

Alcohol and Risk for Ischemic Stroke in Men: The Role of Drinking Patterns and Usual Beverage

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Background: The association of light to moderate alcohol consumption with risk for ischemic stroke remains controversial, as do the roles of beverage type and drinking pattern.

Objective: To assess the association of drinking patterns and beverage type with risk for ischemic stroke among men.

Design: Prospective cohort study.

Setting: United States.

Participants: 38 156 male health professionals who were free of known cardiovascular disease or cancer at baseline in 1986.

Measurements: With a semi-quantitative food-frequency questionnaire, the authors individually ascertained consumption of regular and light beer, red and white wine, and liquor every 4 years. Alcohol consumption was categorized as light (0.1 to 9.9 g/d, or <1 drink daily), moderate (10.0 to 29.9 g/d, or 1 to 2 drinks daily), and heavier (≥ 30.0 g/d, or ≥ 3 drinks daily).

Results: During a follow-up period of 14 years, 412 cases of incident ischemic stroke were documented. Compared with abstainers, light drinkers had a multivariate-adjusted relative risk of 0.99 (95% CI, 0.72 to 1.37), moderate drinkers had a multivariate-

ate-adjusted relative risk of 1.26 (CI, 0.90 to 1.76), and heavier drinkers had a multivariate-adjusted relative risk of 1.42 (CI, 0.97 to 2.09; $P = 0.01$ for trend). Consumption of 10.0 to 29.9 g of alcohol per day on 3 to 4 days per week appeared to be associated with the lowest risk (relative risk, 0.68 [CI, 0.44 to 1.05]). Red wine consumption was inversely associated with risk in a graded manner ($P = 0.02$ for trend), but other beverages were not. The apparently higher risk for ischemic stroke with heavier alcohol use appeared to be most pronounced for the embolic subtype.

Limitations: This study had limited power to examine specific drinking patterns and heavy drinking and could not assess risk for hemorrhagic stroke.

Conclusions: In this sample of male health professionals, light and moderate average alcohol use was generally not associated with an increased risk for ischemic stroke, although drinking pattern and beverage type modified this relation. Intake of more than 2 drinks per day may be associated with a higher risk for ischemic stroke.

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Although epidemiologic studies consistently link moderate alcohol consumption with a lower risk for myocardial infarction (1), the relationship between alcohol consumption and ischemic stroke is less clear. However, previous studies of alcohol consumption and ischemic stroke have often had important limitations, including failure to assess drinking pattern, assessments of alcohol intake that have not been validated, failure to distinguish stroke subtypes, insufficient follow-up to incorporate changes in alcohol use over time, and lack of control for various healthy lifestyle features associated with moderate drinking (2, 3).

Another area of controversy is the role of beverage type. Red wine contains specific phenolic compounds that may prevent oxidation of low-density lipoprotein cholesterol and inhibit smooth-muscle cell proliferation (4, 5). In keeping with these experimental findings, the Copenhagen City Heart Study reported that consumption of wine, but not of beer or liquor, was associated with a lower risk for stroke (mostly ischemic) (6). However, a healthier lifestyle among wine drinkers, rather than the nonalcoholic components of wine, may explain the apparent benefits attributable to wine (7). Most previous studies of alcohol and ischemic stroke did not account for dietary and other lifestyle differences among wine drinkers, drinkers of other alcoholic beverages, and abstainers.

To address these questions, we studied the relationship

between alcohol consumption and incident ischemic stroke over a 14-year period among 38 156 participants of the Health Professionals Follow-up Study (8), a prospective cohort of male health professionals in the United States. In these analyses, we assessed how drinking pattern, baseline and updated measures of alcohol consumption, and individual beverage types influence the association of alcohol consumption with risk for ischemic stroke.

METHODS

The Health Professionals Follow-up Study enrolled 51 529 U.S. male dentists, veterinarians, optometrists, pharmacists, osteopathic physicians, and podiatrists 40 to 75 years of age who returned a mailed questionnaire re-

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Context

Past studies don't clearly show that alcohol consumption affects the risk for ischemic stroke.

Contribution

This prospective cohort study involving 38 156 male health professionals followed for 14 years found that consuming more than 2 drinks daily was associated with an increased risk for ischemic stroke. Two drinks or fewer were not associated with increased risk. Consuming red wine, but not other beverage types, was associated with a lower risk.

