

Alcohol Consumption and Stroke Incidence in Male Smokers

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Background—Studies on alcohol consumption and incidences of stroke subtypes have suggested distinct dose-response relationships. Blood pressure and HDL cholesterol mediate the effect of alcohol on coronary heart disease, but similar evidence on cerebrovascular diseases is not available.

Methods and Results—We studied the risk of stroke in 26 556 male cigarette smokers 50 to 69 years of age without history of stroke. The men were categorized as nondrinkers, light (≤ 24 g/d), moderate (25 to 60 g/d), or heavy (> 60 g/d) drinkers. A total of 960 men suffered from incident stroke: 83 with subarachnoid and 95 with intracerebral hemorrhage, 733 with cerebral infarction, and 49 with unspecified stroke. The adjusted relative risk of subarachnoid hemorrhage was 1.0 in light drinkers, 1.3 in moderate drinkers, and 1.6 in heavy drinkers compared with nondrinkers. The respective relative risks of intracerebral hemorrhage were 0.8, 0.6, and 1.8; of cerebral infarction, 0.9, 1.2, and 1.5. Systolic blood pressure attenuated the effect of alcohol consumption in all subtypes of stroke, whereas HDL cholesterol strengthened the effect of alcohol in subarachnoid hemorrhage and cerebral infarction but attenuated the effect in intracerebral hemorrhage.

Conclusions—Alcohol consumption may have a distinct dose-response relationship within each stroke subtype—linear in subarachnoid hemorrhage, U-shaped in intracerebral hemorrhage, and J-shaped in cerebral infarction—but further studies are warranted. Systolic blood pressure and HDL cholesterol seem to mediate the effect of alcohol on stroke incidence, but evidently additional mechanisms are involved. (*Circulation*. 1999;100:1209-1214.)

Key Words: alcohol ■ blood pressure ■ HDL cholesterol ■ stroke

The epidemiological evidence on the relation between alcohol consumption and risk of stroke has not been consistent.¹ At least part of the inconsistency is due to differences in the assessment of the amount and pattern of alcohol consumption and selection of the reference group. The cutoff points for alcohol consumption categories have varied considerably. Sometimes ex-drinkers have been separated from lifelong abstainers; sometimes they have been pooled with the group of current nondrinkers. In addition, subtyping of stroke has varied; most often it has been entirely neglected.

Heavy drinking (> 60 g/d) is related to increased risk of both hemorrhagic²⁻⁷ and ischemic stroke.^{2,4,8-10} It is somewhat unclear whether light (≤ 24 g/d for men) and moderate (25 to 60 g/d for men) drinking decreases the risk of stroke compared with nondrinking: The risk of hemorrhagic strokes has increased, remained unchanged, or decreased, and the risk of ischemic stroke has either diminished or remained unchanged.¹ In summary, the risk of hemorrhagic stroke seems to increase steeply with increasing alcohol consumption, but the risk of ischemic stroke seems to be J-shaped with nondrinkers, and heavy drinkers have a higher risk than light drinkers.¹¹

Alcohol causes many changes in physiological functions that may modify the risk of stroke. Alcohol increases blood pressure¹² and serum HDL cholesterol (HDL-C) level.¹³⁻¹⁶ Moderate alcohol consumption increases¹⁷ but ethanol intoxication decreases¹⁸ fibrinolytic activity. Immediate heavy alcohol intake decreases platelet aggregation,¹⁹ but in binge drinkers and alcoholics, platelet aggregation is increased after alcohol withdrawal.^{19,20} Cerebral blood flow is increased immediately after alcohol intake,²¹ and alcohol dilates cutaneous capillaries but constricts arteries when given intrarterially.²² On the other hand, alcohol may cause spasm of cerebral arteries,²³ and it increased peripheral but decreased coronary vascular resistance in animal studies.²⁴

The association between alcohol consumption and risk of stroke has been suggested to be mediated, at least partly, by changes in blood pressure and serum HDL-C.¹¹ High blood pressure is a strong risk factor for all types of stroke,^{25,26} but the relation between HDL-C and stroke is less well known. HDL-C has been inversely related to intracerebral hemorrhage (ICH),²⁷ ischemic stroke,²⁷⁻²⁹ and cerebrovascular atherosclerosis.³⁰

