Apolipoprotein E, Alcohol Consumption, and Risk of Ischemic Stroke: The Framingham Heart Study Revisited

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Background: Data on the association between alcohol consumption and ischemic stroke have been inconsistent. It is not known whether allele ϵ_4 of the apolipoprotein E (apoE) gene modifies the alcohol-stroke association. We sought to examine whether ϵ_4 allele of the apoE gene influences the association between alcohol consumption and ischemic stroke or high-density lipoprotein (HDL) cholesterol. *Methods:* We examined a cohort of 7676 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% confidence interval) for ischemic stroke was 0.50 (0.24-1.07) in the absence of ϵ_4 allele and 0.70 (0.24-2.05) in the presence of ϵ_4 allele (P for interaction = .64) for those younger than 65 years. Similarly, we did not observe a statistically significant interaction between ϵ_4 allele and alcohol consumption on the risk of stroke among people aged 65 years and older (P for interaction = .17). Alcohol consumption was positively associated with HDL cholesterol independent of ϵ_4 allele and age. *Conclusions:* Our data do not provide evidence for an interaction between ϵ_4 allele and alcohol consumption on the risk of ischemic stroke in this population. Furthermore, apoE polymorphism did not influence the alcohol-HDL relation. **Key Words:** Alcohol drinking—ischemic stroke—apolipoprotein E gene—lipids.

Despite a decline in the rate of stroke in the United States,[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 (CVD) are partially mediated through high-density lipoprotein (HDL) cholesterol,[8-10] inflammation, and fibrinolytic parameters.[9,11-13] CVD is a complex trait influenced by both environmental factors,

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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 ϵ_4 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 ϵ_4 allele of the apolipoprotein E (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 ϵ_4 allele but not in those with at least one ϵ_4 allele.[22] This suggests that possible beneficial effects of moderate drinking on ischemic stroke may be limited to people without the ϵ_4 allele. Because this hypothesis has not been tested in a population setting, we sought to re-examine the alcohol-stroke relation in the Framingham Heart Study to determine whether the ϵ_4 allele modifies the association between moderate drinking and ischemic stroke previously observed among those aged 64 years or younger.[5] In addition, we assessed whether the ϵ_4 allele influences the relation between alcohol and HDL. Because we have previously reported a lack of association between alcohol consumption and ischemic stroke in patients aged 65 years or older,[5] our a priori hypothesis was to assess the interaction between alcohol and apoE polymorphism in those younger than 65 years. Nevertheless, in a secondary analysis, we examined such relation among older people (age $\geq$ 65 years).

Materials and Methods

The Framingham Study is a population-based prospective cohort study started in 1948 in Framingham, Mass. The original cohort included 5209 participants, aged 28 to 62 years at the first examination. Survivors have been examined every 2 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 re-examined 8 years after the first 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 function, and lung function. Noninvasive cardiovascular tests and a series of laboratory tests are also performed. 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 current study we pooled observation periods of participants free of prevalent stroke who attended one of the 4 baseline examinations, the fourth or sixth offspring cohort, or the 19th or 23rd original cohort examination. Participants thus contributed one or two observation units and were followed up 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 to 15, and 17; all subsequent examinations of the original cohort; and all cycles of the offspring cohort. At each of these examinations, each participant was asked whether alcohol was consumed in the past 12 months. If yes, the average weekly number of drinks consumed during 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 3 investigators (including a neurologist) reviewed all medical records, radiographic images, a medical history, and findings from physical examination performed at the Framingham Study to determine whether a stroke occurred. In addition, since 1968, whenever possible, the Framingham Study neurologists have examined patients 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] Because the number of nonischemic strokes (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] HDL cholesterol 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 fourth and sixth 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