Cautions

The study had limited power to determine the precise drinking patterns that were associated with stroke risk.

Implications

These findings support public health recommendations to avoid consuming more than 2 drinks daily.

—The Editors

garding diet and medical history in 1986. Follow-up questionnaires were sent biennially to update information on exposures and newly diagnosed illnesses. For this analysis, we excluded 5544 men who reported a baseline history of cardiovascular disease or cancer (other than nonmelanoma skin cancer), 1706 who had missing or implausible nutritional information at baseline (including missing alcohol consumption, ≥ 70 missing food items, or estimated daily energy intake ≤ 800 or ≥ 4200 kcal), and 89 whose initial questionnaires had other technical problems. To minimize the inclusion of “sick quitters,” we also excluded 6034 men who consumed no alcohol at baseline but who reported that they had consumed alcohol in the previous 10 years, leaving 38 156 men eligible for analysis.

We assessed alcohol consumption within a 131-item semi-quantitative food-frequency questionnaire. The questionnaire included separate items about beer, white wine, red wine, and liquor. We specified standard portions as a glass, bottle, or can of beer; a 4-ounce glass of wine; and a shot of liquor. For each beverage, participants were asked how often, on average over the past year, they consumed that amount. We calculated ethanol intake by multiplying the frequency of consumption of each beverage by the alcohol content of the specified portion size (12.8 g for beer, 11.0 g for wine, and 14.0 g for liquor) and summing across beverages (9). This process was repeated in 1990, 1994, and 1998, with an added item about light beer in 1994. In 1986, men also reported the number of days per week that they typically drank any form of alcohol.

We previously assessed the validity of alcohol consumption estimated with the food-frequency questionnaire by comparing it with intake from two 1-week dietary

records collected approximately 6 months apart among 136 participants residing in eastern Massachusetts (10, 11); the Spearman correlation coefficient between these 2 measures was 0.86. Estimated mean alcohol intake was 12.8 g/d using dietary records and 12.5 g/d with the food-frequency questionnaire, with no evidence of apparent systematic bias. The correlation coefficient for drinking frequency between our questionnaire and diet records was 0.79. Alcohol consumption estimated from the questionnaires also correlated well with serum high-density lipoprotein cholesterol concentrations, with a Spearman correlation coefficient of 0.31 to 0.35.

We wrote to participants who reported an incident stroke on the follow-up questionnaires to confirm the report and request permission to review medical records. We defined a stroke as confirmed if it produced a typical neurologic deficit of rapid or sudden onset lasting 24 hours or more and was attributable to a cerebrovascular event. Physicians blinded to risk factor status conducted the medical record review. We defined a stroke as probable if we could not obtain medical records but the participant required hospitalization and the diagnosis was corroborated by supplementary correspondence; only 1.2% of included cases were considered probable rather than confirmed, and their exclusion did not affect our results. We categorized stroke types according to National Survey of Stroke criteria (12), with categories of ischemic (embolic or thrombotic), hemorrhagic (subarachnoid or intracerebral), and unknown. We confirmed fatal strokes by using medical records (84%), autopsy reports (2%), or death certificates supplemented by confirmatory evidence from family members or previously collected medical history when medical records and autopsy reports were unavailable (14%). There were too few cases of hemorrhagic stroke to study it separately in these analyses. Deaths were reported by families and postal officials and through the National Death Index. Follow-up for deaths was over 98% complete when these sources were combined in a similar study among women (13).

Covariate information was generally derived from biennial questionnaires. Nutritional information (energy, saturated fat, trans fatty acids, folate, vitamin E, magnesium, potassium, ω -3 fatty acids, dietary fiber, and caffeine) was derived from food-frequency questionnaires administered every 4 years. Participants reported the presence of cardiovascular risk factors (physician-diagnosed hypertension, diabetes, and hypercholesterolemia; cigarette smoking; and parental history of myocardial infarction). Aspirin use included use of aspirin and aspirin-containing products at least twice weekly. Nutritional variables, anthropomorphic measures, aspirin use, and self-reported cardiovascular risk factors have been validated (14–19).

