Alcohol Consumption and Risk of Ischemic Stroke

The Framingham Study

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Background and Purpose—Stroke is a major cause of death in the United States. The association between alcohol consumption and ischemic stroke (IS) remains controversial.

Methods—We used data collected on participants in the Framingham Study to assess the association between total alcohol intake and type of alcoholic beverage and development of IS, overall and according to age.

Results—A total of 196 men and 245 women developed IS during three 10-year follow-up periods. In the categories of never drinkers, drinkers of 0.1 to 11, 12 to 23, and ≥24 g/d of ethanol (a “typical drink” is ≈12 g of ethanol), and former drinkers of 0.1 to 11 and ≥12 g/d, crude incidence rates of IS were 6.5, 5.9, 4.9, 5.0, 6.7, and 17.8 cases per 1000 person-years, respectively, for men and 5.9, 4.1, 4.1, 4.3, 8.3, and 7.1, respectively, for women. Overall, compared with never drinkers in a multivariate Cox regression, current alcohol consumption was not related significantly to IS in either sex. Former drinking of ≥12 g/d of alcohol was associated with a 2.4 times higher risk of IS among men but not among women. When stratified by age, alcohol intake was associated with lower risk of IS among subjects aged 60 to 69 years. In beverage-specific analysis, only wine consumption was related to a decreased risk of IS.

Conclusions—Our data showed no significant association between total alcohol and IS overall but showed a protective effect of alcohol among subjects aged 60 to 69 years. (Stroke. 2002;33:907-912.)

Key Words: alcohol drinking ■ beer ■ cerebrovascular accident ■ stroke, ischemic ■ wine

Stroke remains one of the major causes of death in the United States and is associated with a substantial economic burden.1 Epidemiological studies have been inconsistent on the relation of total alcohol and type of alcoholic beverage to stroke.2–4 While some studies have suggested an increased risk of stroke with alcohol intake,5–9 there is evidence that consumption of small to moderate amounts of alcohol may be associated with lower risk of ischemic stroke (IS).3,10–16 The protective effect of alcohol on blood vessels may be mediated through the effects of alcohol on lipid peroxidation and coagulation.17 Little is known about type of alcoholic beverage and the risk of IS. Some studies have reported that wine consumption, but not beer or spirits intake, was related to a lower risk of stroke.10,18 Beer, wine, and spirits could have different effects on cardiovascular disease from other substances contained in these beverages, such as polyphenols with antioxidant properties that may influence cardiovascular pathophysiology.13,19,20 In the present study we assessed the relation of total alcohol consumption and type of alcoholic beverage to IS, overall and according to age.

Subjects and Methods

The Framingham Study is a population-based cohort study of 5209 subjects that started in 1948 in Framingham, Mass. After the first examination in 1948–1952, participants have been reexamined biennially. Detailed descriptions of the Framingham Study have been published previously.21,22 Informed consent was obtained repeatedly from study participants, and the study protocol was approved by the Institutional Review Board of the Boston University School of Medicine.

Assessment of Alcohol Consumption

Data on alcohol have been collected at examinations 2, 7, 9, 12 to 15, and 17 and at all subsequent examinations with the use of standardized questionnaires. At each of these examinations, each participant was asked if he/she had consumed alcohol in the past 12 months. If the answer was affirmative, the average weekly number of drinks consumed over the past year for spirits, beer, and wine was recorded. For this study, a drink was defined as 360 mL of beer containing 12.6 g of alcohol, 120 mL of wine containing 13.2 g of alcohol, or 37.5 mL of 80 proof spirits (approximately 40% ethanol by volume) containing 15 g of alcohol. At each examination, total alcohol was computed as the sum of ethanol contents in beer, wine, and spirits consumed. We used alcohol information from the second examination to classify former drinkers; thus, follow-up for the present analyses began with examination 7.
Outcome

Stroke events were detected by review of interim Framingham Heart Study examinations, daily surveillance of all admissions to the local hospital, and scrutiny of outside hospital records. For all potential cases of stroke, a panel of 3 investigators (including a neurologist) reviewed all medical records, radiographic images, a medical history, and findings from physical examinations performed at the Framingham Study to determine whether a stroke has occurred. In addition, since 1968, whenever possible, the Framingham Study neurologists have examined subjects in the hospital at the time of acute stroke. A detailed description of the stroke assessment in the Framingham Study has been published previously.23 Stroke events were categorized with previously published criteria as atherothrombotic brain infarction, cerebral embolus, intraparenchymal hemorrhage, or subarachnoid hemorrhage.24 Because of the small number of nonischemic strokes (n=63), the present study was limited to IS.

