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Apolipoprotein E, alcohol consumption, and risk of ischemic stroke: The Framingham Heart Study revisited

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Abstract

Background and purpose—Data on the association between alcohol consumption and ischemic stroke have been inconsistent. It is not known whether allele E4 of the apolipoprotein E (apoE) gene modifies the alcohol-stroke association. We sought to examine whether E4 allele of the apoE gene influences the association between alcohol consumption and ischemic stroke or high-density lipoprotein (HDL) cholesterol.

Methods—Cohort of 7,676 person-observations of the Framingham Heart Study. Incident stroke was ascertained by standardized methods. We used Cox proportional hazard model to estimate hazard ratios of ischemic stroke.

Results—The average age at baseline was 63 years and 55% of the participants were women. During a mean follow up of 7.4 years, 222 new cases of ischemic stroke occurred (56 embolic and 166 atherothrombotic events). Comparing current drinkers with nondrinkers, multivariable adjusted hazard ratio (95% CI) for ischemic stroke were 0.50 (0.24–1.07) in the absence of E4 allele and 0.70 (0.24–2.05) in the presence of E4 allele (p for interaction 0.64) for subjects aged <65 years. Similarly, we did not observe a statistically significant interaction between E4 allele and alcohol consumption on the risk of stroke among people 65 years and older (p for interaction 0.17). Alcohol consumption was positively associated with HDL cholesterol independent of E4 allele and age.

Conclusions—Our data do not provide evidence for an interaction between E4 allele and alcohol consumption on the risk of ischemic stroke in this population. Furthermore, ApoE polymorphism did no influence the alcohol-HDL relation.

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Keywords

Alcohol drinking; ischemic stroke; apolipoprotein E gene; lipids

Despite a decline in the rate of stroke in the US(1;2), cerebrovascular disease remains a major public health issue and is associated with major direct and indirect costs(3;4). Epidemiologic data on the association between alcohol consumption and ischemic stroke remain inconsistent (5–7). Beneficial effects of moderate drinking on cardiovascular disease are partially mediated through HDL-cholesterol(8–10), inflammation, and fibrinolytic parameters (9;11–13). Cardiovascular disease (CVD) is a complex trait influenced by both environmental factors such as alcohol drinking and genetic factors. Several candidate genes have been shown to play a role on the development of CVD. For example, the E4 allele of the apolipoprotein gene has been inconsistently associated with coronary heart disease(14;15), stroke(16–18), and Alzheimer disease(19–21). In a cross-sectional study, the E4 allele of the apoE gene was shown to modify the relation between alcohol consumption and HDL(22). Specifically, alcohol consumption was associated with elevated HDL in subjects without the E4 allele but not in those with at least one E4 allele(22). This suggests that possible beneficial effects of moderate drinking on ischemic stroke may be limited to subjects without the E4 allele. Since this hypothesis has not been tested in a population setting, we sought to re-examine the alcohol-stroke relation in the Framingham Heart Study in order to determine whether the E4 allele modifies the association between moderate drinking and ischemic stroke previously observed among subjects aged 64 y or less(5). In addition, we assessed whether the E4 allele influences the relation between alcohol and HDL. Because we have previously reported a lack of association between alcohol consumption and ischemic stroke in subjects 65+ years⁵, our a priori hypothesis was to assess the interaction between alcohol and apoE polymorphism in subjects younger than 65 years. Nevertheless, in a secondary analysis, we examined such relation among older subjects (65+ y).

