

# The Protective Effect of Moderate Alcohol Consumption on Ischemic Stroke

Ralph L. Sacco, MD, MS

Mitchell Elkind, MD

Bernadette Boden-Albala, MPH

I-Feng Lin, MS

Douglas E. Kargman, MD, MS

W. Allen Hauser, MD

Steven Shea, MD, MS

Myunghee C. Paik, PhD

SEVERAL CASE-CONTROL AND PROSPECTIVE cohort studies have shown that moderate alcohol consumption has a protective effect on the risk of cardiac mortality and myocardial infarction.<sup>1-3</sup> The effect of moderate alcohol consumption on stroke is controversial. While several case-control<sup>4,5</sup> and prospective cohort<sup>6-9</sup> studies have shown that alcohol consumption has a direct dose-dependent effect on the risk of hemorrhagic stroke, the data on infarction, which accounts for approximately 80% of all strokes, are contradictory. Some studies suggest that moderate consumption confers a protective effect on the risk of ischemic stroke in certain populations,<sup>8,10-16</sup> while studies in other populations find no beneficial effect.<sup>6,17-28</sup> It has been speculated that there is a differential effect of alcohol dependent on race/ethnicity since studies in white populations<sup>10-12,14,15</sup> have found a protective effect, while those in Asian populations<sup>9,18,23,27,28</sup> have not. Among blacks, some studies have found a protective effect,<sup>13</sup> while others have not.<sup>21</sup> No study has addressed the relationship between alcohol and stroke among Hispanics. To help clarify the relationship of alcohol consumption to

See also Patient Page.

**Context** Moderate alcohol consumption has been shown to be protective for coronary heart disease, but the relationship between moderate alcohol consumption and ischemic stroke is more controversial.

**Objective** To determine the association between alcohol consumption and risk of ischemic stroke.

**Design** Population-based case-control study conducted between July 1993 and June 1997.

**Setting** Multiethnic population in northern Manhattan, New York, NY, aged 40 years or older.

**Patients and Other Participants** Cases (n = 677) had first ischemic stroke and were matched to community controls (n = 1139) derived through random digit dialing by age, sex, and race/ethnicity. Mean  $\pm$  SD age of cases was 70.0  $\pm$  12.7 years; 55.8% were women; 19.5% were white, 28.4% black, and 50.7% Hispanic.

**Main Outcome Measure** First ischemic stroke (fatal or nonfatal).

**Results** Moderate alcohol consumption, up to 2 drinks per day, was significantly protective for ischemic stroke after adjustment for cardiac disease, hypertension, diabetes, current smoking, body mass index, and education (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.39-0.67). This protective effect of alcohol consumption was detected in both younger and older groups, in men and women, and in whites, blacks, and Hispanics. In a quadratic model of stroke risk, increased risk of ischemic stroke was statistically significant among those consuming 7 or more drinks per day (OR, 2.96; 95% CI, 1.05-8.29).

**Conclusions** Moderate alcohol consumption was independently associated with a decreased risk of ischemic stroke in our elderly, multiethnic, urban subjects, while heavy alcohol consumption had deleterious effects. Our data support the National Stroke Association Stroke Prevention Guidelines regarding the beneficial effects of moderate alcohol consumption.

JAMA. 1999;281:53-60

www.jama.com

ischemic stroke among different racial/ethnic groups, we undertook a population-based case-control study in a multiethnic, elderly population.

## METHODS

The Northern Manhattan Stroke Study (NOMASS) is a population-based study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic, urban population. Northern Manhattan consists of the area in New York City north of 145th Street, south of 218th Street, bordered on the west by the Hudson River and on the east by the

Harlem River. In 1990, nearly 260 000 people lived in the community with 40% older than 39 years and a racial/ethnic mixture consisting of 20% black, 63% Hispanic, and 15% white residents.<sup>29</sup>

**Author Affiliations:** Department of Neurology (Drs Sacco, Elkind, Kargman, and Hauser and Mss Boden-Albala and Lin), Sergievsky Center (Drs Sacco and Hauser), Division of General Medicine, Department of Medicine (Dr Shea), Columbia University College of Physicians and Surgeons, and the Division of Epidemiology (Drs Sacco, Hauser, and Shea), Division of Socio-Medical Science (Ms Boden-Albala), and Division of Biostatistics (Ms Lin and Dr Paik), Columbia University School of Public Health, New York, NY.

**Corresponding Author and Reprints:** Ralph L. Sacco, MD, MS, Neurological Institute, 710 W 168th St, New York, NY 10032 (e-mail: rls1@columbia.edu).

### Selection of Cases

Cases eligible for this population-based case-control study were prospectively enrolled if they met the following criteria: (1) diagnosed as having first cerebral infarction after July 1, 1993; (2) older than 39 years at onset of stroke; and (3) resident in northern Manhattan in a household with a telephone. Patients with intracerebral or subarachnoid hemorrhage or transient ischemic attack, defined as neurologic deficits lasting less than 24 hours and no ischemic infarct found on brain imaging, were excluded. Patients with fatal or nonfatal infarcts were enrolled. The methods of case detection in NOMASS have been described previously.<sup>30</sup> The study was approved by the institutional review boards at Columbia-Presbyterian Medical Center and other primary hospitals, and all participants provided written informed consent.

### Selection of Controls

The methods of control recruitment and enrollment have been described in a previous publication.<sup>31</sup> Random digit dialing of approximately 16 000 households was performed by Audits and Surveys, Inc, New York, NY. Community controls were enrolled if they (1) had never been diagnosed as having stroke, (2) were older than 39 years, and (3) resided in northern Manhattan for 3 months or longer in a household with a telephone. Ninety-four percent of those contacted by telephone provided responses to a telephone survey that included questions about alcohol use, smoking, hypertension, and other risk factors. Of those who provided answers to the telephone survey, 70% participated in an in-person interview and examination. For this analysis, 2 concurrent control participants were prospectively selected and matched to stroke cases by age within 5 years, sex, and race/ethnicity. For those stroke cases for whom additional, individual matched controls were not available (8%), matching to controls already used was permitted.