We calculated person-years for each participant from the date of return of the 1986 questionnaire to the date of the first stroke, the date of death, or January 2000. We calculated incidence rates by dividing the number of ischemic strokes in each category by person-years of follow-up

Table 1. Baseline Characteristics by Alcohol Consumption in 38 156 U.S. Men: The Health Professionals Follow-up Study, 1986*

Characteristic†	Alcohol Consumption‡			
	0 g/d	0.1–9.9 g/d	10.0–29.9 g/d	≥30.0 g/d
Participants, <i>n</i>	4530	16 999	11 441	5186
Mean age, <i>y</i>	53	53	54	55
Mean body mass index, <i>kg/m</i> ²	25.0	24.9	24.7	24.9
Mean days per week alcohol is consumed, <i>n</i>	0	1.4	4.5	6.3
Ethanol consumed, <i>g/d</i>				
Beer	0	1.3	5.1	16.6
Red wine	0	0.5	2.0	3.2
White wine	0	1.0	3.3	4.6
Liquor	0	1.3	5.9	21.9
Current cigarette smoker, %	5	8	10	21
Past cigarette smoker, %	19	39	48	51
Physical activity, <i>METS/wk</i>	24	25	27	25
Hypertension, %	18	19	20	25
Diabetes, %	3.0	2.3	1.6	1.8
Hypercholesterolemia, %	9	11	11	11
Parental history of myocardial infarction, %	10	13	12	13
Lipid-lowering therapy, %	0.2	0.4	0.5	0.7
Medications, %				
β-Blockers	6	7	7	10
Calcium-channel blockers	0.5	0.7	0.7	0.8
Nonloop diuretics	7	8	8	11
Mean daily intakes				
Total energy, <i>kcal/d</i>	1951	1939	2024	2226
Folate, <i>μg/d</i> §	459	488	481	441
Trans fats, <i>g/d</i> §	3.1	2.9	2.8	2.4
Saturated fats, <i>g/d</i> §	26	25	24	22
Dietary fiber, <i>g/d</i> §	22	22	20	17
Vitamin E, <i>mg/d</i> §	78	95	97	90

* MET = metabolic equivalent.

† Except for age, all variables are directly standardized to the age distribution of the study sample.

‡ One standard drink has approximately 11–14 g of alcohol per serving.

§ Adjusted for total energy intake.

in that category. The relative risk was computed as the rate in a specific category of alcohol consumption divided by the rate in abstainers, with direct adjustment for age in 5-year categories and smoking in 6 categories (never, former, 1 to 14 cigarettes/d, 15 to 24 cigarettes/d, ≥25 cigarettes/d, and missing). As in previous multivariate analyses (20), we used pooled logistic regression and updated covariates (21). We simultaneously controlled for age; smoking; body mass index (in quintiles); aspirin use; diabetes; hypercholesterolemia; average daily exertion (in 5 categories); energy intake (in quintiles); parental history of myocardial infarction at or before age 60 years; and energy-adjusted intake of saturated fat, trans fatty acids, folate, vitamin E, and dietary fiber (each in quintiles), along with geographic region (in 4 categories) (22) and energy-adjusted intake of magnesium and potassium (23) and ω-3 fatty acids (24). We did not include hypertension as a covariate in primary analyses but included it in sensitivity analyses to assess the degree to which it may mediate a positive association between alcohol use and risk for stroke.

Dietary variables were updated every 4 years; other potential confounding variables were updated every 2 years. We assigned indicator variables where smoking or exercise information was missing, accounting for 12% and 15% of cumulative person-time, respectively. We stopped updat-

ing alcohol use at development of cancer (other than non-melanoma skin cancer), cardiovascular disease (other than stroke), or hypertension; analyses that censored participants at diagnosis of cancer or cardiovascular disease yielded similar results (Appendix Table 1, available at www.annals.org). We conducted tests of linear trend across increasing categories of alcohol consumption by treating the midpoints of consumption in categories as a continuous variable. In most analyses, we categorized participants as abstainers, light drinkers (0.1 to 9.9 g/d), moderate drinkers (10 to 29.9 g/d), and heavier drinkers (≥30.0 g/d). These categories approximately correspond to average intake of no alcohol, less than 1 standard drink per day, 1 to 2 drinks per day, and more than 2 drinks per day.