Materials and methods

The Framingham Study is a population-based prospective cohort study started in 1948 in Framingham, Massachusetts. The original cohort included 5,209 participants, aged 28 to 62 at the first examination. Survivors have been examined every two years since then. In 1971, children of the original cohort and their spouses were invited to participate in a prospective study, referred to as the Framingham Offspring Study. Since 1971, participants in the offspring cohort were reexamined eight years after the 1st examination and every 4 years thereafter. During each clinic visit, participants in these two studies undergo a series of tests and examinations. These include a detailed medical history, a physician-administered physical examination, and an assessment of blood parameters, cardiac and lung function. Non-invasive cardiovascular tests and series of laboratory tests are also obtained. Detailed descriptions of the Framingham Study have been published previously(23;24). Informed consent was obtained from study participants and the study protocol was approved by the Institutional Review Board of Boston Medical Center. In the present study we pooled observation periods of participants free of prevalent stroke who attended one of the four baseline examinations, the 4th or 6th offspring cohort or the 19th or 23rd original cohort examination. Participants thus contributed one or two observation units and were followed from the baseline examination for up to 8 years or until the start of the next baseline examination.

Assessment of alcohol consumption

Information on alcohol consumption in the Framingham Heart Study has been collected repeatedly using standardized questionnaires. Detailed description of alcohol assessment in this cohort has been published(25;26). Briefly, data on alcohol have been collected at

examinations 2, 7, 9, 12–15, and 17 and all subsequent examinations of the original cohort and all cycles of the offspring cohort. At each of these examinations, each participant was asked if he/she has consumed alcohol in the past 12 months. If yes, the average weekly number of drinks consumed over the past year for spirits, beer, and wine was recorded. For this study, a drink was defined as 360 ml of beer containing 12.6 g of alcohol, 120 ml of wine containing 13.2 g of alcohol, or 37.5 ml of 80 proof spirits (about 40% ethanol by volume) containing 15 g of alcohol. At each examination, total alcohol was computed as the sum of ethanol contents in beer, wine, and spirits consumed.

Outcome

Stroke events were detected by review of interim Framingham Heart Study examinations, daily surveillance of all admissions to the local hospital, and scrutiny of outside hospital records. For all potential cases of stroke, a panel of three investigators (including a neurologist) reviewed all medical records, radiographic images, a medical history, and findings from physical examination performed at the Framingham Study in order to determine whether a stroke has occurred. In addition, since 1968, whenever possible, the Framingham Study neurologists have examined subjects in the hospital at the time of acute stroke. A detailed description of the stroke assessment in the Framingham Study has been published previously (27). Since the number of non-ischemic stroke (n=22) was limited, the current study was limited to ischemic stroke.

Laboratory Assays

ApoE genotypes were determined by polymerase chain reaction amplification as previously described(28). High-density lipoprotein cholesterol (HDL) level was measured after precipitation of plasma with a combination of heparin-manganese(29;30) during the 20th and 23rd examinations in the original cohort and during the 4th and 6th examination in the offspring cohort.

Other Variables

Information on cigarette smoking was obtained through a standardized questionnaire. Resting blood pressure was measured twice by a physician according to a standard protocol, using a mercury sphygmomanometer and appropriately sized cuff. Subjects were asked about antihypertensive medications during each examination. Diabetes mellitus was defined as a history of physician-diagnosed diabetes mellitus or current treatment for diabetes mellitus (insulin and oral agents). Prevalent cardiovascular disease was ascertained by standard protocols described previously. Body mass index was computed as weight in kilograms divided by the square of height in meters.

Statistical Analysis

For interaction analysis, both apoE polymorphism and alcohol consumption were dichotomized to retain sufficient number of cases per category of cross-classification between drinking (yes/no) and E4 allele status (E4 allele present or absent). We used Cox proportional hazard model to estimate relative risks of ischemic stroke comparing drinkers to non-drinkers stratified by E4 allele status. We formally tested for interaction by including main effects along with product term (alcohol $\times$ apoE) in the multivariable regression model. Adjustment was made for age, gender, systolic blood pressure, use of hypertension medications, smoking, and prevalence of diabetes, and cardiovascular disease. Additional control for atrial fibrillation had a negligible effect on the results (data not shown). We repeated these analyses for subjects aged 65+ years. In sensitivity analysis, we repeated the primary analysis after exclusion of subjects consuming more than 2 drinks per day (total alcohol >24 g/d, n=1,071 person-observations).

