Original Contributions

Moderate Alcohol Consumption Reduces Risk of Ischemic Stroke

The Northern Manhattan Study

Mitchell S.V. Elkind, MD, MS; Robert Sciacca, DEngSc; Bernadette Boden-Albala, Dr PH;
Tanja Rundek, MD, PhD; Myunghee C. Paik, PhD; Ralph L. Sacco, MD, MS

Background and Purpose—Moderate alcohol consumption is protective against coronary disease, but its relationship to ischemic stroke (IS) is controversial.

Methods—Stroke-free participants ≥40 years of age identified by random-digit dialing were enrolled in a prospective cohort study between 1993 and 2001. Alcohol consumption was assessed through in-person interview and categorized as none in the past year, ≥1 drink in past month to ≤2 per day (moderate drinkers), and >2 drinks daily. Lifetime drinking was also assessed. Cox proportional hazard regression modeling was used to assess hazard ratios and their 95% CIs for the association of drinking with risk of stroke and vascular events.

Results—Mean age among participants (n=3176) was 69.1±10.3 years; 62.8% were women, 20.8% were non-Hispanic white, 24.5% non-Hispanic black, and 52.4% were Hispanic. No alcohol in the previous year was present in 62.3%, and 32.5% drank moderately. After adjusting for other risk factors compared with those who did not drink in the past year, moderate drinkers had a reduced risk of IS (0.67; 95% CI, 0.46 to 0.99) and IS, myocardial infarction, or vascular death (0.74; 95% CI, 0.59 to 0.94). Results were similar when never-drinkers were used as referent group. Reduction in risk was seen for nonatherosclerotic IS subtypes, and results stratified by age, sex, and race–ethnicity were similar.

Conclusion—Moderate alcohol consumption is associated with decreased risk of IS in a multiethnic population. This effect is independent of other risk factors and holds for nonatherosclerotic stroke subtypes. (*Stroke*. 2006;37:13-19.)

Key Words: alcohol ■ cerebrovascular disorders ■ epidemiology ■ risk factors ■ stroke, ischemic

Prospective cohort studies have shown that moderate alcohol consumption protects against risk of myocardial infarction (MI) and cardiac mortality.[1,2] The balance of effect of moderate alcohol consumption on stroke risk is more complicated. There may be a direct dose-dependent effect of alcohol on the risk of hemorrhagic stroke.[3,4] Some prospective studies provide evidence for a protective effect of alcohol consumption on risk of ischemic stroke (IS), although others do not.[3,4]

There is also evidence for variability in the effect of alcohol on stroke risk by race–ethnicity. No prospective studies have addressed the relationship between alcohol and stroke among Hispanics. We previously reported a protective relationship between moderate alcohol consumption and IS in a population-based case-control study.[5] Case-control studies are subject to recall bias in assessment of alcohol consumption because individuals hospitalized with stroke may inaccurately report alcohol consumption before stroke. Several prospective studies have analyzed the effect of alcohol on stroke, but most have not distinguished hemorrhagic and IS,[3] and some have had small numbers of end points or incompletely adjusted for potential confounding factors such as smoking and cholesterol. Most previous studies did not investigate individual IS subtypes.

We hypothesized that moderate alcohol consumption would have a protective effect on risk of IS in a population-based cohort study in a multiethnic, predominantly Hispanic, elderly population. We further investigated the differential relationship between alcohol consumption and individual IS subtypes.

Study Methods

The Northern Manhattan Study (NOMAS) is a population-based study designed to determine stroke risk factors in a multiethnic, urban population. The race–ethnic mixture consists of 63% Hispanic, 20% non-Hispanic black, and 15% non-Hispanic white residents.[6]

Identification and Recruitment of the Cohort

Methods of participant recruitment and enrollment have been described previously.[7] Participants were identified by random-digit dialing and enrolled if they: (1) had never been diagnosed with stroke, (2) were >39 years of age, and (3) resided in northern Manhattan for ≥3 months in a household with a telephone. In-person evaluations were performed at the hospital or at home. Overall response rate was 68%. The study was approved by the Columbia University Medical Center institutional review board. All participants gave informed consent.