Other Variables

Cigarette smoking information was obtained through a standardized questionnaire. Subjects were asked if they smoked cigarettes in the past year, and, if the answer was affirmative, the number of cigarettes smoked per day was recorded. Resting blood pressure was measured twice by a physician according to a standard protocol, using a mercury sphygmomanometer and appropriately sized cuff. Subjects were asked about antihypertensive medications during each examination. Diabetes mellitus was defined as a history of physician-diagnosed diabetes mellitus or current treatment with hypoglycemic medications. Prevalent coronary heart disease was ascertained by standard protocols described previously.21,22 Height and weight were measured at every examination. Body mass index was computed as weight in kilograms divided by the square of height in meters. Atrial fibrillation and left ventricular hypertrophy were assessed through the review of standard 12-lead ECGs obtained at each visit.

Statistical Methods

Since alcohol consumption and/or the number of cigarettes smoked per day might change over time, a pooling method using subsequent 10-year follow-up periods (nonoverlapping) was used. For each 10-year period, information on alcohol intake and other covariates collected at the beginning of the follow-up period was used. Thus, alcohol consumption at the beginning of each of the three 10-year periods (at examinations 7, 12, and 17) was used as exposure in the pooled data. Of the 9628 person-observations, 457 were excluded for periods (at examinations 7, 12, and 17) was used as exposure in the 10-year period, information on alcohol intake and other covariates contributing to 1 (n=275). The final data set consisted of 9171 person-observations. Each subject could contribute to 1 (n=1100), 2 (n=1203), or 3 (n=1885) observations in the analyses if he/she was free of stroke at the beginning of each 10-year period.

For the initial 10-year follow-up period, each nondrinking participant at examination 7 was classified as “former nondrinker” or “former drinker” on the basis of his/her reported alcohol consumption at examination 2. For subsequent follow-up periods, previous drinking status was based on alcohol data recorded at all examinations preceding the beginning of the period. We classified subjects as never drinkers, current drinkers of 0.1 to 11, 12 to 23, and ≥24 g/d, and former drinkers of 0.1 to 11 and ≥12 g/d. Similar point estimates were obtained for current drinkers of 24 to 35 and ≥35 g/d, and therefore we collapsed these categories. We calculated person-years of follow up as the time from the beginning of each follow-up period to the occurrence of either (1) IS; (2) stroke; or (3) death, hemorrhagic stroke, or end of the 10-year period.

Age is an important determinant of stroke and also relates strongly to alcohol consumption. This is especially true for the elderly (aged >70 years), who may be in nursing homes or other facilities that limit their access to alcohol. Therefore, we examined the risk of IS overall as well as by age categories (<50, 50 to 59, 60 to 69, ≥70 years). Within each age group, we fitted a Cox model to estimate the association of alcohol consumption to IS. The first model adjusted for age only. The full model controlled for age, diabetes mellitus, and body mass index. Additional adjustment for blood pressure, left ventricular hypertrophy (yes/no), atrial fibrillation (yes/no), antihypertensive treatment (yes/no), and prevalence of coronary heart disease (yes/no) at the beginning of each interval did not alter the results. Both sexes were combined for age-specific analyses. Since there were few cases of IS (n=8) in the category <30 years, this stratum was dropped in the stratified analysis. Assumptions for the proportional hazard models were tested and were met.

To assess the association between beverage-specific alcohol and IS, we classified subjects as never or current drinkers for each type of beverage. We excluded former drinkers in this secondary analysis. In addition to the aforementioned covariates, the effects of each beverage type were adjusted for the other 2 beverages (by using 3 indicator variables for the 3 types of beverage in the same model). Thus, while controlling for the intake of other beverages, we evaluated whether each specific type affected the risk of IS differently from other beverages.