We performed primary analyses by using updated measures of alcohol consumption, in which we prospectively assessed the relative risk for ischemic stroke in 4-year increments, based on alcohol consumption derived from the preceding questionnaire. Thus, we used the 1986 questionnaire to determine the risk for stroke during the 1986 to 1990 period, the 1990 questionnaire for 1990 to 1994, and so on. We assessed the risk associated with individual beverage types using updated measures of intake (25). In these analyses, we simultaneously controlled for the standard covariates that we incorporated into other models and

Table 2. Risk for Ischemic Stroke according to Updated and Baseline Alcohol Consumption*

Variable	Alcohol Consumption				P Value for Trend
	0 g/d	0.1–9.9 g/d	10.0–29.9 g/d	≥30.0 g/d	
Updated alcohol use					
Cases, <i>n</i>	54	147	131	80	
Person-years	73 592	218 645	149 050	65 754	
Relative risk (95% CI)	1.00	0.91 (0.66–1.26)	1.23 (0.89–1.70)	1.40 (0.96–2.04)	0.007
Multivariate-adjusted relative risk (95% CI)	1.00	0.99 (0.72–1.37)	1.26 (0.90–1.76)	1.42 (0.97–2.09)	0.01
Multivariate-adjusted relative risk further adjusted for hypertension (95% CI)	1.00	0.92 (0.67–1.28)	1.15 (0.82–1.61)	1.22 (0.83–1.79)	0.07
Baseline alcohol use					
Cases, <i>n</i>	44	148	142	78	
Person-years	60 244	226 200	151 973	68 623	
Relative risk (95% CI)	1.00	0.85 (0.60–1.21)	1.25 (0.88–1.77)	1.32 (0.88–1.98)	0.02
Multivariate-adjusted relative risk (95% CI)	1.00	0.94 (0.66–1.32)	1.26 (0.88–1.79)	1.25 (0.84–1.88)	0.03
Multivariate-adjusted relative risk further adjusted for hypertension (95% CI)	1.00	0.93 (0.66–1.31)	1.22 (0.86–1.74)	1.15 (0.76–1.72)	0.10

* Relative risks are adjusted for age and smoking. Multivariate-adjusted relative risks are adjusted for age; smoking; body mass index; geographic region; parental history of myocardial infarction; physical activity; hypercholesterolemia; aspirin use; diabetes; and intake of vitamin E, folate, energy, saturated fat, trans fats, potassium, magnesium, ω -3 fatty acids, and dietary fiber.

for intake of each of the other beverage types. Analyses that examined beverage types individually yielded similar results and are not shown here. We separated beer, red wine, and white wine intake into 3 categories (none, 0.1 to 9.9 g/d, and ≥ 10.0 g/d); because it was used in larger amounts, we further separated heavier liquor intake into categories of 10.0 to 29.9 g/d and at least 30.0 g/d. We used the SAS statistical package, version 8.2 (SAS Institute, Cary, North Carolina), for all analyses.

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RESULTS

Baseline Characteristics

Table 1 shows the characteristics of men categorized at baseline as abstainers, light drinkers (0.1 to 9.9 g/d), moderate drinkers (10.0 to 29.9 g/d), and heavier drinkers (≥ 30.0 g/d). On average, heavier alcohol consumption was associated with a greater prevalence of smoking and hypertension and a lower prevalence of diabetes (Table 1). Beer and liquor were the alcoholic beverages consumed in greatest quantity.

Average Alcohol Consumption and Ischemic Stroke

During 14 years of follow-up, we documented 412 new cases of ischemic stroke. In multivariate analyses using updated alcohol consumption, light drinking was associated with a risk similar to that seen with abstinence. The relative risk associated with heavier drinking was 1.42 (95% CI, 0.97 to 2.09) (Table 2). The *P* value from a test for linear trend was 0.01; the corresponding *P* value for quadratic trend exceeded 0.2.

Analyses using baseline alcohol consumption demonstrated a similar relationship but yielded a lower estimate of the association with heavier drinking. Additional control for hypertension reduced the estimated relative risk associated

with heavier drinking from 1.42 to 1.22, consistent with the greater prevalence of hypertension among heavier drinkers.