To examine whether the E4 allele modifies the relation between alcohol and HDL, we used analysis of covariance that included a product term (alcohol $\times$ apoE). We used the natural logarithm to normalize HDL distribution. Adjustment was made for age, gender, and smoking. All analyses were performed using SAS 9.1 and the significance level was set at 0.05.

Results

Among the 7,676 person-observations, the average age at baseline was 63 years (range 45 to 85 years), and 55% were female. As expected, E3 allele has the highest frequency (80.4%), by E4 (12.0%), and E2 (7.6%). Table 1 presents the baseline characteristics of the study participants, according to age. During the 56,723 person-years of follow up, 222 new cases of ischemic stroke occurred. There were 56 cases of embolic stroke, 51 cases of lacunar atherothrombotic stroke, and 115 cases of non-lacunar atherothrombotic stroke. In subjects younger than 65 years, alcohol consumption was associated with a 50% and 30% lower risk of ischemic stroke (though non-statistically significant) in a multivariable adjusted model in the absence and presence of the E4 allele of apoE gene, respectively (Table 2, p for interaction between alcohol and apoE = 0.64). For subjects aged ≥ 65 years, alcohol consumption was associated with a non-significant lower risk of ischemic stroke in the absence of the E4 allele and with a non-significant increased risk of stroke in people ≥ 65 years in the multivariable model (Table 2, p for interaction between alcohol and the E4 allele 0.17). Exclusion of heavy drinkers (daily alcohol above 24 g) did not alter these findings (data not shown). We observed a positive linear relation between total alcohol and HDL-cholesterol ($p < 0.001$ for all groups). Such relation was independent of age (p for interaction between age and alcohol = 0.48) and apoE polymorphism (p for interaction between apoE and alcohol = 0.36).

Discussion

In this prospective study of men and women, we found that the association between alcohol consumption and ischemic stroke was not modified by apoE polymorphism in individuals aged < 65 years and those who were ≥ 65 years. In addition, there was no evidence for an influence of the E4 allele on the relation between alcohol consumption and HDL-cholesterol in this population.

To the best of our knowledge, no previous study has prospectively evaluated the influence of apoE polymorphism on the alcohol-stroke association. Our findings of a lack of interaction between E4 allele and alcohol consumption on the risk of ischemic stroke merits considerations. We acknowledge the limited number of events in our stratified analysis of the older group (≥ 65 years). Despite the fact that we observed a suggestive increased risk of stroke with alcohol drinking in the presence of the E4 allele in subjects 65 years and older, the confidence interval of the hazard ratio is wide and include values below 1. This suggests that in older people (≥ 65 years) with the E4 allele, a lower risk of ischemic stroke among drinkers is also compatible with these data. Since we had genotype data only on a sample of participants who survived until the time of blood collection, we can not exclude survival bias as a possible explanation of our findings among older participants. It is possible that survivors had genetic traits and/or lifestyle factors that rendered them more susceptible to potential negative influence of the E4 allele, thus minimizing any beneficial effect of alcohol on ischemic stroke in this group. A differential alcohol effect on HDL cholesterol in people with and those without the E4 allele would lend support to such theory. However, our data showed similar positive relation between alcohol and HDL in subjects with and those without the E4 allele and irrespective of age.

Beneficial effects of alcohol on atherosclerotic disease can also be mediated through inflammation(11), hemostatic factors(13), adiponectin(31), and insulin sensitivity(32–35). Unfortunately, we did not collect data on these biomarkers to further explore such biologic