### Index Evaluation of Cases and Controls

Data were collected through interviews of cases and controls by trained re-

search assistants, medical record review, physical and neurologic examination by the study physicians, in-person measurements, and fasting blood specimens for lipid and glucose measurements, as described elsewhere.<sup>31</sup> In-person evaluations of cases and controls were performed at the medical center or at home for those who could not come in person or who had a nonhospitalized stroke (6% were done at home). When possible, data were obtained directly from participants using the standardized data collection instruments. When the participant was unable to provide answers, a proxy knowledgeable about the participant's history was interviewed. Stroke-free controls were interviewed in person and evaluated in the same manner as cases. Direct participant data were obtained from 70% of cases and 99% of controls.

Standardized questions were adapted from the Behavioral Risk Factor Surveillance System<sup>32</sup> by the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, transient ischemic attack, cigarette smoking, and cardiac conditions such as myocardial infarction, coronary artery disease, angina, congestive heart failure, atrial fibrillation, other arrhythmias, and valvular heart disease. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose level as described in prior publications.<sup>33</sup> Fasting lipid panels, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride, were measured using an automated spectrometer (Hitachi 705, Boehringer, Mannheim, Germany). In 60% of cases the blood was drawn within 72 hours of admission. Hypertension, diabetes mellitus, and body mass index (BMI) were defined as in prior publications.<sup>31,33</sup>

### Alcohol Consumption Assessment

Alcohol use was assessed through structured in-person interviews using questions adapted from the National Cancer Institute food frequency questionnaire

developed by Block et al<sup>34</sup> and the food frequency questionnaire of Willett et al.<sup>35</sup> The questions were modified to provide a defined frequency response set, as in the Willett questionnaire.<sup>35,36</sup> Inquiries were made about consumption of 3 different forms of alcohol (wine, beer, and liquor) both during the past year and on average during the participant's drinking lifetime. The defined responses regarding frequency allowed 9 possibilities ranging from never to 7 or more drinks per day for each beverage type. The responses for each beverage type were then summed to obtain a total overall quantity. A standard drink was considered to be 120 mL of wine, 360 mL of beer, and 45 mL of liquor. In addition, an alcoholism screening questionnaire containing 4 structured questions (CAGE)<sup>37</sup> and questions about binge drinking and hospitalizations for alcohol-related illness were asked to assess for pathologic drinking patterns for which food frequency questionnaires may be less sensitive.<sup>38,39</sup>

### Statistical Analyses

Statistical analysis was performed using SAS software (SAS Institute, Cary, NC). Our main analyses used average daily alcohol consumption during the past year. The frequency and quantity of alcohol consumed were examined in cases and controls. The mean daily quantity of alcohol consumed by each participant was calculated as drinks per day, regardless of beverage type. For the matched data, conditional logistic regression was used to calculate unadjusted odds ratios (ORs) for the 9 drinking frequency categories, with those who had abstained during the past year as the reference group. After exploring the magnitude and direction of the effect estimate for individual frequency categories, alcohol consumption was divided into 4 categories: (1) reference: no drinks during the past year; (2) moderate: at least 1 drink per year up to 2 drinks per day; (3) intermediate: more than 2 but fewer than 5 drinks per day; and (4) heavy: 5 or more drinks per day. Multivariate conditional logistic regression was used to calculate the ORs and 95% confidence intervals (95%

CIs) for alcohol consumption and stroke after adjustment for the potential confounding risk factors (hypertension, diabetes, cardiac disease, current smoking, education, and BMI). Adjusted analyses were performed overall and stratified by age, sex, and race/ethnicity. A separate analysis was performed after controlling for HDL among the participants who had this measurement performed. Because of the small number of individuals (24 cases and 18 controls) who drank 5 or more drinks per day, alcohol consumption was also modeled continuously using a quadratic formula to increase the power to detect an effect among those in higher categories of alcohol consumption.

Further analyses were conducted to evaluate the effects of the type of alcoholic beverage, average lifetime alcohol use, and former heavy drinking. Participants who drank at least 1 drink per month but no more than 2 per day were divided into 4 categories depending on their predominant beverage type. Those who drank 1 type of drink at least monthly were considered predominant drinkers of that beverage type (wine, beer, or liquor), as long as they drank both of the other 2 beverage types less often than monthly. Those who drank more than 1 beverage type monthly were considered combination drinkers.

Substudies were undertaken to assess construct validity and proxy reliability of the alcohol assessments. Among a random sample of stroke cases and their proxies, test-retest and proxy reliability of the alcohol consumption questionnaire was analyzed. To evaluate whether using proxy responses led to bias in estimates of the OR, an additional analysis was performed restricted to non-proxy data. Control selection bias was evaluated using the telephone survey alcohol response data. The log (OR) of being selected as a control dependent on alcohol consumption status was calculated and added to the model log (OR) to correct for potential selection bias.<sup>40,41</sup> The CIs for these bias-corrected estimates were calculated using a selection model estimated from the telephone survey data rather than a known selection

model. A method for the calculation of the CIs that adjusts for the estimated selection model is not yet available in the statistical literature and may produce CIs wider than those reported here. All tests were 2 sided, and significance was accepted at the  $P = .05$  level.

## RESULTS

Over 4.0 years, 688 ischemic stroke patients were enrolled in this population-based case-control study. For this analysis, 677 cases (98.5%) were used; 11 cases were excluded because of lack of available data on alcohol consumption. The 30-day case-fatality rate among enrolled cases was 4.9%, and the mean  $\pm$  SD and median National Institutes of Health Stroke Scores (range, 0-43) were  $7.6 \pm 6.8$  and 5.0, respectively. The 677 ischemic stroke cases were matched by age, sex, and race/ethnicity using expanded strata where necessary, as described above, to 1139 controls. Among stroke cases, the mean  $\pm$  SD age was  $70.0 \pm 12.7$  years. There were 55.8% women, and 19.5% of the subjects were non-Hispanic white, 28.4% non-Hispanic black, 50.7% Hispanic

(black or white), and 1.4% other. The ethnic distribution of our Hispanic case population was 62.7% Dominican, 15.6% Puerto Rican, 11.5% Cuban, and 10.3% other. Cases were more likely to have hypertension, cardiac disease, and diabetes mellitus, and controls were more likely to have a high school education (TABLE 1).