We examined the association of different levels of alcohol consumption with the incidence of stroke and the roles of

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systolic blood pressure (SBP) and HDL-C as possible mediators of the effect. The study comprised male cigarette smokers who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.^{31,32}

Methods

Setting

The ATBC Study was a randomized, double-blind, placebo-controlled, 2×2-factorial-design, primary prevention trial testing the hypothesis that α -tocopherol and β -carotene supplements reduce the incidence of lung and other cancers. During 1985 through 1988, a total of 29 133 male cigarette smokers (≥ 5 cigarettes per day) 50 to 69 years of age from southwestern Finland were randomized to 1 of 4 treatment regimens: α -tocopherol 50 mg/d, β -carotene 20 mg/d, α -tocopherol plus β -carotene, or placebo. Among the exclusion criteria were severe angina on exertion, anticoagulant therapy, chronic renal insufficiency, cirrhosis of the liver, and chronic alcoholism. Of the 29 133 men, 26 556 (91%) were included in the present study, and 2557 (9%) were excluded; 614 men reported a previous stroke, and others provided no information on alcohol consumption. An additional 38 men were excluded from the pathway analysis because of a missing SBP or HDL-C value. Follow-up lasted for a median of 6.1 years with 153 356 person-years. There were no losses to follow-up.

End Points

The primary end point was incident stroke. Strokes were identified by record linkage to the National Hospital Discharge Register and the National Register of Causes of Death, which both use the International Classification of Diseases (ICD).^{33,34} The included diagnoses were ICD-8 codes 430 through 434 and 436 and ICD-9 codes 430, 431, 433, 434, and 436. The ICD-8 codes 431.01 and 431.91 denoting subdural hemorrhage and ICD-9 codes 4330X, 4331X, 4339X, and 4349X denoting cerebral or precerebral artery stenosis or occlusion without cerebral infarction (CI) were excluded. On the basis of the validation study that used specified diagnostic criteria,³⁵ discharge diagnoses of subarachnoid hemorrhage (SAH), ICH, and CI were reliable in 79%, 82%, and 90%, respectively.

Baseline Characteristics

At baseline, the participants completed questionnaires on general background characteristics and medical and smoking histories, including a question about physician-diagnosed stroke, hypertension, diabetes, and heart disease (coronary heart disease, myocardial infarction, valvular disease, arrhythmia, cardiac enlargement, or congestive heart failure). At the first visit, a trained study nurse reviewed the questionnaire with the participant and measured blood pressure, height, and weight. The men were given a detailed dietary history questionnaire³⁶ to be completed at home that included questions about amounts of beer, long drinks, wine, and strong alcoholic drinks consumed daily/weekly/monthly during the previous 12 months. Mean daily alcohol intake (in grams of pure ethanol) was calculated on basis of the dietary history questionnaire.

A blood sample was drawn at the baseline visit after ≥ 12 hours of fasting, and serum was stored at -70°C . Serum total cholesterol and HDL-C were determined enzymatically (CHOD-PAP method, Boehringer Mannheim). HDL-C was measured after precipitation of VLDL and LDL with dextran sulfate and magnesium chloride.

Statistical Analyses

The men were classified as nondrinkers, light (≤ 24.0 g/d), moderate (24.1 to 60.0 g/d), or heavy (>60.0 g/d) drinkers. For specific dose-response analyses, alcohol consumption was categorized by standard drinks (1 standard drink is equivalent to 12 g pure ethanol) consumed daily ($\leq 1/2$, 1, 2, 3, 4, 5, >5 drinks per day). For effect-modification analyses, moderate and heavy drinkers were combined into 1 group, and men were divided into nonhypertensive and hypertensive (SBP <160 or ≥ 160 mm Hg) and into 2 groups by

median value of HDL-C (<1.15 or ≥ 1.15 mmol/L). Body mass index was calculated. Leisure-time physical activity was categorized as sedentary or active (strenuous exercise at least once a week). Education level was categorized as primary school (<7 years), secondary school (7 to 12 years), and university or other higher education (>12 years). The trial supplementation was coded as recipient or nonrecipient of α -tocopherol and as recipient or nonrecipient of β -carotene.