Index Evaluation of Participants

Data regarding baseline status and risk factors were collected through interviews by trained research assistants, physical and neurological examination by study physicians, in-person measurements, and analysis of fasting blood specimens.[7] Data were obtained from participants (99%) or proxy using standardized data collection instruments.

Participants self-identified ethnicity as Hispanic or non-Hispanic and race as white, black, or other. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System[8] by the Centers for Disease Control and Prevention. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose.[9] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, physician diagnosis, or self-report of history of hypertension or antihypertensive use. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or self-report of such a history, or insulin or hypoglycemic use.

Alcohol Consumption Assessment

Alcohol use was assessed as described previously.[5] Research assistants used structured in-person interviews adapted from the National Cancer Institute Food Frequency questionnaire[10] and the Willett food frequency questionnaire.[11] Questions were modified to provide a defined frequency response set.[11,12] Inquiries were made about consumption of wine, beer, and liquor during the past year and on average during each participant's lifetime. The defined responses regarding frequency allowed 9 possibilities ranging from never to >6 drinks per day. The responses for each beverage type were summed to obtain a total quantity, and an average daily quantity was calculated. A standard drink of wine was considered to contain 4 ounces, beer 12 ounces, and liquor 1.5 ounces of ethanol. The reliability and validity of this alcohol assessment has been shown previously to be good in our population.[5]

Follow-Up and Outcomes Assessment

Follow-up evaluations were conducted annually by telephone.[13] When symptoms suggestive of stroke or transient ischemic attack were detected, the participant was invited for outpatient evaluation. When necessary, diagnostic tests were performed. The participant's primary physician was responsible for management decisions. Ongoing surveillance of admissions to our and other local hospitals was used.[14]

Stroke was defined by the first symptomatic occurrence of any stroke including intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, as per World Health Organization criteria.[13] MI was defined by criteria adapted from the Cardiac Arrhythmia Suppression Trial[15] and the Lipid Research Clinics Coronary Primary Prevention Trial.[16] Causes of death were determined using best available information. Research assistants collected death certificates and medical records and interviewed family members, physicians, and health professionals involved in the care of the patient. Cause of death was verified by study physician, and deaths were classified as vascular or nonvascular.[13]

Two neurologists classified strokes independently. Final stroke subtype was decided by consensus, and disagreements were adjudicated by a third neurologist. ISs were classified as extracranial and intracranial atherosclerotic, lacunar (small vessel), cardioembolic, or cryptogenic using the results of the diagnostic evaluation according to a modified stroke data bank scheme.[17] MI was validated by review by a study cardiologist.

Statistical Analyses

Mean daily alcohol consumption was calculated as drinks per day regardless of beverage type. Alcohol consumption was divided into 4 categories: (1) no drinks (<1 drink per month) during the past year (reference group); (2) moderate consumption (≥1 drink per month in the past year and ≤2 drinks daily); (3) intermediate >2 but <5 drinks daily; and (4) heavy (≥5 drinks daily).

Cox proportional hazards regression modeling was used to calculate the hazard ratios (HRs) and 95% CIs for alcohol consumption categories and cerebrovascular end points after adjusting for potential confounders. Because of the small number of participants in intermediate and heavy categories, after exploring magnitude of effect, these were collapsed into 1 category for further analyses. Adjusted analyses were performed overall and stratified by age (<70 years and ≥70 years), sex, race–ethnicity, and smoking status. Further analyses were conducted to evaluate effects of average lifetime alcohol use and current alcohol consumption using lifetime abstainers as the referent group. Analyses were also conducted to estimate effect of alcohol consumption on risk of hemorrhagic stroke and individual IS subtypes. Subarachnoid hemorrhage and intracerebral hemorrhage were collapsed into 1 category, and intracranial and extracranial atherosclerotic stroke were grouped together.

