Regular Light-to-Moderate Intake of Alcohol and the Risk of Ischemic Stroke
Is There a Beneficial Effect?

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Background and Purpose: To evaluate the association between different patterns of alcohol consumption and the risk of ischemic stroke in young or middle-aged men.

Methods: One hundred fifty-six patients and 153 control subjects were included in this case-control study. The pattern and the estimated average weekly intake of alcohol were assessed using a structured questionnaire. The pattern of drinking was defined as regular (daily or almost daily) or irregular (up to three times per week), and the weekly amount of consumption was defined as nondrinking, light-to-moderate drinking (up to 150 g/wk), moderate drinking (>150 to 300 g/wk), and heavy drinking (>300 g/wk). Multiple stepwise logistic regression models were used, and adjustments were carried out for potential confounders.

Results: Heavy alcohol intake associated with an increased risk of stroke (odds ratio, 4.45; 95% confidence interval, 1.09 to 18.1), whereas the risk tended to be reduced in light-to-moderate drinkers (odds ratio, 0.54; 95% confidence interval, 0.28 to 1.05). Accounting for the pattern of alcohol intake in addition to the average weekly amount in grams, regular light-to-moderate drinking showed a significant inverse association with stroke (odds ratio, 0.12; 95% confidence interval, 0.02 to 0.65), and an irregular pattern of consumption attenuated this association. Based on the same multivariate analyses, other significant independent risk factors for stroke were arterial hypertension, coronary heart disease, and history of snoring, whereas the contributions of age, diabetes mellitus, smoking, and body mass index proved to be nonsignificant.

Conclusions: Light-to-moderate alcohol intake appears to have an inverse association with the risk of ischemic stroke. The beneficial effect appears to be most prominent if the consumption of alcohol is regular and evenly distributed throughout the week, whereas a sporadic or an occasional pattern of drinking seems to weaken the association. This study also supports the role of heavy drinking as an independent risk factor for ischemic stroke. (Stroke. 1993;24:1828-1832.)

Key Words • alcohol drinking • cerebral ischemia • risk factors

Reports of the association between alcohol consumption and the risk of stroke are conflicting. Heavy drinking may be a predisposing factor to all stroke subtypes, whereas moderate alcohol intake may reduce the risk of stroke. Based on a comprehensive review by Camargo, a positive linear association appears to exist between alcohol intake and risk of hemorrhagic stroke subtypes, whereas the association between drinking and ischemic stroke may follow a J-shaped pattern. In a recent study by Gill et al., however, moderate alcohol consumption showed an independent inverse association in a similar way with ischemic as well as with hemorrhagic stroke separately.

Several confounding factors may be coincident with ethanol ingestion and the risk of stroke: arterial hypertension, smoking, age, sex, diabetes mellitus, cardiac disease, atherosclerosis, lipids and lipoproteins, and hematological variables. Snoring and sleep apnea are also suggested as risk factors for ischemic stroke, and alcohol intake aggravates snoring and apneas in snorers.

Drinking habits are usually expressed as a binary variable (drinking versus nondrinking), or the estimates of drinking are based on the average amount of alcohol consumed per unit of time (eg, consumption in grams per week). Although the latter approach is considered to be superior, it does not take into account the possible variability in drinking habits. There is evidence that regular drinking does not have the same health effects as does drinking large amounts occasionally, although there may be no difference in the estimated average weekly consumption. Alcohol intoxication or recent heavy drinking may increase the risk of stroke, and failure to differentiate between occasional binge drinkers and regular moderate drinkers may obscure real associations.

In this study, our purpose was to evaluate the association between alcohol consumption and the risk of ischemic stroke while simultaneously accounting for data on the estimated average weekly amount of alcohol intake as well as the frequency of drinking and controlling for potential confounding factors.
Patients and Methods

We studied 177 consecutive male patients up to 60 years of age who were admitted to Helsinki University Central Hospital due to an acute ischemic stroke. In all cases, brain infarction was diagnosed by a neurologist and confirmed in 171 cases (96.6%) by neuroradiological methods.