Results

Table 1 presents the baseline characteristics of the study participants, according to alcohol consumption. During the three 10-year follow-up periods, 196 men and 245 women developed IS. As shown in Table 2, crude incidence rates among men were lowest in those consuming 12 to 23 g/d of ethanol (4.9/1000 person-years) and highest in the former heavier drinker category (17.8/1000 person-years). For women, the lowest incidence rates were in women consuming 0.1 to 11 g/d and 12 to 23 g/d of ethanol (4.1 and 4.1 cases per 1000 person-years, respectively) and highest in former drinkers. In the multivariate model, alcohol consumption was not significantly associated with IS in either sex (Table 2). Among men who were former heavy drinkers, the risk of IS was 2.4 times greater than that of never drinkers among men, but no increase in risk was seen among women (Table 2).

Table 3 presents combined data for men and women stratified by age. A protective effect of alcohol intake on the risk of IS was observed in the age category of 60 to 69 years but not in the age groups of 50 to 59 and ≥70 years. Compared with never drinkers, the multivariate relative risks (95% CI) for 60 to 69 year-old subjects were 0.5 (0.3 to 0.8), 0.3 (0.2 to 0.7), 0.5 (0.3 to 0.9), 0.5 (0.3 to 0.8), and 1.2 (0.6 to 2.4) for the categories of drinkers of 0.1 to 11, 12 to 23, and ≥24 g/d and former drinkers of 0.1 to 11 and ≥12 g/d, respectively (Table 3). These results were not altered when additional risk factors were included in the model.

In a secondary analysis, we assessed the effects of beer, wine, and spirits on the risk of IS. There were 115 cases of IS (23 128 person-years) among wine drinkers compared with 213 cases (34 179 person-years) for nondrinkers of wine. For beer drinkers, 101 cases of IS were registered (18 590 person-years) compared with 227 cases among nondrinkers of beer (38 718 person-years). Corresponding numbers for spirits drinkers were 205 cases (38 749 person-years) and 123 cases of IS (18 559 person-years) among subjects who did not consume spirits. In multivariate analysis, we observed a borderline association of current wine drinking on IS (hazard ratio=0.8 [95% CI, 0.6 to 1.0]) but no effects for beer (hazard ratio=1.0 [95% CI, 0.8 to 1.4]) or spirits (hazard ratio=0.9 [95% CI, 0.7 to 1.2]) on the risk of IS.
Discussion

Our study found that when all ages were combined, total alcohol consumption was not significantly associated with IS. However, a protective effect of alcohol intake was observed among subjects aged 60 to 69 years. In addition, unlike beer and spirits, wine consumption was suggestive of a reduced risk of IS.

Epidemiological studies have been inconsistent on the association between alcohol and the risk of stroke. Some prospective studies have documented the J- or U-shaped relation between alcohol and the risk of stroke, with the estimated magnitude of effect averaging approximately 30% risk reduction for light to moderate drinking. In contrast, several case-control studies and cohort studies did not find an association between alcohol consumption and IS. Some epidemiological studies have reported an increased risk of IS with recent moderate and heavy alcohol consumption.

We found a protective effect of alcohol on IS only among subjects aged 60 to 69 years. We do not have a biological explanation for these findings and can only speculate. First, differential dietary and lifestyle habits across age groups may partially account for the findings. Second, access to alcohol may be different among older subjects than among younger ones. Third, the drinking patterns may vary with age. Younger age, for example, could be associated with unhealthy drinking habits such as binge drinking; heavy drinking has been associated with increased risk of IS. Fourth, the observed association may be due to chance.

Few studies have examined the association between the type of alcoholic beverage and ischemic stroke. We found a borderline significant protective effect of wine on IS in this study. This suggests that substances other than ethanol may be important in preventing atherosclerosis. In the Copenhagen City Heart Study, consumption of 3 to 5 glasses of wine or beer, but not spirits, was associated with a 56% or 28% reduction, respectively, in death from cardiovascular and cerebrovascular disease. Truelsen et al reported that only wine intake was associated with a reduction of the risk of stroke. In a case-control study, wine consumption was found to be associated with lower odds of IS (odds ratio = 0.55 [95% CI, 0.31 to 0.98]) among young women, but beer (odds ratio = 0.92 [95% CI, 0.53 to 1.61]) or spirits (odds ratio = 1.35 [95% CI, 0.73 to 2.49]) consumption did not show a significant effect. Our beverage-specific findings are consistent with these previous studies.
Varying results from studies on the alcohol-IS relation can be partially explained by methodological issues: few studies have separated former drinkers from lifetime abstainers but have used all current nondrinkers as the referent group. As seen in our results, further distinction between former light and former heavier drinkers appears to be important since these categories may have different risks for IS. In addition, classification of the amount of alcohol consumed has varied across studies, making it difficult to compare studies with different cut points of alcohol exposure. In many studies,