The distribution of alcohol use among our elderly control group showed that the majority of the population did not drink alcohol or drank only in moderation (TABLE 2). Among controls, 53.1% stated they did not drink any alcohol over the preceding year, and an additional 40.7% drank up to 2 drinks per day on average. Controls who participated in person had a similar frequency of diabetes, cardiac disease, and current smoking but were more likely to be overweight and less likely to have hypertension than those subjects who did not participate in person based on analyses of telephone response data. No significant relationship existed between moderate or heavy drinking and the likelihood of in-person evaluation, but the likelihood of in-person participation

**Table 1.** Characteristics of Cases and Controls Matched for Age, Sex, and Race/Ethnicity\*

Characteristic	No. (%) of Cases (n = 677)	No. (%) of Controls (n = 1139)
High school diploma	219/662 (33.1)	557/1138 (49.0)
Hypertension	481/677 (71.1)	626/1139 (55.0)
Cardiac disease	276/677 (40.8)	294/1139 (25.8)
Diabetes mellitus	222/676 (32.8)	211/1137 (18.6)
Current cigarette use	129/648 (19.9)	197/1104 (17.8)
Obesity	243/634 (38.3)	483/1136 (42.5)

\*Hypertension was defined as a systolic blood pressure recording of 160 mm Hg or higher or a diastolic blood pressure recording of 95 mm Hg or higher or the patient's self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined by a fasting blood glucose level greater than 7.8 mmol/L (140 mg/dL), the patient's self-report of such a history, or insulin or hypoglycemic use. Obesity was defined as body mass index of 27.8 kg/m<sup>2</sup> or higher for men and 27.3 kg/m<sup>2</sup> or higher for women.<sup>31</sup> Numbers of cases and controls evaluated varied depending on subjects' availability.

**Table 2.** Drinking Behavior Among Cases and Controls\*

Current Drinking Frequency, No. of Drinks	No. (%) of Cases	No. (%) of Controls	Unadjusted OR (95% CI)
<b>Total</b>	<b>677</b>	<b>1139</b>	<b>...</b>
None in past year	455 (67.2)	605 (53.1)	1.0
>0 to <1/mo	38 (5.6)	131 (11.5)	0.37 (0.25-0.55)
$\geq 1$ /mo to <1/d	104 (15.4)	284 (24.9)	0.43 (0.33-0.57)
$\geq 1$ /d to $\leq 2$ /d	23 (3.4)	49 (4.3)	0.51 (0.30-0.86)
>2 to <5/d	33 (4.9)	52 (4.6)	0.58 (0.36-0.96)
$\geq 5$ /d	24 (3.6)	18 (1.6)	1.39 (0.70-2.76)

\*OR indicates odds ratio; CI, confidence interval.

was increased among subjects who consumed intermediate quantities of alcohol.

The reliability and validity of our alcohol assessment tool were good in our sample. Test-retest reliability among 37 stroke-free participants demonstrated good correlation (Pearson  $R = 0.62$ ;  $P < .001$ ). The reliability of proxy respondents among 16 stroke cases was also good (Pearson  $R = 0.81$ ;  $P < .001$ ). Construct validity of the alcohol assessment was measured by comparing responses to the alcohol frequency questions with responses to the CAGE questions and other questions about drinking history. A significant association between alcohol frequency responses and CAGE questionnaire responses was demonstrated ( $\chi^2$  for linear trend,  $P < .001$ ). Results were similar for other questions about problem drinking.

Our case-control analyses, matched by age, sex, and race/ethnicity but unad-

justed for other variables, demonstrated that moderate average daily alcohol consumption in the preceding year was protective against ischemic stroke. Those drinking at least 1 drink per year but less than 1 per month, at least 1 drink per month but less than 1 per day, and at least 1 but no more than 2 drinks per day all had similar risks of ischemic stroke (Table 2) and were combined into 1 group, moderate drinkers, for further analyses. Those drinking up to 2 drinks per day had a statistically significantly reduced risk of ischemic stroke compared with those who were not current drinkers, the reference group (unadjusted OR, 0.58; 95% CI, 0.35-0.94; TABLE 3). The protective effect of moderate alcohol consumption persisted after adjusting for hypertension, diabetes, cardiac disease, current smoking, education, and BMI (adjusted OR, 0.51; 95% CI, 0.39-0.67). These effects were similar in analyses restricted to non-

proxy data. Our telephone survey response data were used to further adjust our estimates for potential control selection bias attributable to differences among alcohol consumption between controls who participated in person and the base population. The protective effect of moderate alcohol use persisted with a new adjusted OR of 0.55 (95% CI, 0.42-0.72).

The protective effect of alcohol consumption in our subjects was not explained by an elevation in HDL levels. The independent protective effect of moderate alcohol use remained after HDL was added to our model in an analysis among the 1458 participants (92.2% of study sample) with HDL data (adjusted OR, 0.53; 95% CI, 0.28-1.0;  $P = .048$ ). No interaction of HDL with moderate drinking was found.

The protective effect of moderate alcohol consumption was demonstrated in subgroup analyses based on age, sex, and race/ethnicity (TABLE 4). No significant interaction was found between age, sex, or race/ethnicity and alcohol consumption. There were differences in consumption in the control group according to age, sex, and race/ethnicity (Table 4).