For each stroke patient, we selected an age-matched (±6 years) male control subject from a series of patients admitted for other reasons who had no history of ischemic cerebrovascular disease. The spectrum of their diseases was wide, including gastrointestinal and genitourinary emergencies (41% and 19%, respectively), cardiovascular disturbances (11%), pulmonary diseases (9%), hematological problems (5%), and others (15%).

When assessing the risk factors for ischemic stroke in patients and control subjects, we used their earlier hospital documents and information from clinical and laboratory examinations during their hospital stay. Each patient and control subject also was interviewed concerning a detailed medical history. If necessary, cohabiting friends or relatives were interviewed.

We determined the presence of arterial hypertension (previous use of antihypertensive medication or systolic or diastolic blood pressure of at least 150 or 100 mm Hg during follow-up, respectively), coronary heart disease (previous myocardial infarction or typical angina pectoris requiring medication), and diabetes mellitus (previous antidiabetic medication or special diet because of impaired glucose tolerance known previously or diabetic blood glucose recordings during follow-up). Body mass index in kilograms per square meter was also calculated.

We used a structured questionnaire to obtain the data on smoking, alcohol consumption, and sleeping habits. The questionnaire was directed at clarifying the frequency of drinking, but the quantity of alcohol consumption on usual occasions also was questioned, and in a vast majority of patients and control subjects (156 of 177 [88.1%] and 153 of 177 [86.4%], respectively), a reliable estimate of the average weekly alcohol intake in grams was obtainable in addition to the frequency of drinking. Twelve grams of alcohol was estimated to be approximately equal to one standard drink.

Snoring history was categorized as “always or almost always” (habitual snoring), “often,” “occasionally,” or “never.” For statistical purposes, arterial hypertension, coronary heart disease, and diabetes mellitus were dichotomized as “yes” versus “no,” and snoring was categorized as “habitually or often” versus “occasionally or never.” Smoking habits were classified as “never smoking,” “ex-smoking,” “>0 to 10 cigarettes/day,” and “>10 cigarettes/day.” The quantity of drinking was categorized as “0 g/wk” (nondrinking), “>0 to 150 g/wk” (light-to-moderate drinking), “>150 to 300 g/wk” (moderate drinking), and “>300 g/wk” (heavy drinking). The pattern of alcohol intake was defined as “regular” (daily or almost daily) versus “irregular” (not exceeding one to three times per week). Body mass index was modeled as a continuous variable.

We included only subjects who had complete data on drinking habits in the following analyses. Therefore, 156 patients and 153 control subjects could be included, and the associations among different amounts of alcohol, the pattern of drinking, and the risk of ischemic stroke were assessed using stepwise multiple logistic regression models, with adjustments carried out for potential confounding variables.

Results

The occurrences of potential risk factors for ischemic stroke in 156 patients and 153 control subjects are shown in Tables 1 and 2. The mean ages of the patients and control subjects were 48.8 years (median, 52 years; range, 16 to 60 years) and 49.6 years (median, 51 years; range, 22 to 65 years), respectively. Table 2 presents the four categories of the average weekly consumption of alcohol in grams together with the pattern of drinking in patients and control subjects. The adjusted risks of an ischemic stroke with different amounts of alcohol intake in patients and control subjects are presented in Table 3. Light-to-moderate drinking (up to 150 g/wk) showed a marginal independent inverse association with ischemic stroke when compared with nondrinking, whereas

<table>
<thead>
<tr>
<th>Table 1. Potential Risk Factors for Ischemic Stroke in 156 Male Patients and 153 Male Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial hypertension, no. (%)</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>53/156 (34.0)</td>
</tr>
<tr>
<td><strong>Coronary heart disease, no. (%)</strong></td>
</tr>
<tr>
<td><strong>Diabetes mellitus, no. (%)</strong></td>
</tr>
<tr>
<td><strong>Snoring habitually or often, no. (%)</strong></td>
</tr>
<tr>
<td><strong>Smoking, no. (%)</strong></td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Ex-smoking</td>
</tr>
<tr>
<td>&gt;10 Cigarettes/day</td>
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<tr>
<td>&gt;10 Cigarettes/day</td>
</tr>
<tr>
<td><strong>Body mass index, Mean (SD)</strong>*</td>
</tr>
</tbody>
</table>

*n=154 for patients, n=153 for control subjects.

