Alcohol Consumption and Carotid Atherosclerosis in Older Adults
The Cardiovascular Health Study

Objective—The association of alcohol use with atherosclerosis is inconsistent in previous studies.

Methods and Results—For the Cardiovascular Health Study, 5888 adults aged 65 years and older underwent a standardized interview and examination. They reported beer, wine, and liquor use individually and underwent B-mode ultrasonography to determine internal and common carotid intima-media thickness (IMT). We compared composite carotid IMT values cross-sectionally using linear regression to adjust for demographic and clinical characteristics. Among 4247 participants free of cardiovascular disease, consumers of 1 to 6 drinks per week had 0.07±0.04-mm lower composite IMT and consumers of 14 or more drinks per week had 0.07±0.05-mm higher IMT than abstainers (P quadratic trend=0.02). We found similar relationships using internal and common carotid thickness measures and among men and women. The higher IMT associated with heavier alcohol use was particularly strong among 1592 participants with confirmed cardiovascular disease (0.24±0.09 mm greater than abstainers). Controlling for HDL cholesterol levels reduced the effect on composite IMT among consumers of 1 to 6 drinks per week by 22%.

Conclusions—Relative to older adults who abstain from alcohol, consumption of 1 to 6 drinks per week had an inverse association with carotid atherosclerosis whereas consumption of 14 or more drinks had a positive association. (Arterioscler Thromb Vasc Biol. 2003;23:2252-2259.)

Key Words: alcohol consumption ■ carotid artery ■ atherosclerosis ■ intima-media thickness ■ epidemiology

Substantial epidemiological evidence links moderate alcohol consumption to a lower risk of cardiovascular disease.1 Moderate alcohol consumption is also specifically associated with lower cardiovascular mortality among elderly adults.2,3

The mechanisms that mediate the inverse association of moderate drinking and cardiovascular disease remain uncertain. Alcohol consumption raises HDL cholesterol levels in a dose-dependent manner and lowers fibrinogen levels in experimental studies4 and has been associated with lower levels of inflammatory markers.5 However, few studies have directly assessed the association of alcohol consumption with atherosclerosis.

The few studies that have assessed alcohol consumption and atherosclerosis have yielded inconsistent findings. A cross-sectional analysis of the Atherosclerosis Risk in Communities (ARIC) study showed no association between alcohol consumption and carotid atherosclerosis.6 Cross-sectional and longitudinal analyses of the Bruneck Study showed J-shaped relationships of alcohol consumption and carotid atherosclerosis,7,8 with the lowest levels among moderate drinkers and the highest levels among the heaviest drinkers. The Kuopio Ischemic Heart Disease Risk Factor Study reported that binge-drinking men, who tended to consume the most alcohol, had the greatest progression of carotid atherosclerosis over 4 years of follow-up.9 None of these studies specifically studied elderly individuals, who are at the greatest risk for cardiovascular disease.

To address the relationship of alcohol consumption and carotid atherosclerosis in older adults, we assessed the cross-sectional association between alcohol consumption and carotid intima-media thickness (IMT) in the Cardiovascular Health Study (CHS), a population-based cohort study.10 Given established differences in the effect of alcohol on cardiovascular risk factors and risk of dementia according to sex and apolipoprotein (apo) E genotype,11,12 we also sought to explore whether these factors modified the relationship of alcohol use and carotid atherosclerosis.
Methods

Study Population and Design
The CHS is a prospective, longitudinal study of 5888 men and women aged 65 years or older who were recruited from a random sample of Medicare eligibility lists in the following 4 communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania. Participants were not institutionalized or wheelchair-dependent in the house, did not require a proxy for consent, were not under treatment for cancer at the time of enrollment, and were expected to remain in their respective regions for at least 3 years. In 1989 and 1990, 5201 consenting participants were recruited and examined (the original cohort); in 1992 and 1993, an additional 687 black participants were recruited and examined (the new cohort). We excluded participants with missing information on alcohol use (n=23) or baseline ultrasonographic measures (n=26), leaving 5839 participants eligible for analysis. The institutional review board at each participating center approved the study, and each participant gave informed consent.

