Stroke Risk From Alcohol Consumption
Using Different Control Groups

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Background and Purpose: Our aim in this study was to investigate the relation between chronic alcohol consumption and stroke.

Methods: A case-control study was carried out using two hospital-based control groups and the results of a community-based survey of alcohol consumption. Hospital-based control subjects were chosen either from "general" medical admissions or a subset of "select" admissions that excluded possible alcohol-related admissions. Cases were selected from hospital inpatients.

Results: The relative risk for stroke associated with alcohol consumption greater than 300 grams per week for general control subjects was 0.73 (95% confidence interval [CI], 0.54-3.49) compared with 1.30 (95% CI, 0.42-4.05) for select control subjects. The odds ratio was further increased to 1.93 (95% CI, 0.87-4.28) using data from the community-based survey. None of these estimates were statistically significant.

Conclusions: These results illustrate how the risk associated with alcohol consumption varies depending on the choice of control groups and may explain the contradictory results from previous case-control studies. Because of different biases associated with control selection, we believe that the results of this study are consistent with those of other studies that demonstrate a modest increased risk for stroke associated with alcohol consumption. (Stroke 1992;23:1093-1098)

Key Words • alcohol drinking • risk factors

Alcohol has been recognized as a possible risk factor for stroke from as early as 1725. Since that time, at least 62 different epidemiological studies have examined this association. A case-control study from Birmingham, UK, was the first to suggest a markedly raised odds ratio for heavy drinking among men. The use of elective surgical patients as control subjects may have overestimated the true odds ratio because of an underrepresentation of heavy drinkers (exclusion bias). As different control groups may produce varying results in case-control studies, we have examined the effect on the relation between chronic alcohol consumption and stroke using two sets of controls: general medical admissions plus a subset of admissions excluding possible alcohol-related conditions, and in addition a community survey from a general practice.

Subjects and Methods

Patients were recruited from admissions to three adjoining hospitals. They were identified through daily contact with the admissions office, accident and emergency department, junior medical staff, and, where available, computed tomography department. Inclusion criteria for cases were age between 15 and 69 years, no past history of stroke or transient ischemic attacks, and diagnosis of possible stroke by admitting medical team. Cases in which subsequent diagnostic information altered the diagnosis were later excluded.

Hospital controls were chosen from the same sources as the cases and met the same inclusion criteria but had an admission diagnosis other than possible or definite stroke. Two control groups were chosen, and these will be referred to as the "general" or "select" controls. Both groups were matched to cases on the basis of sex, hospital of admission, age (5-year age-matching was used for select controls whereas 10-years matching was used for general controls), and time of week of admission (weekend or weekday). Potential control subjects were excluded if the primary reason for current admission was an acute general surgical admission, a social admission, an overdose, or mental illness (including alcoholism); or if the patient was unable to speak English or was not a UK resident. In addition, the select group had as grounds for exclusion a further list of medical conditions as reasons for admission that could possibly be related to alcohol ingestion: cirrhosis of the liver, hemochromatosis, and all other diseases of the liver; acute gastritis; major gastrointestinal disease; myocarditis or cardiomyopathy; neuropathy; epilepsy; or myocardial infarction.

Cases and controls were interviewed as soon after admission as possible. As it was not possible to blind
The discharge diagnoses for all patients with a clinical diagnosis of stroke were independently examined to allocate cases into an appropriate subtype. Using these two methods, only 8 (4.9%) cases were unclassifiable. The purpose of the study was to investigate the role of lifestyle factors in sickness and health. They were not aware that the study was specifically examining cerebrovascular disease and its possible relation with alcohol. Alcohol consumption was assessed by a quantity/frequency measure based on the General Household Survey. Weekly alcohol intake was calculated and grams of alcohol per week estimated assuming 1 unit equals 10 grams. In addition, the CAGE screening questions were asked; the four simple questions used in this screening tool have been shown in several studies to have a sensitivity of 76–93% and specificity of 89–94% and to be superior to biochemical screening tests in detection of problem drinkers.

All cases and controls had the following information extracted from their medical notes: clinical history and examination, biochemical and hematological parameters (specifically, y-glutamyltranspeptidase, aspartate transaminase, and mean corpuscular volume), and other relevant investigations (e.g., lumbar puncture, computed tomographic [CT] scan, and cerebral angiography). The laboratory data were taken from routine clinical workup.