Results

Baseline Characteristics of Cohort and Distribution of Alcohol Consumption

The NOMAS cohort (n=3298) was similar to the random telephone sample with regard to sociodemographics and major stroke risk factors, as reported previously.[5] A total of 3176 (96.3%) participants had an alcohol questionnaire completed and ≥1 year of follow-up. Distribution of baseline characteristics is shown in Table 1.

No alcohol consumption in the previous year was present in 62.3%, and 32.5% drank moderately (≥1 per month to ≤2 drinks per day). Only 5.1% drank >2 drinks daily (Table 2). Alcohol consumption during the past year was associated with demographic characteristics and risk factors. The proportion of men who drank moderately was higher than women (42.3% and 26.8%, respectively; $P<0.0001$). Only 27.1% of those ≥70 years of age drank moderately, compared with 37.4% of those <70 ($P<0.0001$). The proportion of moderate drinkers was highest among white non-Hispanics (42.4% versus 31.7% and 29.0% for non-Hispanic blacks and Hispanics, respectively; $P<0.0001$). Those with a history of smoking were significantly more likely to be moderate drinkers than never-smokers (37.7% versus 26.7%; $P<0.0001$). A history of MI or coronary artery disease, but not atrial fibrillation, was also associated with lower mean alcohol consumption. High-density lipoprotein (HDL) levels were weakly but significantly positively correlated with average alcohol consumption ($r=0.05$; $P=0.009$).

TABLE 1. Characteristics of Participants

Characteristic	Mean±SD or n (%)
n	3176
Age, y, mean±SD	69.1±10.3
Men, n (%)	1180 (37.2)
Race–ethnicity, n (%)	
Hispanic	1665 (52.4)
Non-Hispanic Black	777 (24.5)
Non-Hispanic White	661 (20.8)
High school diploma, n (%)	1464 (46.1)
Risk factors, n (%)	
Hypertension	2154 (67.8)
Diabetes mellitus	687 (21.6)
Hyperlipidemia	1425 (44.9)
History of smoking	1685 (53.1)
Current smoking	547 (17.5)
History of coronary artery disease	672 (21.2)
History of MI	229 (7.2)
History of atrial fibrillation	133 (4.2)
Physiological measures, mean±SD	
Systolic blood pressure, mm Hg	143.7±21.1
Total cholesterol, mg/dL	202.8±40.2
Low-density lipoprotein, mg/dL	129.2±35.8
HDL, mg/dL	46.9±14.4
Body mass index	27.6±5.5
Waist-to-hip ratio	0.9±0.09

Association Between Alcohol Consumption and Risk of Stroke

After a median follow-up of 5.9 years, strokes occurred in 190 patients, including 172 initial IS events, 19 intracerebral hemorrhages, 4 subarachnoid hemorrhages, and 9 strokes of unknown type. Some patients had >1 event. Among the ISs, 24 were atherosclerotic (either extracranial or intracranial), 43 lacunar, 43 cardioembolic, 36 cryptogenic after full evaluation, and 26 undetermined.

TABLE 2. Distribution of Alcohol Consumption Categories Overall, and Stratified by Sex

	Overall, n (%)	Men, n (%)	Women, n (%)
Average alcohol consumption during past year			
<1 drink/mo	1980 (62.3)	564 (47.8)	1416 (70.9)
>1 drink/mo to ≤2 drinks/d	1033 (32.5)	499 (42.3)	534 (26.8)
>2 and <5 drinks/d	115 (3.6)	75 (6.4)	40 (2.0)
≥5 drinks/d	48 (1.5)	42 (3.6)	6 (0.3)
Average lifetime alcohol consumption*			
<1 drink/mo	790 (28.1)	109 (10.9)	681 (37.6)
>1 drink/mo to ≤2 drinks/d	1649 (58.6)	617 (61.6)	1032 (57.0)
>2 and <5 drinks/d	203 (7.2)	128 (12.8)	75 (4.1)
≥5 drinks/d	172 (6.1)	148 (14.8)	24 (1.3)

*Data on average lifetime alcohol consumption available on 2814 participants.