The CHS study design and objectives have been published previously.10 The baseline examination included standardized medical history questionnaires, physical examination, resting electrocardiography, spirometry, carotid ultrasonography, echocardiography, and laboratory examination.

Alcohol Consumption
At the baseline visit, participants individually reported their usual consumption of 12-ounce cans or bottles of beer, 6-ounce glasses of wine, and shots of liquor. These values were summed to determine total alcohol consumption. Participants also additionally answered 2 related questions, whether they changed their pattern of consumption during the last 5 years and whether they ever regularly consumed 5 or more drinks daily. Participants who reported present abstention but responded yes to either or both of these questions were classified as former drinkers.

We categorized participants into categories according to weekly ethanol consumption, as follows: none, former, <1 drink weekly, 1 to 6 drinks weekly, 7 to 13 drinks weekly, and 14+ drinks weekly. We used abstainers without former use as the reference category.

Determination of Carotid Atherosclerosis
A total of 5839 participants with information available on alcohol use completed baseline carotid ultrasonography. In brief, participants underwent high-resolution B-mode ultrasonography, as described.13 Trained technicians acquired 1 longitudinal image of the common carotid artery and 3 images of the internal carotid artery. Readers at a central reading center, who were blinded to all clinical information, reported several measures of IMT. Images from the original and new cohorts were interpreted at the same time using stored digital images.

We summarized these measures, as in previous CHS analyses, in 3 variables. We derived maximal IMT of the common and internal carotid arteries as the mean of the maximal IMT of the near and far wall on the left and right sides. We created a composite variable by averaging the maximal thickness scores for the common and internal carotid arteries after standardization. Because the composite variable is more closely associated with cardiovascular risk factors and cardiovascular disease than either common or internal carotid IMT alone,14,15 we used it as the primary outcome measure in all analyses.

Other Covariates
As in previous CHS analyses,16 we categorized participants into those with (n=1592) and without (n=4247) baseline clinical cardiovascular disease. Clinical cardiovascular disease included a confirmed history of coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, atrial fibrillation, or pacemaker placement. We defined diabetes as fasting blood glucose ≥126 mg/dL or the use of antidiabetic medication. We defined hypertension as an average seated blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or a combination of self-reported hypertension and use of antihypertensive medication. We dichotomized educational attainment (completion of high school or less versus at least some vocational school or college), income (<$16,000 versus ≥$16,000 per year), and marital status (married versus widowed, divorced, separated, or never married). We assessed leisure-time physical activity as a weighted sum of kilocalories expended in specific physical activities.17 ApoE genotype testing was performed as previously described.18 Of the 5865 CHS participants with information available on alcohol use, 275 declined consent for genetic testing for cardiovascular diseases and 378 were not genotyped, leaving 5212 eligible participants for analyses incorporating apoE genotypes.

Statistical Methods
We used SAS (Release 8.01; SAS Institute) for all analyses. We tested univariate associations of continuous variables with ANOVA and binary variables with χ² tests. We used linear regression to adjust for factors that could confound the relationship between alcohol consumption and carotid IMT. These factors were age, race, sex, educational attainment, income, marital status, present smoking, former smoking, diabetes, body mass index, kilocalories expended in daily activities, and use of hormone replacement therapy in women. To confirm the robustness of our analyses, we repeated adjusted analyses with logistic regression, dichotomizing carotid IMT at the 75th percentile.

Because HDL cholesterol and hypertension may be plausible mediators of effects of alcohol consumption, we entered them in sensitivity analyses. We excluded participants with confirmed cardiovascular disease from primary analyses and included them in sensitivity analyses. To explore possible effect modification, we repeated adjusted analyses in men and women and among participants with and without apoE4 alleles. In beverage type analyses, we grouped consumption of beer, wine, and liquor into 4 categories each (none, <1, 1 to 6, and 7+ drinks per week) and assessed IMT in each category, controlling for consumption of other beverages.19 We tested for linear trend by treating the categories of alcohol consumption as a continuous variable, excluding former drinkers. As previously described,12 tests for trend using actual alcohol intake as a continuous variable (following log transformation to minimize skewness) yielded very similar results that are not shown here. For tests of quadratic trend, we squared the linear trend variable after centering it on median consumption.