Intermediate quantities of alcohol also demonstrated a trend toward protection (adjusted OR, 0.58; 95% CI, 0.33-1.03; Table 3). After correction for selection bias, however, the OR for the intermediate group, in whom selection bias was greatest, increased from 0.58 to

**Table 3.** Unadjusted, Adjusted, and Bias-Corrected Odds Ratios for Risk of Ischemic Stroke Dependent on Alcohol Consumption\*

Current Drinking Frequency, No. of Drinks	Unadjusted OR (95% CI)†	Adjusted OR (95% CI)‡	Bias-Corrected OR (95% CI)§
None in past year	1.00	1.00	1.00
Moderate (>0 in past year to ≤2/d)	0.42 (0.33-0.53)	0.51 (0.39-0.67)	0.55 (0.42-0.72)
Intermediate (>2/d to <5/d)	0.58 (0.35-0.94)	0.58 (0.33-1.03)	0.77 (0.44-1.34)
Heavy (≥5/d)	1.38 (0.69-2.74)	1.63 (0.74-3.62)	1.55 (0.70-3.43)

\*Reference group is those not drinking during the past year. OR indicates odds ratio; CI, confidence interval.

†Matched for age, sex, and race/ethnicity.

‡Matched for above factors and adjusted for hypertension, diabetes mellitus, cardiac disease, current cigarette use, education, and body mass index.

§Adjusted for above factors and corrected for control selection bias based on alcohol reporting as assessed by responses to telephone survey data.

**Table 4.** Adjusted Odds Ratios for Ischemic Stroke Stratified by Sex, Age, and Race/Ethnicity\*

Stratum	No. of Cases/Controls	Abstainer, 0 Drinks/Past Year		Moderate, ≤2 Drinks/d		Intermediate, >2 to <5 Drinks/d		Heavy, ≥5 Drinks/d	
		Prevalence in Controls	Prevalence in Controls	OR† (95% CI)	Prevalence in Controls	OR† (95% CI)	Prevalence in Controls	OR† (95% CI)	
Sex									
Men	299/447	37.8	49.7	0.54 (0.36-0.80)	8.7	0.72 (0.38-1.36)	3.8	1.33 (0.56-3.17)	
Women	378/692	63.0	35.0	0.49 (0.34-0.71)	1.9	0.23 (0.05-1.08)	0.1	5.35 (0.51-56.67)	
Age, y									
<65	212/333	46.3	45.4	0.44 (0.26-0.75)	6.3	0.70 (0.30-1.63)	2.1	2.39 (0.79-7.21)	
≥65	465/806	56.0	38.8	0.53 (0.39-0.73)	3.9	0.43 (0.19-0.96)	1.4	1.13 (0.32-4.03)	
Race/ethnicity									
White	132/256	44.5	50.4	0.51 (0.29-0.90)	4.3	0.31 (0.07-1.34)	0.8	1.49 (0.13-17.78)	
Black	192/358	47.2	45.3	0.45 (0.28-0.73)	5.3	0.43 (0.14-1.30)	2.2	1.43 (0.37-5.49)	
Hispanic	343/514	61.5	32.7	0.53 (0.35-0.81)	4.3	0.75 (0.35-1.63)	1.6	1.64 (0.52-5.10)	

\*Reference group is those not drinking during the past year. OR indicates odds ratio; CI, confidence interval.

†Matched for age, sex, and race/ethnicity and adjusted for hypertension, diabetes mellitus, cardiac disease, current cigarette use, education, and body mass index.

0.77. Heavy drinking ( $\geq 5$  drinks per day) was associated with an increased risk of stroke (OR, 1.63; 95% CI, 0.74-3.62), with minimal change (OR, 1.55; 95% CI, 0.70-3.43) after adjusting for selection bias. The relationship between alcohol consumption and stroke fit a quadratic model. The results (FIGURE) demonstrated a J-shaped relationship between alcohol consumption and stroke risk, with a statistically significant increase in stroke risk among those drinking 7 or more drinks per day (OR for those drinking 7 drinks per day, 2.96; 95% CI, 1.05-8.29).

We found no differential protective effects among the types of alcoholic beverages. Our sample of moderate drinkers was subdivided into 4 groups based on predominant drink type: 17.2% drank predominantly wine, 17.2% beer, and 30.2% liquor; 35.3% were classified as combination drinkers. On average, those who were predominantly wine drinkers consumed less alcohol than those who drank beer or liquor or were combination drinkers (TABLE 5). A similar protective effect of drinking up to 2 drinks per day in each of the 4 beverage categories was observed.

To address the possibility that those stroke patients not currently drinking may in fact represent individuals who curtailed their drinking because of early symptoms of cerebrovascular disease, we performed a separate analysis using those identified as lifetime abstainers as the reference group. The protective effects of moderate average daily alcohol consumption in the preceding year persisted (adjusted OR, 0.43; 95% CI, 0.31-0.58). Average daily alcohol consumption over the participant's lifetime was analyzed in the subset of 62.6% of participants in whom these data were collected (372 cases and 623 controls). The protective effect of moderate average lifetime drinking was similar to that of drinking over the preceding year when compared with lifetime abstainers (258 cases, 307 controls; adjusted OR, 0.54; 95% CI, 0.38-0.78). Those who during their lifetime drank 5 or more drinks per day but were currently drinking 2 or fewer drinks per day (ie, reformed heavy drinkers, 24

cases, 26 controls) did not have a significantly increased stroke risk (OR, 0.66; 95% CI, 0.31-1.41).

## COMMENT

Our results demonstrate a protective effect of moderate alcohol consumption on ischemic stroke risk in a multiethnic, elderly population. Moderate consumption—up to 2 drinks of liquor, 2 cans of beer, or 2 glasses of wine per day—was protective with an OR of 0.5. This protective effect of moderate alcohol consumption persisted after adjusting for other stroke risk factors and was found in younger and older participants, men and women, and in whites, blacks, and Hispanics. In addition, we found that very heavy alcohol consumption—7 or more drinks per day—was associated with an increased risk of ischemic stroke.