### TABLE 2. Risk and Hazard Ratio of IS According to Total Ethanol Intake Among Participants of the Framingham Study

<table>
<thead>
<tr>
<th>Ethanol, g/d</th>
<th>Case/Person-Years</th>
<th>Incidence Rate, Cases/1000 Person-Years</th>
<th>Age-Adjusted Hazard Ratio</th>
<th>Multivariate Adjusted Hazard Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>15/2300</td>
<td>6.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1–11</td>
<td>59/10 035</td>
<td>5.9</td>
<td>1.0 (0.6–1.7)</td>
<td>0.8 (0.4–1.5)</td>
</tr>
<tr>
<td>12–23</td>
<td>24/4910</td>
<td>4.9</td>
<td>0.8 (0.4–1.6)</td>
<td>0.7 (0.4–1.4)</td>
</tr>
<tr>
<td>≥24</td>
<td>60/12 042</td>
<td>5.0</td>
<td>0.9 (0.5–1.6)</td>
<td>0.8 (0.4–1.5)</td>
</tr>
<tr>
<td>Former (0.1–11)</td>
<td>18/2703</td>
<td>6.7</td>
<td>0.8 (0.4–1.6)</td>
<td>0.8 (0.4–1.6)</td>
</tr>
<tr>
<td>Former (≥12)</td>
<td>20/1127</td>
<td>17.8</td>
<td>2.6 (1.3–5.1)</td>
<td>2.4 (1.2–4.8)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54/9186</td>
<td>5.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1–11</td>
<td>77/19 034</td>
<td>4.1</td>
<td>0.9 (0.6–1.3)</td>
<td>0.9 (0.6–1.3)</td>
</tr>
<tr>
<td>12–23</td>
<td>19/4670</td>
<td>4.1</td>
<td>0.8 (0.5–1.4)</td>
<td>0.8 (0.5–1.4)</td>
</tr>
<tr>
<td>≥24</td>
<td>28/6517</td>
<td>4.3</td>
<td>1.2 (0.7–1.9)</td>
<td>0.9 (0.5–1.5)</td>
</tr>
<tr>
<td>Former (0.1–11)</td>
<td>59/7151</td>
<td>8.3</td>
<td>1.1 (0.8–1.6)</td>
<td>1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Former (≥12)</td>
<td>8/1129</td>
<td>7.1</td>
<td>1.0 (0.5–2.0)</td>
<td>0.8 (0.4–1.7)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI.  
*Adjusted for age, body mass index, smoking, and diabetes mellitus.

### TABLE 3. Risk and Hazard Ratio of IS According to Age and Total Ethanol Intake Among Participants of the Framingham Study