Pattern of Alcohol Consumption and Ischemic Stroke

We assessed baseline drinking frequency and quantity of alcohol consumed per drinking day to determine whether specific patterns of consumption were associated with risk for ischemic stroke (Table 3). Overall, abstinence and intake of alcohol 1 to 2 or 3 to 4 days per week were associated with similar risks. Intake of alcohol 5 to 7 days per week was associated with a relative risk of 1.20 (CI, 0.91 to 1.58). However, the quantity of alcohol use per drinking day modified the association among men who drank alcohol 3 to 4 days per week. In this group of men, consumption of less than 30 g of alcohol per drinking day (that is, ≤ 2 drinks) was associated with a multivariate-adjusted relative risk of 0.72 (CI, 0.48 to 1.10) compared with abstainers. In contrast, consumption of at least 30 g per drinking day was associated with a relative risk of 1.47 (CI, 0.94 to 2.32). When categorized more precisely, consumption of 10 to 29.9 g of alcohol (that is, 1 to 2 drinks) 3 to 4 days per week was associated with a multivariate-adjusted relative risk of 0.68 (CI, 0.44 to 1.05; *P* = 0.08).

Beverage Type and Ischemic Stroke

We compared the associations of intake of red wine, white wine, beer, and liquor with risk for ischemic stroke in updated analyses (Table 4). In these analyses, multivariate adjustment attenuated the inverse relation of white wine intake with risk but had less effect on other beverages. Red wine intake was associated with significantly lower risk in a graded fashion, beer consumption was not associated with risk, and liquor consumption had a borderline association with lower risk only at a level of 0.1 to 9.9 g/d. Pairwise tests of the

Table 3. Risk for Ischemic Stroke according to Baseline Frequency and Quantity of Alcohol Consumption among 38 156 Male Health Professionals*

Variable	Drinking Days per Week				P Value
	0	1–2	3–4	≥5	
Cases, <i>n</i>	93	101	57	161	
Person-years	123 710	153 326	83 303	145 564	
Relative risk (95% CI)	1.00	0.87 (0.66–1.15)	0.87 (0.62–1.21)	1.14 (0.88–1.47)	0.05
Multivariate-adjusted relative risk (95% CI)	1.00	0.93 (0.70–1.24)	0.94 (0.66–1.32)	1.20 (0.91–1.58)	0.06
Multivariate-adjusted relative risk further adjusted for hypertension (95% CI)	1.00	0.92 (0.69–1.22)	0.91 (0.64–1.28)	1.13 (0.86–1.50)	0.17

Variable	Average Alcohol Use per Drinking Day							
	0	<30 g/d	≥30 g/d	<30 g/d	≥30 g/d	<30 g/d	≥30 g/d	
Cases, <i>n</i>	93	67	34	30	27	80	81	
Relative risk (95% CI)	1.00	0.89 (0.65–1.22)	0.82 (0.55–1.21)	0.63 (0.42–0.96)	1.40 (0.91–2.16)	1.05 (0.77–1.42)	1.18 (0.87–1.60)	
Multivariate-adjusted relative risk (95% CI)	1.00	0.95 (0.69–1.30)	0.89 (0.60–1.33)	0.72 (0.48–1.10)	1.47 (0.94–2.32)	1.17 (0.86–1.61)	1.25 (0.90–1.74)	
Multivariate-adjusted relative risk adjusted for hypertension (95% CI)	1.00	0.94 (0.68–1.29)	0.88 (0.59–1.31)	0.70 (0.46–1.07)	1.41 (0.90–2.22)	1.13 (0.83–1.55)	1.15 (0.82–1.60)	

* Relative risks are adjusted for age and smoking. Multivariate-adjusted relative risks are adjusted for age; smoking; body mass index; geographic region; parental history of myocardial infarction; physical activity; hypercholesterolemia; aspirin use; diabetes; and intake of vitamin E, folate, energy, saturated fat, trans fats, potassium, magnesium, ω-3 fatty acids, and dietary fiber.

effects of the 4 individual beverage types modeled as continuous variables demonstrated significant differences between red wine and both beer ($P = 0.01$) and liquor ($P = 0.01$). Consumption of beverages other than liquor was insufficient to compare their relative effects at heavy levels of intake.