The risk of IS was reduced by ≈44% among moderate drinkers (unadjusted HR, 95% CI, 0.56, 0.39 to 0.81; Table 3). By fitting polynomial models using drinks per day as a continuous measure of alcohol consumption, the point of maximum protection was calculated as 1.2 drinks daily. The effect of moderate alcohol consumption on IS, MI, or vascular death was similar (unadjusted HR, 0.63; Table 3).

After adjusting for stroke risk factors, including age, sex, race–ethnicity, hypertension, diabetes, atrial fibrillation, HDL, and current smoking, moderate alcohol use remained independently associated with reduced risk of IS (adjusted HR, 0.67, 0.46 to 0.99). Results were similar for the end point of IS, MI, or vascular death (Table 3; Figure). The results changed minimally in additional analyses adjusted for other potential confounding factors, including lifetime smoking history, body mass index, waist-hip ratio, coronary artery disease, low-density lipoprotein, homocysteine, and leukocyte count.

In a further analysis, we categorized moderate consumption within the past year into >1 drink per month and <1 drink per day (n=893; 28.1% of all participants) and ≥1 drink per day, up to 2 drinks daily (n=141; 4.4% of all participants). In fully adjusted models, the point estimates of the risks were very similar: adjusted HR, 0.68; 95% CI, 0.46 to 1.02 for those drinking <1 drink daily, and adjusted HR, 0.71; 95% CI, 0.29 to 1.77 for those drinking ≥1 drink to ≤2 drinks daily.

Moderate drinking was associated with a reduction in risk, adjusted for demographic characteristics, of most IS subtypes. However, because of smaller numbers, these risk reductions were not statistically significant for each subtype. The reduction in risk was most prominent among participants with cryptogenic stroke (adjusted HR, 0.28; 95% CI, 0.10 to 0.80). There was a trend toward a risk reduction among lacunar (adjusted HR, 0.44; 95% CI, 0.19 to 1.01) and cardioembolic (0.50; 95% CI, 0.24 to 1.07) stroke subtypes, although we did not have power to detect a definite effect in each subtype. The reduction in risk was not clearly evident for the atherosclerotic subtype (adjusted HR, 0.77; 95% CI, 0.30 to 1.94).

Consumption of >2 drinks daily was not associated with a statistically significant effect on IS risk, although there was only a small number in this category, and the confidence intervals did not exclude the possibility of protection at this level of consumption (Table 3). Consumption of >2 drinks daily was associated with a trend toward increased hemorrhagic stroke risk: HR adjusted for demographic characteristics, 2.27; 95% CI, 0.60 to 8.64.

In analyses using lifetime alcohol consumption, there was no definite evidence of moderate consumption being protective for IS (unadjusted HR, 0.79; 0.55 to 1.13). The results were further attenuated after adjusting for other confounding variables (adjusted HR, 0.88; 0.60 to 1.29).

To address the possibility that participants not currently drinking represent individuals who curtailed drinking because of early cerebrovascular symptoms, those identified as lifetime abstainers were used as referent group in separate analyses (Figure). Of 3009 participants for whom data on current and lifetime consumption was available; 790 partici-

TABLE 3.   Risk of IS, Hemorrhagic Stroke, Total Stroke, and Combined Vascular End Points Associated With Recent Alcohol Consumption Category*