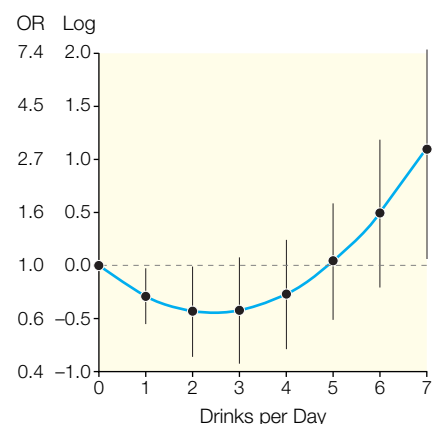
The protective relationship between moderate alcohol consumption and coronary artery disease has been well studied and confirmed in several case-control and cohort studies.<sup>1-3</sup> A meta-analysis of the data found a summary relative risk of 0.83 for moderate drinkers compared with lifetime abstainers.<sup>1</sup> The relationship of alcohol consumption to stroke risk is more controversial, partly because many studies fail to distinguish between hemorrhagic and ischemic stroke. Many studies have shown an increased risk of hemorrhagic stroke associated with increasing alcohol consumption in a dose-dependent fashion.<sup>4-9</sup> Those studies that have investigated alcohol as a risk factor for ischemic stroke have found conflicting results and have not agreed on the optimal protective dose of alcohol.<sup>6,8,10-26</sup>

Our finding of a protective effect of moderate drinking agrees with several case-control studies of the relationship between ischemic stroke and alcohol,<sup>10-12,14-16</sup> conducted predominantly among white subjects. Other case-control studies of ischemic stroke found possible trends toward a protective effect of alcohol<sup>24</sup> but failed to confirm an independent relationship between ischemic stroke and alcohol.<sup>17,20,25</sup> In a study mostly among black participants, current weekly alcohol consumption was associated with an increased risk for cerebral infarction but failed to be significant after controlling for confounding by smok-

ing and hypertension.<sup>21</sup>

Among prospective cohort studies, 2 have found a protective relationship between moderate drinking and ischemic stroke.<sup>8,13</sup> The US Nurses' Health Study found a protective effect of moderate alcohol consumption (up to 1.2 drinks per day) on ischemic stroke among women.<sup>8</sup> In a study using an administrative database, all levels of alcohol consumption were associated with a decreased risk of hospitalization for ischemic stroke in both men and women, but a stronger protective effect was found in blacks than in whites.<sup>13</sup> Other cohort studies looking specifically at ischemic stroke<sup>6,19,22</sup> have failed to confirm this relationship.

**Figure.** Relationship Between Alcohol and Ischemic Stroke



Reference group is those not drinking during past year. Analysis is matched for age, sex, and race/ethnicity and adjusted for hypertension, diabetes mellitus, cardiac disease, current cigarette use, and education. OR indicates odds ratio. Vertical lines indicate 95% confidence intervals.

**Table 5.** Comparison of Odds Ratios for Moderate Drinkers Stratified by Predominant Drink Type\*

Predominant Drink Type	Mean Daily Alcohol Consumption, Drinks/d $\pm$ SD	Adjusted OR (95% CI)†
Wine	0.21 $\pm$ 0.36	0.40 (0.23-0.70)
Beer	0.69 $\pm$ 1.15	0.56 (0.35-0.90)
Liquor	1.03 $\pm$ 1.64	0.63 (0.44-0.92)
Combination	1.37 $\pm$ 2.01	0.54 (0.38-0.77)

\*Moderate drinkers in this table are those drinking at least 1 drink per month up to 2 drinks per day. Reference group is those not drinking during the past year. OR indicates odds ratio; CI, confidence interval.

†Matched for age, sex, and race/ethnicity and adjusted for hypertension, diabetes mellitus, cardiac disease, current cigarette use, and education.

Many prospective studies have analyzed total stroke (approximately 80% of which is ischemic) and found a protective effect of moderate drinking,<sup>26,42-46</sup> while others have not. Some of these studies, however, did not classify drinkers by quantity consumed or relied on data about alcohol abuse only.

No study among Japanese subjects has shown a protective effect of alcohol,<sup>9,18,23,27,28</sup> suggesting that alcohol's effect on stroke risk may vary by race/ethnicity. Recent data also suggest there may be different subgroups among American blacks, some of whom may share the risk factor profiles typical of white populations.<sup>47</sup> Our finding of a protective relationship between moderate alcohol consumption and ischemic stroke in blacks, unlike other studies, may reflect underlying differences between our black population and those examined in other studies.<sup>21</sup> Hispanics have rarely been enumerated separately in stroke and cardiovascular epidemiologic studies, and our study is the first to find a protective relationship between moderate alcohol and ischemic stroke in this racial/ethnic subgroup. Like blacks, Hispanics comprise a heterogeneous group. The northern Manhattan Hispanic population is predominantly from the Dominican Republic and may be quite different from the Mexican Americans of the southwestern United States. Our study is also different from others in that it allows study of different racial/ethnic groups living in the same community and thereby may minimize the environmental effects seen when racial/ethnic groups from separate communities are studied.

The protective effect of alcohol on heart disease appears to be partially mediated by the increase in HDL-2 and HDL-3 associated with alcohol consumption.<sup>2,3,48,49</sup> The relative importance of HDL in mediating alcohol's effect on stroke has not been well studied; none of the other studies correlated alcohol intake, HDL, and stroke. In our analyses, much of the protective effect of alcohol on stroke risk was independent of HDL. Data from NOMASS using repeated measures of lipid levels at intervals after acute stroke, moreover, suggest that the level

of HDL is not significantly altered by acute stroke.<sup>50</sup> In other studies,<sup>51</sup> serum lipid levels decreased slightly after stroke, but HDL remained relatively more constant than other lipid or lipoprotein fractions. Other potential alcohol-induced protective mechanisms that were not evaluated in our study include decreased platelet aggregability, increased prostacyclin-thromboxane ratios, and a decrease in fibrinogen levels.<sup>21,52</sup>

Some investigators have suggested that certain types of alcoholic beverages, particularly wine, are more protective than others.<sup>53,54</sup> We investigated whether any differential protective effect by beverage type exists and found that wine, beer, and liquor all had approximately the same effect, although in our study wine drinkers consumed less alcohol. This is in accord with most other studies of the protective effect of alcohol on coronary artery disease.<sup>3,48</sup> Our data did not permit us to distinguish between consumption of red wine and white wine.