Stratified Analyses of Ischemic Stroke

We found generally consistent relations of alcohol use and risk for ischemic stroke in stratified analyses (Table 5). As we recently suggested (26), folate intake apparently modified the relation of alcohol use to risk for ischemic stroke, although this interaction was not statistically signif-

Table 4. Risk for Ischemic Stroke according to Updated Consumption of Individual Alcoholic Beverages*

Alcohol Consumption	Cases, <i>n</i>	Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk Further Adjusted for Hypertension (95% CI)
Red wine†				
0 g/d	252	1.00	1.00	1.00
0.1–9.9 g/d	151	0.78 (0.63–0.95)	0.77 (0.61–0.98)	0.82 (0.64–1.04)
≥10.0 g/d	9	0.54 (0.27–1.05)	0.54 (0.27–1.12)	0.61 (0.30–1.24)
White wine‡				
0 g/d	187	1.00	1.00	1.00
0.1–9.9 g/d	214	0.96 (0.79–1.17)	1.14 (0.90–1.44)	1.08 (0.85–1.37)
≥10.0 g/d	11	0.74 (0.41–1.37)	0.89 (0.48–1.66)	0.82 (0.44–1.52)
Beer‡				
0 g/d	190	1.00	1.00	1.00
0.1–9.9 g/d	180	1.01 (0.82–1.23)	1.09 (0.87–1.37)	1.02 (0.82–1.28)
≥10.0 g/d	42	1.07 (0.77–1.49)	1.23 (0.86–1.74)	1.08 (0.76–1.54)
Liquors§				
0 g/d	200	1.00	1.00	1.00
0.1–9.9 g/d	110	0.79 (0.63–1.00)	0.84 (0.66–1.08)	0.85 (0.67–1.09)
10.0–29.9 g/d	58	0.97 (0.72–1.30)	0.99 (0.72–1.35)	0.97 (0.71–1.32)
≥30.0 g/d	44	1.16 (0.83–1.62)	1.14 (0.80–1.64)	1.09 (0.76–1.56)

* Relative risks are adjusted for age and smoking. Multivariate-adjusted relative risks are adjusted for age; smoking; body mass index; geographic region; parental history of myocardial infarction; physical activity; hypercholesterolemia; aspirin use; diabetes; and intake of vitamin E, folate, energy, saturated fat, trans fats, potassium, magnesium, ω-3 fatty acids, dietary fiber, and the other 3 beverages.

† The P value for trend was 0.007 for relative risk, 0.02 for multivariate-adjusted relative risk, and 0.06 for multivariate-adjusted relative risk further adjusted for hypertension.

‡ The P value for trend was >0.2 for relative risk, multivariate-adjusted relative risk, and multivariate-adjusted relative risk further adjusted for hypertension.

§ The P value for trend was 0.19 for relative risk and >0.2 for multivariate-adjusted relative risk and for multivariate-adjusted relative risk further adjusted for hypertension.

Table 5. Multivariate-Adjusted Relative Risk for Ischemic Stroke according to Updated Alcohol Consumption, Stratified by Selected Clinical Characteristics*

Characteristic	Multivariate-Adjusted Relative Risk according to Alcohol Consumption (95% CI)				P Value for Trend
	0 g/d	0.1–9.9 g/d	10.0–29.9 g/d	≥30.0 g/d	
Age					
40–59 y	1.00	0.84 (0.40–1.79)	1.15 (0.51–2.57)	2.05 (0.83–5.07)	0.03
≥60 y	1.00	1.03 (0.72–1.47)	1.31 (0.90–1.89)	1.44 (0.94–2.21)	0.02
Body mass index					
Below median level	1.00	1.11 (0.68–1.80)	1.44 (0.87–2.38)	1.82 (1.02–3.23)	0.01
Above median level	1.00	0.89 (0.58–1.37)	1.13 (0.72–1.77)	1.15 (0.68–1.94)	>0.2
Aspirin use					
Yes	1.00	0.80 (0.51–1.27)	1.16 (0.73–1.84)	0.93 (0.52–1.65)	>0.2
No	1.00	1.19 (0.75–1.88)	1.33 (0.82–2.15)	2.00 (1.18–3.40)	0.006
Hypertension					
Yes	1.00	0.95 (0.59–1.51)	1.22 (0.76–1.97)	1.09 (0.64–1.86)	>0.2
No	1.00	0.92 (0.59–1.44)	1.08 (0.67–1.75)	1.49 (0.84–2.64)	0.07
Folate intake					
Below median level	1.00	1.32 (0.80–2.18)	1.78 (1.06–2.98)	1.79 (1.01–3.18)	0.03
Above median level	1.00	0.77 (0.50–1.17)	0.91 (0.58–1.44)	1.16 (0.68–1.99)	0.18
Caffeine intake					
Below median level	1.00	1.06 (0.71–1.59)	1.24 (0.80–1.93)	1.60 (0.95–2.70)	0.04
Above median level	1.00	1.02 (0.59–1.76)	1.45 (0.84–2.51)	1.53 (0.84–2.81)	0.04