	HR (95% CIs)		
	Unadjusted	Adjusted for Demographic Factors†	Adjusted for Demographics and Risk Factors‡
IS			
None**	1.0	1.0	1.0
≥1 drink/mo and ≤2 drinks/d	0.56 (0.39–0.81)	0.61 (0.42–0.89)	0.67 (0.46–0.99)
>2 drinks/d	1.11 (0.61–2.00)	1.23 (0.67–2.28)	1.30 (0.69–2.45)
Hemorrhagic stroke (intracerebral and subarachnoid hemorrhage)			
None**	1.0	1.0	1.0
≥1 drink/mo and ≤ 2 drinks/d	1.24 (0.51–3.04)	1.17 (0.46–2.97)	–¶
>2 drinks/d	2.80 (0.79–9.92)	2.27 (0.60–8.64)	–¶
Total stroke			
None**	1.0	1.0	1.0
≥1 drink/mo and ≤2 drinks/d	0.58 (0.41–0.82)	0.61 (0.43–0.87)	0.68 (0.47–0.98)
>2 drinks/d	1.19 (0.69–2.06)	1.24 (0.70–2.20)	1.28 (0.71–2.32)
IS, MI, or vascular death			
None**	1.0	1.0	1.0
≥1 drink/mo and ≤2 drinks/d	0.63 (0.51–0.79)	0.67 (0.54–0.85)	0.74 (0.59–0.94)
>2 drinks/d	0.83 (0.54–1.26)	0.94 (0.61–1.45)	0.95 (0.61–1.49)

*Recent alcohol consumption refers to consumption in past year before interview; **referent group is those consuming no alcohol (<1 alcoholic drink/month) in past year; †demographic factors are age (continuous), sex, race–ethnicity, and education (high school graduate vs not); ‡risk factors are history of hypertension, diabetes mellitus, current cigarette smoking, atrial fibrillation, and levels of HDL; ¶fully adjusted models were not calculated for hemorrhagic stroke because of the smaller No. of events.

pants (26.3%) were classified as lifetime nondrinkers (ie, never-drinkers), 1023 (34.0%) past but not current drinkers ("former" drinkers), and 1033 (34.3%) current moderate drinkers. The magnitude of the protective effect of moderate drinking on IS was similar (adjusted HR, 0.65; 95% CI, 0.41 to 1.04) to that using current nondrinkers as the referent group. Results were similar for combined ischemic events (Figure). There was no protective benefit for former drinkers (adjusted HR for IS, 1.00; 0.67 to 1.50).

A protective effect was seen in subgroups stratified by age, sex, and race–ethnicity (Table 4). A marked protective effect of moderate alcohol consumption was found among former smokers and never-smokers. There was no protective effect in current smokers, although the number of current smokers was relatively small (n=547), and the CI included the possibility of a 45% reduction in risk. Although there was a trend, a formal test of interaction was not statistically significant (P=0.11).

Discussion

Our results demonstrate a strong protective effect of recent moderate alcohol consumption on risk of IS in a multiethnic, elderly population. Moderate consumption, defined as ≤2 drinks of liquor, cans of beer, or glasses of wine, reduced the risk of IS by ≈50%. Overall, using a continuous measure of alcohol consumption in a nonlinear (quadratic) model, the point of maximum protection was ≈1.2 drinks daily, consistent with our category of moderate consumption. The results were similar when lifetime abstainers were used as referent group, reducing the chance that our findings were attributable to incipient cerebrovascular disease in nondrinkers. However, there was no definite effect of average lifetime consumption of alcohol on IS risk, indicating that the effect may be more directly related to the recency of the alcohol behavior. These results from our prospective cohort study extend previous findings in a case-control study[5] from the same population to individual IS subtypes and provide less biased estimates of the magnitude of the reduction in risk.

The protective relationship between alcohol consumption and coronary artery disease has been confirmed in several studies.[1,21] A meta-analysis found a summary relative risk of 0.83 for moderate drinkers compared with lifetime abstainers.[1] The relationship of alcohol consumption to stroke risk is more controversial, partly because many studies fail to distinguish hemorrhagic and IS. Some studies have shown an increased risk of hemorrhagic stroke associated with increasing alcohol consumption in dose-dependent fashion.[3,4] Those studies that investigated alcohol as a risk factor for IS have found conflicting results and not agreed on the optimal protective dose of alcohol.[3,4] Moreover, most previous studies have not investigated individual IS subtypes.[18]