In our study, a quadratic model demonstrated that there is a J-shaped relationship between alcohol consumption and risk of ischemic stroke. Drinking 7 or more drinks daily is associated with a statistically significant increased risk of ischemic stroke. Because of the small number of subjects who reported drinking heavily, however, we are obliged to interpret these results with caution. Nonetheless, these observations are consistent with those of several other studies that have found higher doses of alcohol to be a risk factor for ischemic stroke<sup>10,12,14,18,23,26,55</sup> and extend these observations to a multiethnic population. We were also able to demonstrate that former heavy drinkers who decrease their drinking to no more than 2 drinks per day do not maintain an increased risk of stroke.

Proposed mechanisms for the increased risk of ischemic stroke among those who drink heavily include hypertension, alcohol-induced cardiomyopathy, and atrial fibrillation.<sup>52</sup> Our data show that the increased risk persists even after controlling for potential mediators such as hypertension and cardiac disease, suggesting there may be other unidentified mechanisms by which exces-

sive alcohol use leads to an increased risk of stroke. Other possible mechanisms include cerebral vasoconstriction and spasm,<sup>56</sup> arterial dissection associated with trauma, hyperviscosity due to dehydration, increased platelet reactivity,<sup>57,58</sup> and hyperhomocysteinemia.<sup>59</sup>

The methodological problems of the study of alcohol as a risk factor for stroke have been reviewed by others.<sup>24,42,60</sup> Not all studies are consistent in their definitions of moderate alcohol consumption. We defined our category of moderate alcohol consumption based on the similarity in risk of ischemic stroke observed among those in subcategories of drinking up to 2 drinks per day. We chose 2 drinks per day as the upper limit of moderate consumption because this quantity has been accepted by several investigators<sup>13,42,45</sup> and also because this is a commonly encountered, clinically meaningful quantity.

In case-control studies, control selection can lead to a variety of biases. The use of community-based controls, as in our study, probably gives the best estimate of the underlying prevalence of an exposure, as long as study participation is not related to alcohol use. Our telephone survey response analyses did not demonstrate a significant bias with regard to alcohol use, and where a trend toward bias existed, it spared moderate and heavy drinking groups. Moreover, no significant changes in the associations of either moderate or heavy drinking with stroke risk were found when we corrected for selection biases. In addition, data available from the US Census<sup>29</sup> indicate that, on other markers of socioeconomic status, such as education, our control sample is similar to that of the underlying population. In our control group older than 40 years, 79.3% of whites, 63.3% of blacks, and 23.2% of Hispanics completed high school, and the US Census data from northern Manhattan for all age groups indicate that 90.7%, 72.3%, and 43.5%, respectively, completed high school. Our stroke cases, furthermore, should be representative of the spectrum of stroke in the underlying population. We included both mild, non-hospitalized stroke cases and severe fa-

tal strokes, and our results should therefore be generalizable to most populations of stroke patients.

Recall bias may also affect case-control studies, but it would have to be postulated that the bias operated in different directions among moderate and heavy drinkers since a J-shaped relationship was found. Moreover, measurement of alcohol consumption was assessed using structured in-person interviews, a method used and validated in other large epidemiologic studies.<sup>61,62</sup> Our construct validity analysis suggested a good correlation between other measures of problem drinking and drinking more than 5 drinks per day, quantities for which food frequency questionnaires may be less sensitive.<sup>38,39</sup>

One of the major methodological weaknesses of any epidemiologic studies of alcohol and stroke is the bias attributable to the "sick quitter" hypothesis: persons who are ill or experiencing early, preclinical symptoms of disease may decrease their usual alcohol consumption.<sup>42</sup> Assessment of current or recent alcohol exposure may underestimate true lifetime alcohol exposure and lead to a misclassification of exposure status. Moreover, people tend to drink less as they age.<sup>63</sup> Therefore, assessment of current alcohol use in an elderly population is likely to systematically underestimate lifetime exposure. We attempted to minimize this potential misclassification in several ways. First, we performed our analysis using 2 different reference groups, those who were not current drinkers and lifetime abstainers, and obtained similar results. Second, we used as our measure of alcohol exposure both consumption during the past year and average lifetime consumption and found a similar protective effect. Third, we controlled for other confounding diseases that may have both predisposed an individual to stroke and led to a decrease in alcohol consumption.

In conclusion, our study demonstrates that moderate alcohol consumption may have important health benefits in terms of reducing the risk of ischemic stroke, particularly in an elderly, urban, multiethnic population.

These benefits, of course, need to be weighed against the overall risk of morbidity and mortality due to excess alcohol consumption. Additionally, our study supports the advice that heavy drinkers can decrease their risk of ischemic stroke by decreasing or discontinuing their alcohol intake. While no study has shown benefit in recommending alcohol consumption to those who do not drink, our data support the view, endorsed by the National Stroke Association in its Stroke Prevention Guidelines,<sup>64</sup> that, among those who are moderate drinkers, continued consumption may provide a reduction of ischemic stroke risk.

**Funding/Support:** This work was supported by grants from the National Institute of Neurological Disorders and Stroke (R01 NS 27517, R01 NS 29993, and T32 NS 07153) and the General Clinical Research Center (2 M01 RR00645).

**Previous Presentation:** This work was presented in part in abstract form at the American Heart Association's 22nd International Joint Conference on Stroke and Cerebral Circulation, Anaheim, Calif, February 7, 1997.

**Acknowledgment:** We acknowledge the support of J. P. Mohr, MD, MS, director of cerebrovascular research, the processing of the lipids by Henry Ginsberg, MD, and Lars F. Berglund, MD, PhD, in the Division of Preventative Medicine and Nutrition and the Irving Center for Clinical Research, and the help provided by J. Kirk Roberts, MD, MS, and Robert Gan, MD.