Patients were accepted as cases only if they had objective evidence of a stroke from CT scans, which were performed in 54% of cases, or from lumbar puncture/cerebral angiography. The remaining subjects with a clinical diagnosis of stroke were independently reviewed by either a consultant neurologist or one of the investigators and were included if they fulfilled the World Health Organization criteria for stroke: "A focal or global disturbance of cerebral function leading to death or persisting for more than 24 hours, with no apparent cause other than vascular." Subdivision of stroke types into hemorrhage or infarction was based on either a clinically/radiologically proven diagnosis or the Allen criteria with an 80% cutoff. This scale uses routine information from clinical history and physical examination to allocate cases into an appropriate subtype. Using these two methods, only 8 (4.9%) cases were unclassifiable. The discharge diagnoses for all hospital controls were obtained and coded according to the ninth revision of the International Classification of Diseases (ICD). As an additional source of data on alcohol consumption, we surveyed patients from a general practice whose catchment area included two of the three hospitals. The age-sex register for all patients 16–70 years of age was the sampling frame for the survey. The survey questionnaire used wording identical to that in the case–control study for questions concerning alcohol consumption. Questions on smoking and exercise were also included because subjects were informed that they were taking part in a health survey. The questionnaire was tested on 25 individuals to check for comprehensibility and ambiguity. Because this central London population is known to be very mobile and approximately 25% of registered patients are living in temporary residences, accurate practice lists are impossible to maintain. Each letter had a post office return sticker so that questionnaires not delivered would be returned with some indication as to why they had failed to reach the subject. We found 3,382 potential subjects from the register. However, 14 addresses were duplicated, and 85 subjects had addresses with insufficient detail. The post office returned 1,264 questionnaires due to either an inaccurate address or the subject no longer residing at the address, leaving 2,018 questionnaires.

All data on occupation were classified by the Registrar General's criteria for social class. This groups occupations into six categories from social class I (highest) to social class V (lowest). Those subjects who were retired were classified according to their last full-time occupation. Women were classified according to their husband's occupation if married or classified by their occupation if unmarried.

The data were analyzed using SAS/PC and EGRET for regression analysis. Comparison of proportions was performed by the $\chi^2$ test and mean values by $t$ tests. Because aspartate transaminase values were not normally distributed and transformations were relatively ineffective, the Wilcoxon rank sum score was used. Odds ratios were calculated by logistic regression. Because data on alcohol consumption were missing from some cases, analysis of the hospital control groups using individual matching resulted in a reduced sample size and power. In this study, however, the four matching criteria for the hospital control subjects gave rise to relatively few strata. In this situation, it has been shown that a superior analysis is achieved by stratifying the cases and controls according to their matching criteria and analyzing the data using conditional logistic regression. In our data set, the size of some of the strata became so large that conditional logistic regression became computationally unfeasible. We therefore analyzed the data using unconditional logistic regression but at the same time ensuring that there were sufficient terms in the models to control for the matching factors. This, in fact, enabled us to control for age more precisely than did the original matching criteria. The community control subjects were not individually matched and were analyzed in a conventional fashion by unconditional logistic regression. Possible confounding variables were chosen for inclusion in the models if they could be related to both the risk of disease outcome and possible exposure, e.g., smoking. A history of medication was also included as a broad marker of a chronic disease process. Social class was used in the early models but did not alter the odds ratios for the hospital control groups and was therefore excluded. Tests of significance were calculated using likelihood ratio tests, and odds ratios and 95% confidence intervals were calculated from the logistic regression coefficients and standard errors.

Results

One hundred sixty-four eligible cases were selected for the study: 111 (68%) cases of thromboembolic
stroke, 25 (15%) of hemorrhagic stroke, 20 (12%) of subarachnoid hemorrhage, and 8 (5%) of unclassified stroke; 165 general control and 115 select control subjects were also recruited. Because select controls had far more exclusion criteria, they were harder to obtain. Occasionally, control subjects were interviewed before a case was confirmed, which resulted in a greater number of general control subjects than cases and an unequal number of men and women in each group. Cases and controls did not differ significantly by age, sex, and social class. Non-Caucasians were significantly more common among the cases (p<0.02). The select controls also had a greater representation of single men (p<0.02), although this was not significant if marital status for males and females was combined.