* Multivariate-adjusted relative risks adjusted for age; smoking; body mass index; geographic region; parental history of myocardial infarction; physical activity; hypercholesterolemia; aspirin use; diabetes; and intake of vitamin E, folate, energy, saturated fat, trans fats, potassium, magnesium, ω -3 fatty acids, and dietary fiber, except for the stratifying characteristic.

icant when modeled with 4 alcohol and 2 folate categories ($P = 0.11$). In general, men with lower folate intake had a graded positive relation of alcohol use and risk, while men with greater folate intake appeared to have somewhat lower risk at light levels of intake. Unexpectedly, we found a similar result for aspirin intake, with a graded positive relationship of alcohol use with ischemic stroke risk among those who did not use aspirin but no apparent relationship among those who did ($P = 0.04$ for interaction). Despite evidence that alcohol and caffeine administered together may reduce cortical infarct volume during ischemic stroke (27), caffeine intake dichotomized at median intake did not demonstrably modify the relationship of alcohol consumption and risk for ischemic stroke.

Updated Alcohol Consumption and Stroke Subtypes

As suggested by Dulli (28), thrombotic and embolic strokes, the 2 subtypes of ischemic stroke, may differ in their pathogenesis and association with alcohol use. To explore this hypothesis further, we examined the risks for thrombotic and embolic stroke according to updated alcohol consumption (Appendix Table 2, available at www.annals.org), although our exploratory analyses were limited by the smaller numbers of each stroke subtype. Risk for embolic stroke appeared to have a positive association with alcohol use. In contrast, alcohol intake was generally not associated with risk for thrombotic stroke.

DISCUSSION

In this prospective analysis of more than 38 000 men who were free of known cardiovascular disease, alcohol consumption appeared to be associated with a higher risk for ischemic stroke among those who consumed more than 2 drinks per day. However, alcohol was apparently not associated with risk at lower levels of intake. A pattern of intake characterized by moderate use 3 to 4 days per week appeared to be associated with the lowest risk. Red wine consumption was inversely associated with ischemic stroke risk, an association that was significantly different from the comparable associations of other beverages.

Despite the substantial epidemiologic evidence linking moderate alcohol use to a lower risk for coronary heart disease, the link between moderate alcohol use and ischemic stroke remains less consistent, particularly in recent cohort studies (29–33). A Swedish study found relative risks of 1.3, 1.3, and 1.1 among men who consumed more than 0 g but less than 5 g of alcohol per day, 5 to 14.9 g of alcohol per day, and at least 15 g of alcohol per day, respectively (29). Investigators from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial reported results very similar to ours, with relative risks of 0.9, 1.2, and 1.5 among male smokers whose daily alcohol consumption was 24.0 g or less, 24.1 to 60.0 g, and more than 60.0 g, respectively (30). The Framingham Heart Study found nonsignificant relative risks of 0.7 to 0.8 for men who consumed light, moderate, and heavier amounts of alcohol

(31). Although case-control studies have often reported strong protective effects of moderate alcohol consumption (34, 35), Reynolds and colleagues (36) found summary relative risks for ischemic stroke of 0.82 and 0.94 among consumers of an average of less than 12 g and 12 to 24 g of alcohol per day, respectively, in a meta-analysis of cohort studies. When our results are taken together with this meta-analysis, current data seem to suggest that men who consume roughly 1 drink every other day may have a modestly lower risk for ischemic stroke, but heavier alcohol consumption is associated with higher risk.