Ischemic Stroke   **Total Stroke**   **Ischemic Stroke, MI, Vascular Death**
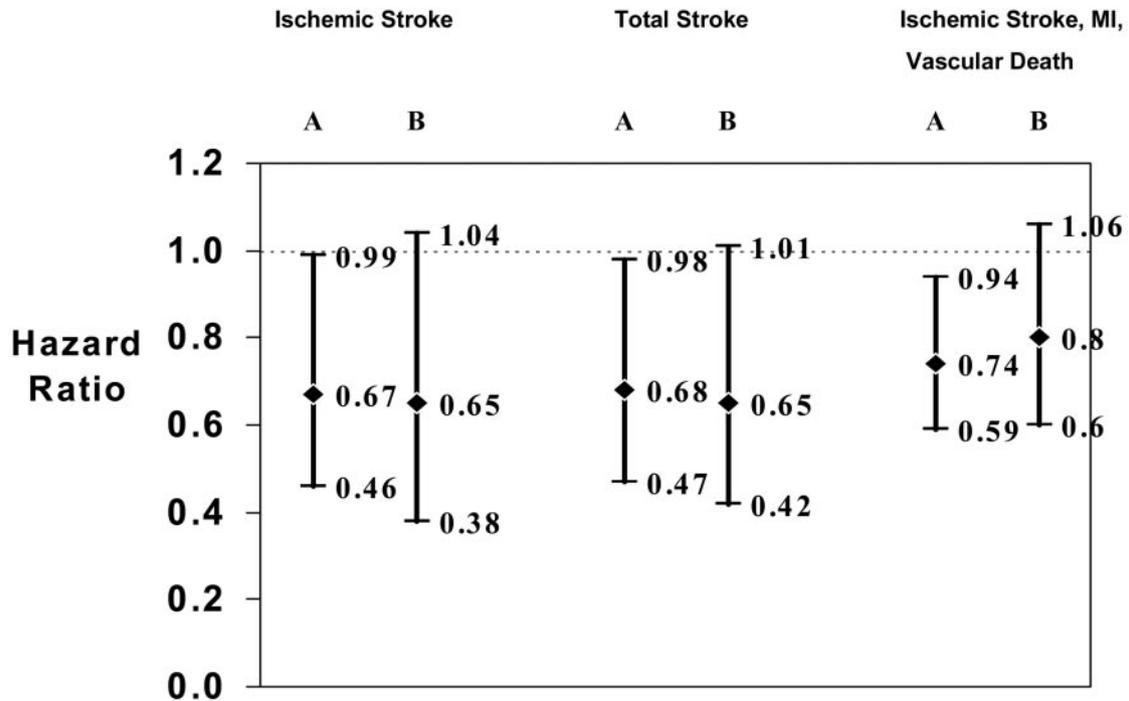
Association between moderate alcohol consumption and risk of stroke and other vascular events. HRs and 95% CIs for moderate drinking (≥1 drink per month and ≤2 drinks per day), using as the referent group those who did not drink in the past year (A) and those who classified themselves as never-drinkers (B). Analyses are adjusted for age (continuous), sex, race–ethnicity, education (high school graduate vs not), hypertension, diabetes mellitus, current cigarette smoking, atrial fibrillation, and levels of HDL.

The US Nurses' Health Study found a protective effect of moderate alcohol consumption (up to 1.2 drinks daily) on IS among women.[19] In a study using an administrative database, all levels of alcohol consumption were associated with decreased risk of hospitalization for IS in both men and women, but a stronger protective effect was found in blacks than in whites.[20] Other cohort studies of IS[3,4,21,22] have failed to confirm this relationship. In the Framingham Heart Study, no protective effect of moderate consumption was seen overall, although there was a protective effect among those 60 to 69 years of age.[21] No significant protective effect of moderate consumption was found in an analysis of data from the Health Professionals Follow-Up Study, but generalizability of those results may be limited by the educational status and homogeneity of this cohort.[22]

A major methodological weakness of past studies is the bias attributable to the "sick quitter" hypothesis: persons who are experiencing preclinical symptoms of disease may decrease their usual alcohol consumption.[23] Assessment of recent alcohol exposure may thus underestimate true lifetime alcohol exposure and lead to misclassification of exposure status. We attempted to minimize this potential misclassification by performing analyses with 2 different referent groups, nonrecent drinkers and lifetime abstainers, and by adjusting for confounding diseases that may predispose an individual to stroke and lead to decreased alcohol consumption.