The three most common diagnoses among the general controls were ischemic heart disease (ICD 410-414) (35%), other circulatory diseases excluding ischemic heart disease (ICD 390-409, 415-459) (20%), and respiratory diseases (ICD 460-519) (11%). For the select controls, the most common diagnoses were respiratory diseases excluding acute respiratory diseases (ICD 467-519) (29%), other circulatory diseases excluding ischemic heart disease (ICD 390-409, 415-459) (16%), and acute respiratory diseases (ICD 460-466) (15%). This variation reflects the different exclusion criteria for the select group.

From the total sample of 164 cases, data on alcohol consumption were only obtained on 115 cases. No data were obtained for 49 cases because in 29 cases (18%), the patients either died or were severely dysphasic, and no history could be obtained from a relative; in nine cases (5%), the patients were discharged before interview; and in 11 cases (7%), the patients did not give consent to participate in the study. These cases with missing alcohol data were compared with the 115 cases included (Table 1). No significant differences were found for demographic variables or laboratory results. Mean aspartate transaminase values were greater for cases with missing alcohol data, but this was not significant (p=0.07 by Wilcoxon rank sum score).

The relation between stroke and alcohol consumption is shown in Table 2 as odds ratios comparing cases with each control group. There were no significant associations between alcohol consumption or the classification based on the CAGE questions and risk of stroke. All analyses using the hospital-based control subjects were adjusted for age, sex, hospital, and day of admission (weekday/weekend). When using hospital-based control subjects, there were no significant associations between reported alcohol consumption or classification based on the CAGE questions and risk of stroke. The relation between stroke and alcohol consumption (grams per week), adjusted for cigarette smoking, history of hypertension, diabetes, heart disease, and race, is shown in Table 3. There was no significant interaction between sex and grams of alcohol consumed on the risk of stroke. All levels of alcohol consumption were associated with an increased odds ratio for the select controls, but these were not significant and did not show a dose-response relation. For the general control subjects, the highest level of consumption resulted in an odds ratio of less than one. Biochemical and hematological markers again showed no consistent relation, but aspartate transaminase levels showed an inverse relation for only the general control group, which indicated that general control subjects were more likely than stroke patients to have raised aspartate transaminase levels.

Among the hospital-based control subjects were 22 (8%) with known liver disease who might be expected to have abnormal liver function tests, compared with only four (2%) subjects among the cases (χ², p=0.067). These 22 subjects were mainly found in the general control group (21 of 22). The biochemical parameters were thus reanalyzed after exclusion of all subjects with a history of liver disease. This further analysis showed only minor alterations to the odds ratios (data not shown).

Strokes were subdivided into type and the analyses repeated for thromboembolic strokes. There were too few cerebral hemorrhages to permit separate analyses. Because thromboembolic strokes formed the bulk of the cases, the reanalysis resulted in only minor differences from that for all strokes. Because there were small numbers of non-Caucasian subjects, excluding these did not materially alter the results.

The analyses in Tables 2 and 3 use nondrinkers as the baseline reference group. The multivariate analysis was repeated first excluding ex-drinkers from the nondrinkers and then both ex-drinkers and drinkers who reported drinking much less. This resulted in minor differences from the odds ratios seen in Table 3.
TABLE 2. Relation Between Stroke, Alcohol Consumption, and CAGE Questionnaire

<table>
<thead>
<tr>
<th>Exposure variable</th>
<th>Stroke cases (n)</th>
<th>Select group</th>
<th>General group</th>
<th>Community survey subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Odds ratios (95% CI)</td>
<td>(n)</td>
<td>Odds ratios (95% CI)</td>
</tr>
<tr>
<td>Current alcohol drinker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>16 1.00</td>
<td>14 1.00</td>
<td>106 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>97</td>
<td>68 1.26 (0.57-2.80)</td>
<td>105 0.79 (0.36-1.76)</td>
<td>611 1.26 (0.71-2.26)</td>
</tr>
</tbody>
</table>

(χ²=0.33, df=1, p=0.57) (χ²=0.32, df=1, p=0.57) (χ²=0.67, df=1, p=0.41)

Alcohol consumption (grams per week)