<table>
<thead>
<tr>
<th>Table 2. Estimated Weekly Consumption of Alcohol and Pattern of Drinking in Male Stroke Patients and Male Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohol Consumption, g/w</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>0 (Nondrinkers)</td>
</tr>
<tr>
<td>&gt;0 to 150</td>
</tr>
<tr>
<td>Irregular*</td>
</tr>
<tr>
<td>Regular†</td>
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<tr>
<td>&gt;150 to 300</td>
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<tr>
<td>Irregular</td>
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<tr>
<td>Regular</td>
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<tr>
<td>&gt;300</td>
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<tr>
<td>Irregular</td>
</tr>
<tr>
<td>Regular</td>
</tr>
</tbody>
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*Up to one to three times per week.
†Daily or almost daily.
TABLE 3. Adjusted Risks of Ischemic Stroke With Different Average Weekly Amounts of Alcohol Consumption in 156 Male Patients and 153 Male Control Subjects From a Multiple Stepwise Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Alcohol Consumption, g/wk</th>
<th>Coefficient</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Nondrinkers)</td>
<td>...</td>
<td>...</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>&gt;0 to 150</td>
<td>-0.61077</td>
<td>0.3371</td>
<td>0.54</td>
<td>0.28 to 1.05</td>
</tr>
<tr>
<td>&gt;150 to 300</td>
<td>-0.15616</td>
<td>0.4748</td>
<td>0.86</td>
<td>0.34 to 2.18</td>
</tr>
<tr>
<td>&gt;300</td>
<td>1.4838</td>
<td>0.7120</td>
<td>4.41</td>
<td>1.09 to 17.8</td>
</tr>
</tbody>
</table>

SE indicates standard error of the coefficient; OR, odds ratio; and CI, confidence interval.

Other factors studied in the same multiple stepwise logistic regression analysis were arterial hypertension, coronary heart disease, smoking, body mass index, diabetes mellitus, history of snoring, and age.

Heavy drinking (more than 300 g during a week) proved to increase the risk of stroke by more than fourfold. Other significant risk factors for stroke from the same logistic regression analysis were arterial hypertension (odds ratio, 2.85; 95% confidence interval [CI], 1.53 to 5.33), coronary heart disease (odds ratio, 2.70; 95% CI, 1.38 to 5.29), and snoring (odds ratio, 2.20; 95% CI, 1.32 to 3.68), whereas the contributions of diabetes mellitus, smoking, and body mass index were not significant.

An additional logistic regression analysis was carried out to evaluate the adjusted combined influences of the pattern of drinking and average weekly amount of alcohol (Table 4). Compared with nondrinkers, there appeared to be a clear independent inverse association between light-to-moderate consumption of alcohol and the risk of stroke if drinking was evenly distributed throughout the week (daily or almost daily) (odds ratio, 0.12; 95% CI, 0.02 to 0.65). On the other hand, irregular drinking (not more than three times a week), even within the same range of average weekly amount in grams, did not show any significant beneficial effect, although a tendency toward benefit was still present (odds ratio, 0.59). The apparent beneficial effect of regular drinking on stroke was most prominent if the amount of weekly consumption ranged between 50 and 150 g (odds ratio, 0.06; 95% CI, 0.01 to 0.55).

After matching by age (±6 years), a slight difference in mean age existed between patients and control subjects in the groups with complete data on alcohol consumption (48.8 and 49.6 years, respectively). Although this difference was not significant, the possible confounding effect of age was also tested in multiple stepwise logistic regression models as an additional independent variable. It did not enter the final models as a significant variable, nor did it affect the independent contributions of other factors tested.

Exclusion of the 16 patients who were not able to give their drinking history themselves did not affect the results, nor did exclusion of 18 patients with previous strokes have a notable influence.