## REFERENCES

- Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev*. 1993;15:328-351.
- Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med*. 1993;329:1829-1834.
- Rimm EB. Alcohol consumption and coronary heart disease: good habits may be more important than just good wine. *Am J Epidemiol*. 1996;143:1094-1098.
- Petitti DB, Winger J, Pellegrin F, Ramcharan S. Risk of vascular disease in women: smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *JAMA*. 1979;242:1150-1154.
- Stemmerman GN, Hayashi T, Resch JA, et al. Risk factors related to ischemic and hemorrhagic cerebrovascular disease at autopsy: the Honolulu Heart Study. *Stroke*. 1984;15:23-28.
- Peacock PB, Riley CP, Lampton TD, Raffel SS, Walker JS. The Birmingham Stroke, Epidemiology and Rehabilitation Study. In: Stewart G, ed. *Trends in Epidemiology: Applications to Health Service Research and Training*. Springfield, Ill: Charles C Thomas; 1972: 231-345.
- Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke: the Honolulu Heart Study. *JAMA*. 1986;255:2311-2314.
- Stampfer MJ, Colditz GA, Willett WA, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med*. 1988;319: 267-273.
- Tanaka H, Ueda Y, Hayashi M, et al. Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. *Stroke*. 1982;13:62-73.
- Gill JS, Zeszulka AV, Shipley MJ, Gill SK, Beevers DGB. Stroke and alcohol consumption. *N Engl J Med*. 1986;315:1041-1046.
- Gill JS, Shipley MJ, Hornby RH, Gill SK, Beevers DG. A community case-control study of alcohol consumption in stroke. *Int J Epidemiol*. 1988;17:542-547.
- Gill JS, Shipley MJ, Tsementzis SA, et al. Alcohol consumption: a risk factor for hemorrhagic and non-hemorrhagic stroke. *Am J Med*. 1991;90:489-497.
- Klatsky AL, Armstrong MA, Friedman GD. Alcohol use and subsequent cerebrovascular disease hospitalizations. *Stroke*. 1989;20:741-746.
- Rodgers H, Aitken PD, French JM, Curless RH, Bates D, James OFW. Alcohol and stroke: a case-control study of drinking habits past and present. *Stroke*. 1993;24:1473-1477.
- Jamrozik K, Broadhurst RJ, Anderson CS, Stewart-Wynne EG. The role of lifestyle factors in the etiology of stroke: a population-based case-control study in Perth, Western Australia. *Stroke*. 1994;25:51-59.
- Palomäki H, Kaste M. Regular light-to-moderate intake of alcohol and the risk of ischemic stroke: is there a beneficial effect? *Stroke*. 1993;24: 1828-1832.
- Abu-Zeid HAH, Choi NW, Maini KK, Hsu P, Nelson NA. Relative role of factors associated with cerebral infarction and cerebral hemorrhage: a matched pair case-control study. *Stroke*. 1977;8:106-112.
- Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Alcohol and mortality: a cohort study of male Japanese physicians. *Int J Epidemiol*. 1986;15: 527-532.
- Boysen G, Nyboe J, Appleyard M, et al. Stroke incidence and risk factors for stroke in Copenhagen, Denmark. *Stroke*. 1988;19:1345-1353.
- Henrich JB, Horwitz RI. Evidence against the association between alcohol use and ischemic stroke risk. *Arch Intern Med*. 1989;149:1413-1416.
- Gorelick PB, Rodin MB, Langenberg P, Hier DB, Costigan J. Weekly alcohol consumption, cigarette smoking, and the risk of ischemic stroke: results of a case-control study at three urban medical centers in Chicago, Illinois. *Neurology*. 1989;39:339-343.
- Harmsten P, Rosengren A, Tsipogianni A, Wilhelmsen L. Risk factors for stroke in middle-aged men in Goteborg, Sweden. *Stroke*. 1990;21:223-229.
- Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. *Stroke*. 1985;16:390-396.
- Ben-Shlomo Y, Markowe H, Shipley M, Marmot MG. Stroke risk from alcohol consumption using different control groups. *Stroke*. 1992;23:1093-1098.
- Shinton R, Sagar G, Beevers G. The relation of alcohol consumption to cardiovascular risk factors and stroke: the West Birmingham Stroke Project. *J Neurol Neurosurg Psychiatry*. 1993;56:458-462.
- Hansagi H, Romelsjö A, Gerhardsen de Verdier M, Andréasson S, Leifman A. Alcohol consumption and stroke mortality: 20-year follow-up of 15 077 men and women. *Stroke*. 1995;26:1768-1773.
- Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Fujishima M. The impact of alcohol and hypertension on stroke incidence in a general Japanese population: the Hisayama Study. *Stroke*. 1995;26:368-372.
- Okada H, Horibe H, Ohno Y, Hayakawa N, Aoki N. A prospective study of cerebrovascular disease in Japanese rural communities, Akabane and Asahi, 1: evaluation of risk factors in the occurrence of cerebral hemorrhage and thrombosis. *Stroke*. 1976; 7:599-607.
- US Census of Population and Housing, 1990 (Public Use Microdata Sample). Available at: <http://www.venus.census.gov>. Accessed August 1, 1997.
- Sacco RL, Boden-Albala B, Gan R, et al, and the Northern Manhattan Stroke Study Collaborators. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke

- Study. *Am J Epidemiol*. 1998;147:259-268.
31. Sacco RL, Gan R, Boden-Albala B, et al. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke*. 1998;29:380-387.
  32. Gentry EM, Kalsbeek WD, Hegelin GC, et al. The Behavioral Risk Factor Surveys, II: design, methods, and estimates from combined state data. *Am J Prev Med*. 1985;1:9-14.
  33. Sacco RL, Roberts JK, Boden-Albala B, et al. Race-ethnicity and determinants of carotid atherosclerosis in a multi-ethnic population: the Northern Manhattan Stroke Study. *Stroke*. 1997;28:929-935.
  34. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. 1986;124:453-469.
  35. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51-65.
  36. Mayer EJ, Newman B, Quesenberry CP, Friedman GD, Selby JV. Alcohol consumption and insulin concentrations: role of insulin in associations of alcohol intake with high-density lipoprotein cholesterol and triglycerides. *Circulation*. 1993;88(pt 1):2190-2197.
  37. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry*. 1974;131:1121-1123.
  38. Colditz GA, Willett WC, Stampfer MJ, et al. The influence of age, relative weight, smoking, and alcohol intake on the reproducibility of a dietary questionnaire. *Int J Epidemiol*. 1987;16:392-398.
  39. Romelsjö A, Leifman H, Nystrom S. A comparative study of two methods for the measurement of alcohol consumption in the general population. *Int J Epidemiol*. 1995;24:929-936.
  40. Maclure M, Hankinson S. Analysis of selection bias in a case-control study of renal adenocarcinoma. *Epidemiology*. 1990;1:441-447.
  41. Weinberg CR, Wacholder S. The design and analysis of case-control studies with biased sampling. *Bio-metrics*. 1990;46:963-975.
  42. Camargo CA. Case-control and cohort studies of moderate alcohol consumption and stroke. *Clin Chim Acta*. 1996;246:107-119.
  43. Kozarevic DJ, Vojvodic N, Gordon T, Kaelber CT, McGee D, Zukel WJ. Drinking habits and death: the Yugoslavia Cardiovascular Disease Study. *Int J Epidemiol*. 1983;12:145-150.
  44. Gordon T, Doyle JT. Drinking and mortality: the Albany Study. *Am J Epidemiol*. 1987;125:263-270.
  45. Wolf PA, D'Agostino RB, Odell P, Belanger AJ, Hodges D, Kannel WB. Alcohol consumption as a risk factor for stroke: the Framingham Study [abstract]. *Ann Neurol*. 1988;24:177.
  46. Browner WS, Pressman AR, Nevitt MC, Cauley JA, Cummings SR. Association between low bone density and stroke in elderly women. *Stroke*. 1993;24:940-946.
  47. Fang J, Madhavan S, Alderman MH. The association between birthplace and mortality from cardiovascular causes among black and white residents of New York City. *N Engl J Med*. 1996;335:1545-1551.
  48. Marques-Vidal P, Ducimetiere P, Evans A, Cambou J-P, Arveiler D. Alcohol consumption and myocardial infarction: a case-control study in France and Northern Ireland. *Am J Epidemiol*. 1996;143:1089-1093.
  49. Criqui MH, Cowan LD, Tyroler HA, et al. Lipoproteins as mediators for the effects of alcohol consumption and cigarette smoking on cardiovascular mortality: results from the Lipid Research Clinics Follow-Up Study. *Am J Epidemiol*. 1987;126:629-637.
  50. Kargman DE, Tuck C, Berglund L, et al. Lipid and lipoprotein levels remain stable in acute ischemic stroke: the Northern Manhattan Stroke Study. *Atherosclerosis*. 1998;139:391-399.
  51. Aull S, Lalouchek W, Schnider P, Sinzinger H, Uhl F, Zeiler K. Dynamic changes of plasma lipids and lipoproteins in patients after transient ischemic attack or minor stroke. *Am J Med*. 1996;101:291-298.
  52. Gorelick PB. Alcohol and stroke. *Curr Concepts Cardiovasc Dis Stroke*. 1986;21:21-25.
  53. Rosenberg L, Slone D, Shapiro S, Kaufman DW, Miettinen OS, Stolley PD. Alcoholic beverages and myocardial infarction in young women. *Am J Public Health*. 1981;71:82-85.
  54. Renaud SC, Beswick AD, Fehily AM, Sharp DS, Elwood PC. Alcohol and platelet aggregation: the Caerphilly Prospective Heart Disease Study. *Am J Clin Nutr*. 1992;55:1012-1017.
  55. Beghi E, Bogliuni G, Cosso P, et al. Stroke and alcohol intake in a hospital population: a case-control study. *Stroke*. 1995;26:1691-1696.
  56. Altura BM, Altura BT, Gebrewold A. Alcohol-induced spasms of cerebral blood vessels: relation to cerebrovascular accidents and sudden death. *Science*. 1983;220:331-333.
  57. Hillbom M, Kangasaho M, Kaste M, Numminen H, Vapaatalo H. Acute ethanol ingestion increases platelet reactivity: is there a relationship to stroke? *Stroke*. 1985;16:19-23.
  58. Haselager EM, Vreeken J. Rebound thrombocytosis after alcohol abuse: a possible factor in the pathogenesis of thromboembolic disease. *Lancet*. 1977;1:774-775.
  59. Hultberg B, Berglund M, Andersson A, Frank A. Elevated plasma homocysteine in alcoholics. *Alcohol Clin Exp Res*. 1993;17:687-689.
  60. Camargo CA. Moderate alcohol consumption and stroke: the epidemiologic evidence. *Stroke*. 1989;20:1611-1626.
  61. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol*. 1990;43:1327-1335.
  62. Giovanucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol*. 1991;133:810-817.
  63. Wannamethee SG, Shaper AG. Patterns of alcohol intake and risk of stroke in middle-aged British men. *Stroke*. 1996;27:1033-1039.
  64. Stroke Prevention Advisory Board. National Stroke Association Stroke Prevention Guidelines. *J Stroke Cerebrovasc Dis*. 1998;7:162-164.

## Change

Nothing endures but change.

—Heraclitus (c 540-c 480 BC)

Human nature will not change. In any future great national trial, compared with the men of this, we shall have as weak and as strong, as silly and as wise, as bad and as good.

—Abraham Lincoln (1809-1865)

In spite of illness, in spite even of the archenemy sorrow, one can remain alive long past the usual date of disintegration if one is unafraid of change, insatiable in intellectual curiosity, interested in big things, and happy in small ways.

—Edith Wharton (1862-1937)

What man has made, man can change.

—Frederick Moore Vinson (1890-1953)

That's why it's time for change.

—Thomas Edmund Dewey (1902-1971)