<table>
<thead>
<tr>
<th>Exposure variable</th>
<th>Stroke cases (n)</th>
<th>Select group</th>
<th>General group</th>
<th>Community survey subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Odds ratios (95% CI)</td>
<td>(n)</td>
<td>Odds ratios (95% CI)</td>
</tr>
<tr>
<td>Nondrinker or &lt;10</td>
<td>43</td>
<td>30 1.00</td>
<td>48 1.00</td>
<td>247 1.00</td>
</tr>
<tr>
<td>10-100</td>
<td>35</td>
<td>25 1.01 (0.49-2.09)</td>
<td>29 1.55 (0.77-3.10)</td>
<td>307 0.97 (0.58-1.62)</td>
</tr>
<tr>
<td>100-300</td>
<td>20</td>
<td>16 0.85 (0.37-1.99)</td>
<td>17 1.39 (0.62-3.13)</td>
<td>108 1.58 (0.83-3.00)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>17</td>
<td>13 1.16 (0.45-3.00)</td>
<td>26 0.99 (0.44-2.42)</td>
<td>55 2.31 (1.11-4.82)</td>
</tr>
</tbody>
</table>

(χ²=0.36, df=3, p=0.95) (χ²=2.14, df=3, p=0.55) (χ²=6.85, df=3, p=0.08)

Score of ≥2 on CAGE screening questions

<table>
<thead>
<tr>
<th>Exposure variable</th>
<th>Stroke cases (n)</th>
<th>Select group</th>
<th>General group</th>
<th>Community survey subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Odds ratios (95% CI)</td>
<td>(n)</td>
<td>Odds ratios (95% CI)</td>
</tr>
<tr>
<td>No</td>
<td>80</td>
<td>57 1.00</td>
<td>88 1.00</td>
<td>518 1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>9 1.39 (0.55-3.47)</td>
<td>17 1.30 (0.59-2.86)</td>
<td>83 1.67 (0.86-3.24)</td>
</tr>
</tbody>
</table>

(χ²=0.50, df=1, p=0.48) (χ²=0.41, df=1, p=0.52) (χ²=2.20, df=1, p=0.14)

Cases are compared with each control group and the community survey. All models using hospital controls were adjusted for age and sex and include a term for hospital and day of admission (weekday/weekend). Model comparing cases with community survey was adjusted only for age and sex. n, Number of cases or control subjects.

The response rate from the community questionnaires was 37% (752 of 2,018) for all residents, 49% (684 of 1,401) for permanent residents, and 11% (68 of 617) for temporary residents. The latter were simply determined by the address (e.g., hotel, YMCA, B&B); temporary residents registered at a domestic home address would thus not be identified. Therefore, the response rate for permanent residents is probably an underestimate of the true rate because temporary residents were far less likely to respond. The basic demographic details of the community sample were compared with routine census data for the health authority by guest on April 15, 2017 http://stroke.ahajournals.org/ Downloaded from
area in which this practice is located. For males there was a relative underrepresentation of young subjects ($\chi^2=37.2, df=5, p<0.001$), and social classes IV and V (lower social classes) were also underrepresented in the survey ($\chi^2=12.2, df=2, p<0.01$).

Using the community group, the odds ratios for alcohol consumption and stroke were calculated initially controlling for age and sex (Table 2) and then controlling for age, sex, social class, smoking status, and a history of hypertension (Table 3). Both the odds ratio for alcohol consumption greater than 300 grams and the $\chi^2$ test for trend were significant ($p=0.02$). However, after adjustment for confounding, both the odds ratio for consumption greater than 300 grams and the $\chi^2$ test for trend were no longer significant ($p=0.09$).

**Discussion**

The results of this study illustrate how the risk associated with alcohol consumption may vary depending on the choice of controls. The results using the general medical controls support other studies that suggest this population has an overrepresentation of heavy drinkers,$^7$13,14 Because this was expected, a select control group was chosen excluding possible alcohol-related admissions and this resulted in an increased risk, odds ratio 1.30 (95% confidence interval [CI], 0.42–4.05). However, a relation may still exist between alcohol consumption and other medical conditions. In addition, heavy drinkers may still be overrepresented in the hospital population if, given the same severity of illness, they have a greater probability of admission than other people with that illness (Berksonian bias).

The risk associated with alcohol consumption greater than 300 grams per week was further increased when comparison was made with the community control group but was altered after controlling for confounding variables to an odds ratio of 1.93 (95% CI, 0.87–4.28). Community-based studies are known to underestimate population alcohol consumption as estimated from Customs and Excise data.$^{15}$ In particular, compared with a hospital control group, are the problems of nonresponse and recall bias. Nonresponders are more likely to contain a greater proportion of heavy drinkers,$^{13,14}$ and heavy drinkers are also less likely to be registered with a general practitioner,$^{17}$ thus excluding them from a general practice sampling frame. The response rate in this study was low partly because of the highly mobile population found in central London practices. However, the proportion of identified heavy drinkers was remarkably similar to another general practitioner–based study in North London,$^{18}$ which had a 75% response rate. This adds credibility to the findings of the community survey but does not negate the problem of nonresponse bias, which may have affected both studies. “Recall bias” would be a further problem if “healthy” community control subjects underreported alcohol consumption more than “sick” hospital control subjects. Little empirical information is available to examine this issue, but a study comparing dietary and alcohol consumption data between hospital control subjects and community control subjects$^{19}$ does not support this suggestion.