**Discussion**

In the present case-control study, alcohol consumption appeared to exhibit a nonlinear relation to ischemic stroke among young or middle-aged men. With nondrinkers as the baseline, regular light-to-moderate intake of alcohol (daily or almost daily consumption not exceeding the average amount of 150 g/wk) showed an inverse association with the risk of ischemic stroke. This association was independent of the influences of arterial hypertension, coronary heart disease, history of snoring, age, diabetes mellitus, smoking, and body mass index. The significant reduction of the risk did not hold true for irregular drinking despite the same range of average weekly consumption in grams, nor did larger amounts of alcohol (>150 g/wk) show a significant beneficial effect regardless of the regularity of drinking. By contrast, more than 300 g/wk (heavy drinking) proved to have an opposite effect, thereby increasing the risk of stroke by more than fourfold. In other words, a J-shaped association between alcohol intake and ischemic stroke was evident in young or middle-aged men, and light-to-moderate regular drinking appears to be a potential protecting factor against ischemic stroke in this patient group.

The results of our study are in agreement with earlier observations regarding both the potential beneficial effect of light drinking and the detrimental effects of heavy drinking on ischemic stroke. In a case-control study by Gill et al, the risk of stroke was significantly less in light drinkers (those consuming 10 to 90 g/wk of alcohol) than in nondrinkers (adjusted relative risk, 0.5) but was fourfold higher in heavy drinkers (consuming ≥300 g/wk). In a cohort study in female nurses (Nurses’ Health Study), alcohol intake was significantly associated with a decreased risk of ischemic stroke. For 5 to 14 g/d of alcohol, the relative risk was 0.3 after adjustments were carried out for 14 factors.

The epidemiological evidence linking light or moderate alcohol consumption to ischemic stroke is still controversial. Two of several case-control studies re-
viewed by Camargo\textsuperscript{6} found evidence for a J-shaped association between level of alcohol intake and total stroke, but three studies specifically addressing the risk of ischemic stroke found no association. In the same review, five of nine cohort studies reported evidence for a U-shaped relation between drinking and total stroke, but of the four studies specifically concentrating on ischemic stroke, only one found an independent U-shaped association.\textsuperscript{6}

The influences and consequences of alcohol consumption may be dependent on differences in drinking pattern at a given level of average consumption.\textsuperscript{12-14} Although average alcohol intake emerged as a significant predictor of both systolic and diastolic blood pressure, drinking large amounts at one time increased blood pressure more than did spreading the same amount of alcohol drank over several days.\textsuperscript{13} In another study, the relation between patterns of alcohol intake and coronary occlusion was studied in 526 male patients with coronary arteriography.\textsuperscript{12} Higher levels of occlusion were found among nondrinkers and drinkers with patterns of variable intake, whereas significantly lower levels of occlusion were observed for regular drinkers who drank relatively consistent amounts. The findings suggested that the potential beneficial effect of alcohol appeared to be reversed by a sporadic pattern of alcohol intake.\textsuperscript{13} It has also been shown that moderate, regular daily consumption of ethanol may produce a favorable lipoprotein profile as far as coronary heart disease is concerned, whereas unfavorable alterations in lipoprotein composition occur when the same average weekly dose is concentrated in a bing cycle.\textsuperscript{14} Recent binge drinking may also be a strong determinant of the risk of stroke instead of giving any beneficial effects.\textsuperscript{1,2} Accordingly, the associations between alcohol and stroke may be obscured if different intake patterns are merged, although no differences might exist in the average long-term amounts of consumption.

We do not have accurate data on the types of alcohol consumed by patients in our study. However, the types of alcohol may differ according to the pattern of drinking, which might contribute to the differences in risks between different drinking patterns. This possibility should be evaluated in future studies.

When the estimates of alcohol intake are based on questionnaire data, response errors are possible. In particular, the acute stage of stroke may affect the ability to accurately answer questions. In all cases, alcohol intake habits obtained from relatives or friends may be more accurate than self-reported data, and heavy drinkers especially might give underestimated data on their own drinking. The data on alcohol use were obtained from relatives concerning 16 stroke patients, whereas all control patients were able to give their own history of drinking. To avoid information bias in the present study, repeated analyses were carried out including patients and control subjects with self-reported data only, but it did not affect the results. In earlier work, self-reported data have been in agreement with biochemical markers of drinking.\textsuperscript{3,16}