<table>
<thead>
<tr>
<th>Ethanol, g/d</th>
<th>Case/Person-Years</th>
<th>Incidence Rate, Cases/1000 Person-Years</th>
<th>Age- and Sex-Adjusted Hazard Ratio</th>
<th>Multivariate-Adjusted Hazard Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4/3028</td>
<td>1.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1–11</td>
<td>14/9267</td>
<td>1.5</td>
<td>1.1 (0.4–3.4)</td>
<td>1.4 (0.4–4.4)</td>
</tr>
<tr>
<td>12–23</td>
<td>5/2951</td>
<td>1.7</td>
<td>1.2 (0.3–4.4)</td>
<td>1.5 (0.4–6.3)</td>
</tr>
<tr>
<td>≥24</td>
<td>20/6486</td>
<td>3.1</td>
<td>2.1 (0.7–6.4)</td>
<td>2.2 (0.6–7.5)</td>
</tr>
<tr>
<td>Former (0.1–11)</td>
<td>6/2058</td>
<td>2.9</td>
<td>2.1 (0.6–7.6)</td>
<td>2.3 (0.6–8.5)</td>
</tr>
<tr>
<td>Former (≥12)</td>
<td>2/546</td>
<td>3.7</td>
<td>2.4 (0.4–13.3)</td>
<td>1.6 (0.2–14.9)</td>
</tr>
<tr>
<td>60–69 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>34/4094</td>
<td>8.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1–11</td>
<td>53/9978</td>
<td>5.3</td>
<td>0.6 (0.4–0.9)</td>
<td>0.5 (0.3–0.8)</td>
</tr>
<tr>
<td>12–23</td>
<td>14/3373</td>
<td>4.2</td>
<td>0.4 (0.2–0.8)</td>
<td>0.3 (0.2–0.7)</td>
</tr>
<tr>
<td>≥24</td>
<td>40/6171</td>
<td>6.5</td>
<td>0.6 (0.4–1.0)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>Former (0.1–11)</td>
<td>18/3902</td>
<td>4.6</td>
<td>0.5 (0.3–0.9)</td>
<td>0.5 (0.3–0.8)</td>
</tr>
<tr>
<td>Former (≥12)</td>
<td>14/843</td>
<td>16.6</td>
<td>1.7 (0.9–3.3)</td>
<td>1.2 (0.6–2.4)</td>
</tr>
<tr>
<td>≥70 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>30/2912</td>
<td>10.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1–11</td>
<td>63/4989</td>
<td>12.6</td>
<td>1.3 (0.8–2.0)</td>
<td>1.2 (0.7–1.8)</td>
</tr>
<tr>
<td>12–23</td>
<td>24/1719</td>
<td>14.0</td>
<td>1.3 (0.8–2.3)</td>
<td>1.3 (0.7–2.3)</td>
</tr>
<tr>
<td>≥24</td>
<td>27/2340</td>
<td>11.5</td>
<td>1.1 (0.7–1.9)</td>
<td>1.0 (0.5–1.8)</td>
</tr>
<tr>
<td>Former (0.1–11)</td>
<td>53/3194</td>
<td>16.6</td>
<td>1.5 (1.0–2.4)</td>
<td>1.4 (0.8–2.2)</td>
</tr>
<tr>
<td>Former (≥12)</td>
<td>12/670</td>
<td>17.9</td>
<td>1.7 (0.9–3.3)</td>
<td>1.7 (0.8–3.3)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI.  
*Adjusted for age, sex, body mass index, smoking, and diabetes mellitus.
alcohol exposure has been assessed only at baseline, and it has been shown that there is a tendency for alcohol consumption to decrease with aging.\textsuperscript{35} Ignoring the changes in drinking habits with time could lead to misclassification of alcohol intake and bias the estimate of effect.

Our study has some limitations: (1) We were not able to identify binge drinkers, who may have a different risk of IS than regular moderate drinkers. Binge drinking has been associated with raised systolic and diastolic blood pressure\textsuperscript{36} and could thus increase the risk of stroke. (2) Despite a standardized questionnaire, underreporting of alcohol intake by the study participants may have biased our results. (3) We were unable to control confounding by dietary factors since we did not collect adequate data on diet among subjects used in these analyses. The large number of subjects, the use of standardized protocols, and the repeated data collection are strengths of this study.

Alcohol may protect against atherosclerosis by decreasing lipoprotein(a),\textsuperscript{37} increasing HDL cholesterol,\textsuperscript{38,39} or inhibiting LDL oxidation. Alcohol consumption is also associated with decreased platelet aggregation,\textsuperscript{40} decreased fibrinogen levels,\textsuperscript{41} increased concentration of tissue plasminogen activator,\textsuperscript{42,43} and enhanced insulin sensitivity.\textsuperscript{44} Wine also contains phenolic compounds with antioxidant properties,\textsuperscript{45} and consumption of polyphenols from other sources is associated with a decreased risk of cardiovascular disease.\textsuperscript{46}

In conclusion, our study found no significant association between moderate alcohol consumption and IS in the overall population but found a protective effect among subjects aged 60 to 69 years. Wine, but not beer or spirits, appeared to be protective against IS.

Acknowledgment

This study was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (contract N01-HC-38038).

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Stroke. 2002;33:907-912
doi: 10.1161/hs0402.105245

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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This study was supported in part by grant NS17950 from the National Institute of Neurological Diseases and Stroke, National Institutes of Health, and by contract HC38038 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.

The authors apologize for this error.