The calculation of person-years of the follow-up ended at stroke death, or April 30, 1993, the end of the trial. The crude incidence rates were calculated per 10 000 person-years. Unspecified stroke was not included in subtype analyses. Relative risks, holding nondrinkers or the lowest alcohol consumption level (half a drink per day or less) as the reference category, were adjusted for age, body mass index, serum total cholesterol, number of cigarettes smoked daily, education, leisure-time physical activity, diabetes, heart disease, and trial supplementation by use of the Cox proportional-hazards method. Baseline SBP and HDL-C were excluded from the models because of their suspected roles as mediators for the effect of alcohol. The multivariate-adjusted Cox models having alcohol as either a continuous variable or a set of categorical dummy variables were evaluated by comparing the log-likelihood test results. To test log-linear trend, alcohol was set in the multivariate-adjusted Cox models as a single categorical variable with even-spaced values for each alcohol consumption level. The effect modification by SBP and HDL-C was evaluated by both stratified multivariate-adjusted Cox models and comparison of multivariate-adjusted Cox models with and without an interaction term formed by alcohol and SBP or by alcohol and HDL-C. In pathway analysis, SBP and HDL-C were added to the regression model each at time after adjustment for potential confounding factors mentioned above.

Results

The baseline characteristics by alcohol consumption are given in Table 1. Most men (61%) were light drinkers, 11% did not drink alcohol, and only 5% were heavy drinkers. Of the 23 625 men who reported any alcohol consumption, 25% consumed at most 5 g/d; the median consumption was 13 g/d and the overall range was 0.04 to 278 g/d. Alcohol consumption correlated inversely with age and previous heart disease and directly with SBP, diastolic blood pressure, previous hypertension, HDL-C, number of cigarettes smoked per day, and higher education.

A total of 960 incident strokes occurred during the follow-up: 83 SAHs, 95 ICHs, 733 CIs, and 49 unspecified strokes (Table 2). The adjusted relative risk of SAH increased linearly with increasing alcohol consumption, whereas the association between alcohol consumption and the risk of ICH was U-shaped, with the lowest risk among light to moderate drinkers and heavy consumers showing the highest risk. The association between alcohol consumption and the risk of CI was J-shaped, with the lowest risk among light drinkers. The log-linear trend test was significant in CI ($P=0.002$), yet the only statistically significant difference in the adjusted relative risks of stroke subtypes was in CI between nondrinkers and heavy drinkers. Repeating the analyses in quartiles of alcohol use had no material effect on the results, except the risk of ICH became less steep.

Dose-response relationships between alcohol consumption and stroke risk were also examined in drinkers, with men with an alcohol intake of at most half a drink per day as the reference category (Table 3). The relationship was almost linear in SAH and CI, but there was no consistent relationship

TABLE 1. Baseline Characteristics by Alcohol Consumption

Characteristic	Alcohol Consumption			
	None	Light	Moderate	Heavy
n	2931	16 258	6116	1251
Age, y	58.8	57.9	56.6	56.3
Blood pressure, mm Hg				
Systolic	139.6	141.1	144.2	146.6
Diastolic	85.3	86.9	89.7	91.5
Body mass index, kg/m ²	26.0	26.2	26.5	26.5
Serum cholesterol, mmol/L				
Total	6.27	6.25	6.22	6.17
HDL	1.08	1.17	1.28	1.36
Smoking, cigarettes/d	19.6	19.5	22.4	25.6
Previous diseases, %				
Hypertension	14.9	17.7	21.9	24.0
Heart disease	28.1	24.6	23.4	23.0
Diabetes	5.6	3.8	4.1	4.8
Education, %				
Primary school	83.5	79.8	74.0	67.1
Secondary school	11.9	12.8	16.7	20.6
University level	4.6	7.4	9.3	12.3
Leisure-time physical activity, %				
Sedentary	44.4	38.2	45.3	55.0
Active	55.6	61.8	54.7	45.0

Values given are mean and proportions.

in ICH. The log-linear trend test was significant in CI ($P < 0.001$).