mechanisms according to age. Other limitations of our study include possible reporting bias associated with self-reported alcohol consumption. Since stroke cases occurred after alcohol assessment, such reporting bias is more likely to be non-differential and attenuate the hazard ratios. The generalizability of these data is limited as the majority of participants were Caucasians. Furthermore, most individuals in this study consumed alcohol mainly in light-to-moderate range, thus, precluding the assessment of heavy drinking on the risk of ischemic stroke. Since DNA was not collected at baseline in this cohort, it is possible that attrition mainly due to death might have altered the study population. Such alteration could lead to biased estimate if for example subjects with E4 allele were more likely to die than those without E4 allele. We have a relatively low statistical power in this study to detect smaller effects; in particular, we have very limited number of stroke subtypes for separate analyses. Lastly, since our findings are derived from an observational study design, we can not exclude chance, residual or unmeasured confounding as an explanation for our results. On the other hand, the standardized method for outcome adjudication in the Framingham Heart Study, the longer follow-up period, and the robustness of the findings in sensitivity analyses are major strengths of this paper.

In conclusion, the current study does not provide evidence for an interaction between E4 allele and alcohol consumption on the risk of stroke. In addition, these data do not lend support to a possible interaction between apoE and alcohol on blood levels of HDL.

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Table 1

Baseline characteristics

Characteristics	Total population N = 7,676 [†]	Age		Apo E	
		< 65 years N = 4,445	≥ 65 years N = 3,231	ε ₄ allele absent N = 5957	ε ₄ allele present N = 1719
					p-value
Age (year)	62.6±10.4	55.0±5.6	73.0±5.1	62.7±10.4	0.011
Alcohol intake (g/d)	10.1±16.4	10.8±16.8	9.0±15.7	9.9±16.5	0.086
Systolic BP (mm Hg)	132.9±19.7	127.2±17.5	140.7±20.0	133.1±19.9	0.079
HDL-cholesterol (mg/dl)	50.2±16.0	50.5±15.9	49.6±16.1	50.5±16.0	0.002
Total cholesterol(mg/dl)	209.7±39.6	208.9±39.8	211.0±39.4	208.5±40.0	<0.001
Body Mass Index	27.4±4.9	27.6±5.1	27.2±4.6	27.5±4.8	0.035
Current smoking (%)	16.4	20.9	10.1	16.7	0.13
Diabetes mellitus (%)	9.0	6.6	12.4	8.9	0.49
Cardiovascular disease (%)	13.4	7.4	21.7	13.2	0.32
Atrial fibrillation (%)	3.5	1.4	6.4	3.5	0.91
Treated hypertension (%)	30.4	20.8	43.6	30.5	0.75

* Data are presented as means ± standard deviation or percentage.

[†] Person-observations, since individuals could contribute more than once.

Table 2
Risk and Hazard ratio of ischemic stroke according to age, ϵ_4 allele, and alcohol intake in the Framingham Heart Study

Alcohol use	ϵ_4 allele absent				ϵ_4 allele present			
	Cases	Incidence*	HR (95% CI) Model 1 [†]	HR (95% CI) Model 2 [‡]	Cases	Incidence*	HR (95% CI) Model 1 [†]	HR (95% CI) Model 2 [‡]
All								
None	87	50.9	1.0	1.0	19	42.0	1.0	1.0
Any	80	29.6	0.72 (0.53–0.98)	0.79 (0.57–1.08)	36	44.7	1.24 (0.70–2.20)	1.11 (0.62–1.97)
< 65 years								
None	15	16.9	1.0	1.0	6	24.2	1.0	1.0
Any	14	8.1	0.40 (0.19–0.83)	0.50 (0.24–1.07)	9	16.6	0.62 (0.22–1.76)	0.70 (0.24–2.05)
≥ 65 years								
None	72	87.9	1.0	1.0	13	63.8	1.0	1.0
Any	66	67.1	0.81 (0.58–1.14)	0.88 (0.62–1.25)	27	103.1	1.63 (0.83–3.21)	1.40 (0.71–2.77)

* Crude incidence rate per 10,000 person-years. HR (95% CI): Hazard ratio (95% confidence interval)

[†] Adjusted for age and sex

[‡] Adjusted for age, sex, systolic blood pressure and treatment for hypertension, cigarette smoking, and history of diabetes mellitus, and cardiovascular disease.