The interpretation of our results is limited by two factors. Some patients were unable to provide an adequate alcohol history. Missing alcohol data in cases resulted predominantly from patients dying or being severely dysphasic and unable to give a history (29 of 49). This is a problem in all case–control studies of stroke and can be only partially overcome by the use of proxy information from relatives. Comparison of demographic data, smoking histories, and biochemical parameters from cases with and without alcohol data showed no significant differences. However, the possibility that patients with fatal and severe cases of stroke had heavier alcohol intakes cannot be completely excluded and limits the generalizability of our results. The measurement of alcohol consumption for the community survey was not identical with that for the hospital control group; the former completed a postal questionnaire whereas the latter were interviewed. Cutler et al$^{20}$ have shown that subjects reported greater alcohol consumption when they were interviewed than when they completed an identical postal questionnaire. Their method of assessing alcohol consumption was very similar to that used in the present study. This bias would result in an underestimate of alcohol consumption for the community compared with the hospital group.

There are two possible interpretations for our results. First, there may be no significant association between chronic alcohol consumption and risk of ischemic stroke in a middle-aged European population. This conclusion is supported by the lack of a relation in the majority of other studies. However, many of these studies,$^{21–23}$ including the present study, had insufficient power to significantly detect a modest increased risk associated with alcohol consumption. Alternatively, the variation in odds ratios may help explain why other case–control studies have shown apparently contradictory results. Because of the different biases involved in choosing control groups, the “true risk” may be underestimated by hospital-based control groups while overestimated by community-based controls. Our results suggest that alcohol may increase the risk of stroke by 30–90%. This estimate is consistent with the results of many other case–control studies$^{21,22,24–26}$ and cohort studies.$^{24,27,28}$ Could our findings explain the differences found in other case–control studies of alcohol consumption and stroke?

Nine case–control studies$^{21–26,29,30}$ have reported findings on alcohol and stroke, although the two studies from Birmingham, UK, actually used the same cases with a different control group.$^{2,26}$ Six of these used hospital inpatient control subjects, one used outpatients, and only two used community-based control subjects. Four of these studies found a significantly increased risk with heavy alcohol consumption or a linear trend with consumption. Both studies that used community controls found a significant risk, but one failed to control for confounding variables such as smoking.$^{24}$ and the other, although finding a significant trend with consumption, reported a nonsignificant odds ratio of 1.8 (95% CI, 0.8–4.5) for the highest alcohol consumption group (more than 300 grams of alcohol per week). The remaining significant study, which also controlled for potential confounding variables, was a hospital-based case–control study$^{2}$ whose controls were patients admitted for routine surgical procedures. Interestingly, this study is the only one using only elective surgical controls as opposed to acute medical and/or surgical controls. The results showed that an alcohol intake of at least 300 grams per week was associated
with a relative risk of 4.2 (95% CI, 1.7–10.0) for men. However, the strict selection criteria used for the control group excluded those conditions with a recognized association with excessive alcohol use (such as trauma, fractures, and peptic ulcer) or diseases known to alter liver function, including carcinoma and infection, which may also have an association with alcohol consumption. In addition, “healthy” elective admissions may underrepresent the alcohol consumption of the population.

Henrich and Horwitz23 directly tested the effect of selecting elective surgical patients in their hospital-based case–control study. They chose both medical and surgical admissions and found no significant relation between alcohol and ischemic stroke. They also reanalyzed their data using only controls chosen according to the Birmingham criteria, which resulted in a proportional increase in the odds ratio of 50%. This increase in the estimated odds ratios was interpreted as an effect of exclusion bias.

We believe that the contradictory results from case–control studies of alcohol consumption and stroke may be explained by methodological differences predominately in control selection. The variations of risk found in this study with different comparative groups favors a hypothesis that alcohol consumption may modestly increase the risk of stroke, despite the lack of a statistically significant finding. Future studies must attempt to overcome the different biases associated with control selection and have a sufficiently large sample size to enable detection of a modest increased risk.

Acknowledgments

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