In effect-modification analyses, there were no significant or consistent findings that the risk of stroke caused by alcohol consumption would be different for men with SBPs ≥ 160 mm Hg compared with men with lower SBPs or for men with HDL-C ≥ 1.15 mmol/L compared with men with lower HDL-C levels.

In pathway analyses, inclusion of SBP in the regression model diminished the effect of alcohol in all stroke subtypes: in SAH by 7% to 37%, in ICH by 5% to 35%, and in CI by 3% to 19% (the Figure). When HDL-C was added, the effect of alcohol was strengthened in SAH by 6% to 31% and in CI by 3% to 16% but attenuated in ICH by 5% to 31%. When both SBP and HDL-C were included in the model, the net effect of alcohol was practically the same as the effect in the model without them in SAH and CI. The effect of alcohol in ICH was instead diminished by 9% to 55%.

Discussion

The analyses in the present study were based on the hypothesis that each stroke subtype has a distinct dose-response relationship with alcohol consumption, as suggested by Camargo in his review.¹ Furthermore, this study elucidates the mediator role of blood pressure and HDL-C in the effects of alcohol on stroke incidence, as described in coronary heart disease.^{13,14}

Alcohol consumption was self-reported at study baseline. Because we had no information on past drinking habits, we

assumed that the reference group, the nondrinkers, probably included both lifelong abstainers and ex-drinkers. Neither did we have information on the pattern of consumption, eg, binge drinking versus regular drinking, or on the possible changes on alcohol habits during the follow-up. However, in a random sample of about 3700 men who recompleted the dietary questionnaire at some point during the follow-up, alcohol consumption remained unchanged.

The reliability of stroke diagnosis varied from 79% to 90%, depending on stroke subtype, in the ATBC Study.³⁵ Bias caused by possible differential reliability of stroke subtype diagnoses cannot be totally excluded. However, in the sample of diagnoses reviewed for the validation study, the reliability of stroke diagnosis did not depend on the level of alcohol consumption; thus, this kind of bias was not evident.

The nondrinkers more often reported diabetes and heart disease than the drinkers, which may indicate that some of the nondrinkers had stopped drinking because of the diseases. They may, however, have a higher stroke risk than the true lifelong abstainers. This bias might erroneously lead to a conclusion of a J-shaped dose-response relationship, suggesting that light drinking protects from stroke. On the other hand, the risks caused by alcohol consumption were not different among those with compared with those without previous heart disease. Chronic alcoholics with the highest consumption level of alcohol were excluded from the ATBC Study, which probably attenuated the risk of stroke in heavy drinkers.

Other studies concerning alcohol consumption have met similar unavoidable methodological problems.^{11,37} Men tend to underestimate their alcohol consumption, and the underreporting may weaken the true effects of alcohol on stroke risk. Unless the underreporting was not grossly differential, the dose-response patterns by alcohol consumption would reflect reality. However, underreporting is most likely differential,³⁸ especially in that heavy drinkers do not report as nondrinkers but as light or moderate drinkers, which consequently may make the slope of the risk of hemorrhagic stroke more gentle and level off the bottom of the J-shaped curve of the CI risk. It is unlikely that differential reporting of drinking habits differs by stroke subtype. Thus, the specific response curves for each subtype would still differ even if biased by differential reporting. Despite equal average weekly consumption, irregular drinking, including binge drinking, may be more harmful than daily drinking.⁹

The association between alcohol consumption and the risk of SAH was nearly linear; in ICH, U-shaped; and in CI, J-shaped. There was a significant log-linear trend in CI; the trend in SAH was similar but nonsignificant, probably because of lack of power, whereas there was no trend in ICH. Heavy drinking clearly increased the risk of all stroke subtypes, as has been confirmed in many previous studies.²⁻⁹ Light drinking, on the other hand, had no effect on the risk of SAH and decreased the risks of ICH and CI compared with nondrinking. In the literature, light drinking has decreased⁴ or increased^{2,5,6} the risk of SAH; decreased⁴ or increased^{2,7} the risk of ICH; and decreased,^{4,9} increased,⁸ or had no effect^{2,10} on the risk of CI. The true effects of light to moderate drinking still seem to be unsettled, but the beneficial effects,