Hispanics have rarely been enumerated separately in epidemiologic studies, and our study is the first prospective cohort study to find a protective relationship between alcohol and stroke in a population composed predominantly of Hispanics. The effect of alcohol on stroke risk may vary by race–ethnicity.[20] There is evidence that there may be different subgroups among American blacks, some of which, because of environmental factors, may share the risk profiles typical of white populations.[24] Such subpopulations may account for the differences between our results and negative findings in other black populations.[25]

TABLE 4.   Risk of IS Associated With Recent Moderate Alcohol Consumption, Stratified by Age, Sex, Race–Ethnicity, and Smoking Status*

	Adjusted HR (95% CI)†
Age <70 y	0.81 (0.45–1.46)
Age ≥70 y	0.54 (0.33–0.90)
Men	0.76 (0.44–1.32)
Women	0.59 (0.34–1.03)
Hispanic	0.54 (0.29–1.02)
Non-Hispanic Black	0.86 (0.46–1.60)
Non-Hispanic White	0.67 (0.32–1.42)
Nonsmokers	0.51 (0.26–1.00)
Former smokers	0.61 (0.32–1.15)
Current smokers	1.12 (0.55–2.29)

*Referent group is those who drank no alcohol (<1 drink/mo) in past year; †models adjusted for age (continuous), sex, race–ethnicity, and education (high school graduate vs not), hypertension, diabetes mellitus, atrial fibrillation, levels of HDL, and current cigarette smoking.

In each case, the model is not adjusted for the stratification variable.

The protective effect of alcohol on heart disease appears to be partially mediated by an increase in HDL associated with alcohol consumption.[26] In the present study, the effect of alcohol on stroke risk was independent of HDL. In addition, the protective effect was greater among those with cryptogenic, cardioembolic, and lacunar strokes, rather than among only atherosclerotic strokes. Other investigators studying specific IS subtypes also found a reduction in risk of lacunar stroke with moderate alcohol consumption.[18] Of note, our estimate of the protective effect of alcohol for atherosclerotic stroke subtypes (HR, 0.81) is close to the summary estimate (0.83) obtained from a meta-analysis in cardiac disease,[1] for which the main mechanism is atherosclerotic disease. Other potential alcohol-induced protective mechanisms that may explain the effects of alcohol consumption on these other stroke subtypes were not evaluated in our study, including decreased platelet aggregability, increased prostacyclin/thromboxane ratios, and decreased fibrinogen levels.[27]

We also found that alcohol consumption within the year before baseline evaluation was associated with reduced risk of IS and other vascular events, but average lifetime consumption was not. This provides further indirect support for the hypothesis that the protective effect of alcohol is related to other physiological effects besides reduced development of chronic atherosclerosis.[27]

Our study has several strengths. We used a population-based, prospective cohort study design. Subjects were identified by random-digit dialing, and we had high rates of participation and excellent follow-up. Our measurement of alcohol consumption was assessed using structured in-person interviews, and we adjusted for a variety of demographic and medical risk factors.

Our study also has limitations. Our assessment of alcohol is subject to measurement error. We found a small number of heavy drinkers, limiting our ability to draw conclusions about this level of consumption. However, the inclusion of those who are actually heavier drinkers among the moderate drinking category would bias our estimate away from the null value, leading to an underestimate of the protective effect of moderate consumption. Binge drinking was also not directly assessed in our population. Our population may also differ from that of other US subpopulations, and therefore generalization to other US subpopulations should be undertaken cautiously.

Summary
Our study demonstrates that moderate alcohol consumption may have important health benefits in reducing risk of many types of IS. Although alcohol consumption should not be recommended to those who do not drink, because of its potential adverse effects, our data support the view, endorsed by national stroke prevention guidelines,[28,29] that among those who are moderate drinkers, continued consumption may reduce stroke risk.

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