of stroke associated with alcohol consumption were similar among all studies and only those studies that controlled for important risk factors for stroke, such as cigarette smoking and hypertension. Additionally, our results were unlikely to result from publication bias as demonstrated by the funnel plot and rank correlation analysis.

Several methodological issues regarding epidemiologic research on the health impact of alcohol consumption are worth considering. First, the selection of the reference group may vary among studies. For instance, some studies used the lowest consumption level as the reference group while others used abstainers. In an effort to avoid combining studies that were not comparable, we chose to include only those studies that used abstainers as the reference group. It has been suggested that the U- or J-shaped association between alcohol consumption and mortality from cardiovascular disease may be due to the inclusion of ex-drinkers in the reference group of abstainers. Ex-drinkers may have stopped alcohol consumption due to health problems and they are at increased risk for death from cardiovascular disease.47,75,76 However, several studies have examined this potential bias and concluded that the J- or U-shaped relationship between alcohol consumption and risk of cardiovascular disease mortality held true.6,13,27,77 Moreover, we conducted a sensitivity analysis in which only prospective cohort studies that excluded prevalent stroke cases at baseline were included, and we found that the shape of association remained unchanged.

Second, the health effects of binge drinking may be different than those for regular drinkers. The failure to differentiate between these 2 groups could possibly obscure the observation of any true association. Therefore, we only included studies that examined the effect of usual alcohol consumption rather than acute alcohol consumption. Third, the measurement units, especially the definition of an alcohol drink, varies among studies. We attempted to overcome this problem by applying a com...
monly used and validated method suggested by Turner. Finally, assessment methods for alcohol consumption may also vary among studies. The assessment of alcohol consumption is usually based on self-reported alcohol habits. Such data are subject to errors of recall. For example, heavy drinkers may be more likely to underreport their alcohol consumption. The majority of studies in this meta-analysis used in-person interviews, while 11 studies used self-administered questionnaires, 1 study conducted telephone interviews, and 1 study used alcohol consumption diaries.

There are several advantages of our study. The discrepancies among studies regarding the association between level of alcohol consumption and relative risk of stroke also may be attributable to a small sample size in the individual studies, resulting in insufficient statistical power. This meta-analysis included a large number of people from different populations throughout the world. Additionally, we were able to assess the pattern of the association between level of alcohol consumption and relative risk of stroke with precision due to the large sample size. Finally, the association between alcohol consumption and relative risk of stroke was consistent among subgroups by study design, sex, and stroke subtype.

Our findings have important clinical and public health implications. In the United States, 4% of adults, aged 18 years or older, are current drinkers who have consumed at least 12 drinks in the preceding year. Stroke is a major cause of death and disability in the United States and other countries. In the United States, there are approximately 600,000 new stroke cases each year. Given the widespread consumption of alcohol in the general population and the recognized health and economic burdens of stroke, our findings are both important and timely. Our study strongly suggests that reducing alcohol consumption in heavy drinkers should be an important approach to prevention of stroke in the general population. Our study also suggests that moderate alcohol consumption reduces risk of ischemic stroke. However, the implications of these findings should be examined cautiously. Any advice regarding the consumption of alcohol should be tailored to the individual patient’s risks and potential benefits.

Author Contributions: Study concept and design: Reynolds, Lewis, Nolen, Kinney, Sathya, He. Acquisition of data: Reynolds, Lewis, Nolen, Kinney, Sathya, He. Analysis and interpretation of data: Reynolds, Lewis, Nolen, Kinney, Sathya, He. Drafting of the manuscript: Reynolds, Nolen, Kinney, Sathya, He. Critical revision of the manuscript for important intellectual content: Reynolds, Lewis, Nolen, Kinney, Sathya, He. Obtained funding: He. Administrative, technical, or material support: Lewis, Kinney, Sathya. Study supervision: He.

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widely, with particularly high rates of use by internists and physicians in the Northeast and the South.

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### CORRECTIONS

**Name Omitted:** In the Original Contribution entitled “Combination Therapy With Hormone Replacement and Alendronate for Prevention of Bone Loss in Elderly Women: A Randomized Controlled Trial” published in the May 21, 2003, issue of *THE JOURNAL* (2003;289:2525-2533), Michael McClurg, MD, should be added to the list of members of the Data and Safety Monitoring Board on page 2532 after Peggy A. Norton, MD.

**Error in Author’s Name:** In the Review article entitled “Alcohol Consumption and Risk of Stroke: A Meta-analysis” published in the February 5, 2003, issue of *THE JOURNAL* (2003;289:579-588) in the byline, the initial letter “L.” was incorrectly placed in front of the name of author Brian Lewis, MPH.

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