TABLE 2. Crude Incidence Rates and Adjusted Relative Incidences of Stroke Subtypes by Alcohol Consumption

Stroke Subtype	Alcohol Consumption	n	Crude Incidence per 10 000 Person-Years	Adjusted* Relative Risk (95% CI)	Test for Trend (P)
SAH	None	8	4.8	1.00	0.20
	Light	45	4.8	1.00 (0.47–2.13)	
	Moderate	24	6.8	1.33 (0.59–2.99)	
	Heavy	6	8.4	1.58 (0.54–4.63)	
ICH	None	14	8.4	1.00	0.84
	Light	58	6.2	0.83 (0.46–1.50)	
	Moderate	15	4.2	0.64 (0.31–1.35)	
	Heavy	8	11.2	1.77 (0.73–4.31)	
CI	None	92	55.3	1.00	0.002
	Light	410	43.6	0.91 (0.72–1.14)	
	Moderate	183	51.6	1.17 (0.91–1.51)	
	Heavy	48	67.2	1.54 (1.08–2.19)	
All strokes†	None	121	72.7	1.00	0.002
	Light	541	57.5	0.90 (0.74–1.10)	
	Moderate	234	66.0	1.12 (0.89–1.39)	
	Heavy	64	89.6	1.52 (1.12–2.08)	

*Adjusted for age, body mass index, serum total cholesterol, number of cigarettes smoked daily, history of diabetes, history of heart disease, education, leisure-time physical activity, and supplementation with α -tocopherol or β -carotene.

†Includes unspecified strokes.

if any, are most likely weak. In addition to the methodological problems related to studies on alcohol and stroke subtypes, another problem has been the low power of the studies. In only 3 of 31 studies reviewed by Camargo¹¹ has the total number of stroke cases been >300; the highest number of patients with SAH has been 193⁴ and that for patients with ICH has been 156.⁹

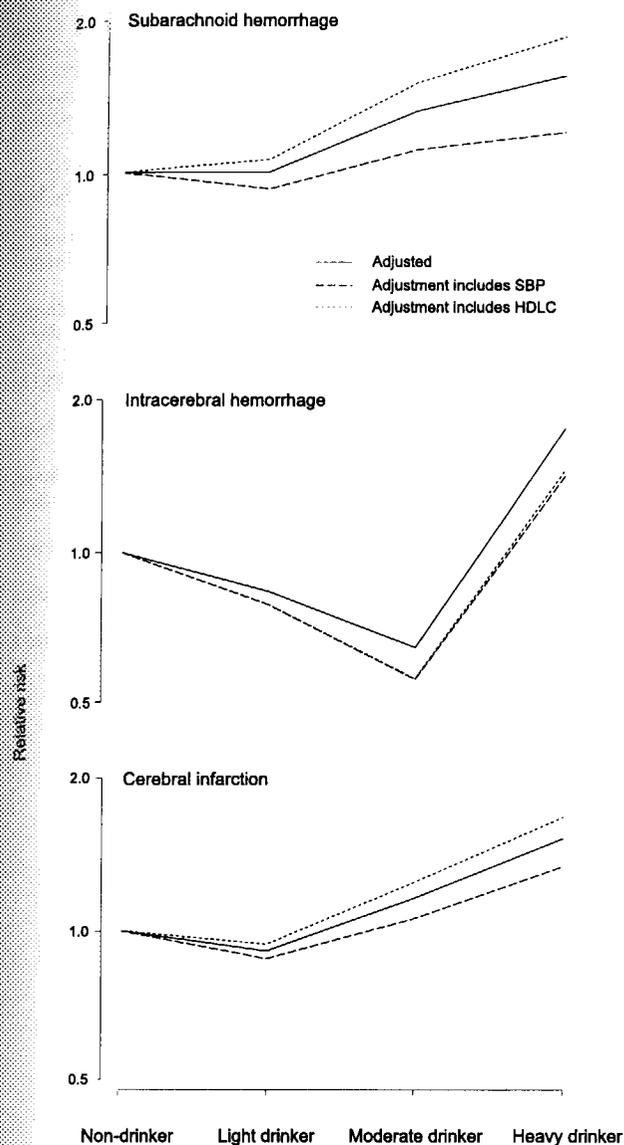
SBP and HDL-C did not seem to modify the effect of alcohol on stroke risk. Instead, in pathway analysis, inclusion of SBP in the regression model consistently decreased the effect of alcohol in all subtypes of stroke, indicating that alcohol increases the risk of stroke by raising SBP. When HDL-C was added to the regression model, the effect of