Our study identified 2 additional possible sources of heterogeneity with other studies. First, our results support the hypothesis that even ischemic strokes represent a heterogeneous outcome with respect to alcohol intake (28). Embolic strokes were associated with higher risk in a stepwise manner, while thrombotic strokes showed only a possible inverse relation among light drinkers. Second, we found that assessing alcohol use with a single baseline measurement may underestimate the deleterious effects of heavier alcohol use when compared with measurements prospectively updated during the follow-up period. Nearly all previous studies have relied on a single measurement of alcohol use as the exposure of interest, often obtained more than a decade or two before the end of follow-up (where the most cases are concentrated).

We know of no cohort studies that have assessed drinking pattern and risk for stroke in detail. One Finnish case-control study of 56 patients and 153 controls found the lowest risk for ischemic stroke among men who reported daily or almost daily light to moderate alcohol consumption (≤ 150 g/wk), roughly consistent with our findings (37). The lower risk for stroke in our study among men who consumed 1 to 2 drinks on 3 to 4 days per week parallels previous findings from this cohort on risk for diabetes (38) and coronary heart disease (20) and emphasizes the importance of regular, limited alcohol use among men who drink.

Our results suggest that beverage type may modify the relation of alcohol use and risk for ischemic stroke, in contrast to our previous findings on coronary heart disease (20). Although some studies have yielded similar findings (6, 31, 35), others have not (34). The constituents of red wine have potentially beneficial vascular effects (4, 5), enhance endothelial nitric oxide release (39), and reduce atherosclerosis in apolipoprotein E-deficient mice (40, 41). It is unclear why these effects would affect the risk for stroke but not coronary heart disease, and therefore this finding needs to be explored in other studies.

Specific limitations of our study warrant discussion. As in any observational study, our results could be influenced, at least in part, by differences between participants in factors other than alcohol consumption. However, we controlled for diet, exercise, body mass index, aspirin use, geographic region, diabetes, age, and smoking, and our sample was homogeneous with respect to occupational class and

sex. We also excluded abstainers who reported decreased alcohol consumption at baseline to minimize the possibility that abstainers were "sick quitters" (42). Nonetheless, it remains possible that unmeasured factors confounded our results, particularly factors related to beverage type, since wine drinkers appear to differ from drinkers of other beverages in a variety of characteristics (7, 43). This is further complicated by the difficulty of isolating effects of individual beverage types when multiple types are consumed (25).

By following more than 38 000 men for 14 years, we confirmed 412 cases of ischemic stroke. Despite the size of our study, the precision of our risk estimates, particularly in subgroup analyses, was limited. Likewise, only 3.5% of the men in our study reported average daily consumption of 50 or more g of alcohol, limiting our ability to define the well-known effects of heavy drinking. Because of the preponderance of ischemic strokes in this and other studies based in the United States (approximately 85% of all incident strokes), we did not address the risk for hemorrhagic stroke in these analyses, although previous studies suggest that even moderate drinking increases this risk (44). It would also be of interest to specifically examine lacunar infarcts in the future because silent lacunar infarcts may be inversely associated with alcohol use (45, 46).

Although our analyses were chosen a priori on the basis of previous work (20), we nonetheless conducted an extensive number. As a result, we cannot exclude the possibility that some results, either positive or negative, may be spurious, and our findings are best viewed in the context of previous work on alcohol intake and ischemic stroke.

Our results are consistent with the hypothesis that heavier drinking increases the risk for ischemic stroke in part by raising blood pressure. However, we did not have information on the degree to which the blood pressure of men with hypertension was controlled. As a result, we urge caution regarding the absence of a clear relation between heavy alcohol use and risk for ischemic stroke among men with established hypertension.

In summary, alcohol consumption appeared to be associated with a higher risk for ischemic stroke among men who consumed more than 2 drinks per day, but this association was not apparent at lower levels of intake. A trend toward lower risk for stroke associated with light drinking was most evident for thrombotic stroke and for consumption of 1 to 2 drinks 3 to 4 days per week. Red wine consumption had an inverse association with ischemic stroke, but other beverages did not. Our findings directly support current public health recommendations stating that men should consume fewer than 2 drinks per day to help prevent ischemic stroke (47). At the same time, our findings support the safety of continued light alcohol consumption among adults who have been able to appropriately regulate the quantity and timing of their alcohol use.

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