To obtain as reliable data on alcohol consumption as possible, the data on drinking habits were based on data from the recent years, and we used current nondrinkers as the reference group. Past heavy drinkers and lifelong abstainers may differ in their general health and behavior factors.\textsuperscript{17-19} In particular, former heavy consumers of alcohol may have stopped drinking due to their increased morbidity, which might lead to biased associations between alcohol intake and stroke when current nondrinkers are used as the reference group. However, in earlier studies,\textsuperscript{4,16} the J- or U-shaped relation between drinking and stroke has held true even after taking into account this potential source of bias, suggesting that it is not an artifactual finding. Although the morbidity of past heavy drinkers may resemble that of current heavy drinkers, these groups may also share other unfavorable risk factor profiles with regard to stroke. A bias introduced by possible excess of risk factors in our nondrinking patient group could be avoided because the associations between stroke and different categories of alcohol intake were adjusted for several important determinants of stroke, such as arterial hypertension, smoking, and diabetes mellitus. Moreover, excluding all patients with earlier strokes and carrying out repeated analyses concerning first-time strokes only did not affect the results.

The use of other hospitalized patients as control subjects for stroke patients requires special attention. The risk of hospitalization may be related to alcohol use among control subjects, which might affect the observed associations between alcohol consumption and the risk of stroke in our study. Control patients were selected on the basis of not having either positive or negative associations with alcohol intake and their present illness. However, the control group also included many patients with diseases probably unrelated to alcohol, such as acute appendicitis, acute cholecystolithiasis, or acute ureterolithiasis, which could explain the relatively low proportion of heavy drinkers among the control subjects. On the other hand, the impact of other established risk factors on the risk of ischemic stroke was in overall agreement with that derived from several community-based surveys, suggesting that our sample of control subjects is not significantly biased. Also, the odds ratios of diabetes mellitus and current smoking for stroke (1.7 and 1.5, respectively) were in keeping with earlier studies, although due to wide confidence intervals their contributions were not significant.

Because of the relatively small number of subjects in the category of light-to-moderate alcohol use in our study, the strong inverse association between this drinking pattern and the risk of brain infarction must be interpreted with caution. It is not even possible to reform a real causal relation on the basis of a case-control study. However, light-to-moderate alcohol consumption may exert a protective effect on ischemic stroke similar to that proposed for coronary heart disease.\textsuperscript{12,16,20,22} Among the mechanisms that could mediate the potential protective effect of ethanol for ischemic cerebrovascular diseases are elevated levels of prostacyclin and beneficial shifts in the prostacyclin-to-thromboxane ratio,\textsuperscript{23-25} decreased levels of fibrinogen,\textsuperscript{26} and an augmented fibrinolytic activity due to enhanced secretion of plasminogen activator.\textsuperscript{27} Moderate doses of alcohol may also influence blood lipid or lipoprotein levels,\textsuperscript{14,28,29} and elevations of high-density lipoprotein cholesterol as well as apolipoproteins A-I and A-II are suggested as most plausible mechanisms of the inverse relation between coronary heart disease and moderate alcohol intake.\textsuperscript{14,21,28} An inverse relation has also been docu-
mented between alcohol intake and atherosclerosis in the large arteries of the circle of Willis, and in 11 major cervical arteries. Accordingly, by limiting the extent of atherosclerosis, moderate amounts of alcohol might also limit the basic pathophysiological process leading to atherothrombotic events.

Snoring and sleep apnea are suggested to be independent determinants of brain infarction, and heavy drinking may aggravate snoring and apneic breathing disturbances in snorers. However, based on logistic regression models, heavy drinking and snoring proved to show independent associations with stroke, and the numbers of snorers and nonsnorers in different drinking categories did not differ significantly.

In conclusion, this case-control study supports the view that heavy alcohol consumption increases the risk of ischemic stroke. The association between drinking and stroke appears to be nonlinear, and regular light-to-moderate alcohol intake may be a protecting factor against ischemic stroke, at least in young or middle-aged men. The potential beneficial effect appears to be reduced by an irregular or sporadic pattern of alcohol intake, ie, binge drinking, although the total weekly amount consumed would remain "moderate." Accordingly, in future studies dealing with alcohol intake and the risk of stroke, accounting for the differences in drinking patterns in addition to the quantitative estimations of average alcohol consumption might give more consistent results.

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References

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World Wide Web at:
http://stroke.ahajournals.org/content/24/12/1828