alcohol was strengthened in SAH and CI, indicating that HDL-C may mediate the beneficial effects of alcohol as in coronary heart disease.^{13,14,39} The effect of alcohol, however, was attenuated in ICH, suggesting that the HDL-C changes caused by alcohol are harmful in ICH, especially as the finding was consistent between the levels of alcohol consumption. One very speculative explanation could be weakening of the endothelium of smaller intracerebral arteries because of low serum total cholesterol levels further aggravated by hypertension, as suggested by Bronner et al.⁴⁰ The fact that SBP and HDL-C affect SAH and CI in opposite directions indicates that there are still other mediators for the effect of alcohol on the risk of stroke.

TABLE 3. Adjusted Relative Incidences of Stroke Subtypes by Alcohol Consumption in Men Reporting Any Alcohol Consumption (Nondrinkers Excluded)

Alcohol Consumption, drinks/d	SAH			ICH		CI	
	Participants	Cases	Adjusted* Relative Risk (95% CI)	Cases	Adjusted* Relative Risk (95% CI)	Cases	Adjusted* Relative Risk (95% CI)
≤1/2	6784	20	1.00	30	1.00	165	1.00
–1	4198	8	0.64 (0.28–1.46)	9	0.53 (0.25–1.11)	112	1.17 (0.92–1.49)
–2	5276	17	1.06 (0.55–2.03)	19	0.91 (0.51–1.63)	133	1.15 (0.91–1.45)
–3	3494	14	1.26 (0.63–2.52)	8	0.61 (0.28–1.33)	100	1.35 (1.05–1.73)
–4	1677	6	1.13 (0.45–2.84)	6	1.01 (0.41–2.46)	54	1.53 (1.12–2.09)
–5	945	4	1.35 (0.45–3.99)	1	0.29 (0.04–2.12)	29	1.44 (0.97–2.15)
>5	1251	6	1.46 (0.57–3.75)	8	1.82 (0.81–4.08)	48	1.86 (1.34–2.59)
Test for trend (P)			0.21		0.67		<0.001

*Adjusted for age, body mass index, serum total cholesterol, number of cigarettes smoked daily, history of diabetes, history of heart disease, education, leisure-time physical activity, and supplementation with α -tocopherol or β -carotene.



Alcohol consumption and risk of stroke. Relative risks were adjusted for age, body mass index, serum total cholesterol, number of cigarettes smoked daily, history of diabetes, history of heart disease, education, leisure-time activity, and supplementation with α -tocopherol or β -carotene. SBP and HDL-C were added separately to multivariate-adjusted Cox proportional-hazards model to examine effect of alcohol on stroke through these factors (logarithmic scale).

This study was done among male smokers only. It is known that smokers have a slightly lower blood pressure⁴¹ and that their serum total cholesterol is increased and HDL-C is reduced⁴² compared with nonsmokers. It is also known that smoking and alcohol consumption are associated with each other, which was seen in this study. Our findings apply only to male smokers; the shapes of the stroke risk curves may be different in women and in nonsmokers. Nevertheless, it is unlikely that the hypothesized mediator roles of SBP and HDL-C were different by sex or smoking status.

In conclusion, light drinking had no effect on the risk of SAH but decreased slightly the risk of ICH and CI. Heavy drinking increased the risk of all subtypes of stroke. Blood pressure and HDL-C seemed to be involved in the develop-

ment of stroke. They did not, however, thoroughly explain the association between alcohol consumption and the risk of stroke; thus, the mechanisms of alcohol in stroke are basically still unexplained.

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