Results
Table 1 shows the sociodemographic and clinical characteristics of the 4247 eligible CHS participants free of confirmed cardiovascular disease according to usual baseline alcohol consumption. Consistent with previous reports,20 heavier alcohol consumption was more common among participants who were male, white, married, current or former smokers, and more physically active. The unadjusted prevalence of hypertension was lowest among light-to-moderate drinkers and highest among the heaviest drinkers.

Alcohol Consumption and Baseline Carotid IMT
Table 2 demonstrates the cross-sectional association of alcohol consumption with baseline carotid IMT among participants free of confirmed cardiovascular disease. For the composite variable and both of its components, the relationships were J-shaped, with the lowest IMT values among consumers of 1 to 6 drinks per week and the highest among heavier drinkers. For example, composite IMT was 0.07±0.04 mm lower among consumers of 1 to 6 drinks per week than it was among abstainers. The shape of these relationships was similar before and after adjustment for...
potential confounders. As expected, former drinkers had higher average IMT levels than abstainers that were markedly attenuated by adjustment for diabetes and hypertension. Consumers of \(<1\) drink per week had IMT levels nearly identical to abstainers.

### Sensitivity Analyses

In models that additionally controlled for HDL (Table 2), the inverse association of moderate drinking per week and carotid IMT was consistently attenuated. For example, addition of HDL attenuated the estimated effect of moderate drinking on the composite IMT variable by \(\approx 22\%\). Controlling for HDL level also tended to increase the higher IMT levels associated with heavier drinking, consistent with the hypothesis that heavier drinking has direct atherogenic effects that are partially offset by higher HDL levels among heavier drinkers.

Controlling for hypertension had different effects in different drinking categories (Table 2), as expected from the differences in prevalence of hypertension across drinking categories seen in Table 1. In general, adjustment for hypertension attenuated the difference in carotid IMT values between drinking groups and abstainers, both at intermediate and heavier levels of consumption. This observation is consistent with the hypothesis that differences in the prevalence of hypertension associated with drinking, whether inverse for intermediate use or positive for heavier use, may partly mediate the relationship of alcohol use and carotid atherosclerosis.

To determine whether our results were robust, we repeated our analyses using logistic regression (Figure). In these analyses, the outcome variable was a carotid IMT level above the 75th percentile. We found similar relationships in these analyses, with generally J-shaped cross-sectional associations between alcohol consumption and carotid IMT.

In stratified analyses of participants without cardiovascular disease (Table 3), we did not find consistent differences in the association of alcohol consumption with carotid IMT according to sex, although the lowest IMT was found among consumers of 1 to 6 drinks per week among men and 7 to 13 drinks per week among women. ApoE genotype seemed to modify the association of alcohol use with carotid atherosclerosis. Among 2831 apoE4-negative participants, we found a J-shaped relationship, with the lowest composite IMT levels among consumers of 1 to 6 drinks per week (\(P\) for quadratic trend, ANOVA).
0.04). Among 954 participants with an apoE4 allele, we found a generally positive trend between alcohol use and carotid IMT, with higher IMT levels even among consumers of 1 to 6 drinks per week.

Table 4 shows the results of analyses of individual beverage types. For beer and wine, consumption of 1 to 6 drinks per week was associated with the lowest composite carotid IMT values; results for common and internal carotid IMT values were similar. In contrast, liquor consumption had a stepwise positive association with composite IMT, with particularly higher values among consumers of 7 to 13 (0.11±0.07 mm difference relative to abstainers) and 14 or more (0.18±0.06 mm difference) drinks of liquor per week. The associations of wine and liquor consumption with IMT levels were modified by apoE genotype in a manner similar to that seen for overall alcohol consumption.

Table 3 shows the cross-sectional association of alcohol use and carotid IMT among participants with confirmed clinical cardiovascular disease. Among these individuals, carotid IMT was lowest among consumers of 7 to 13 drinks per week but markedly higher among consumers of 14 or more drinks per week (0.24±0.09-mm difference relative to abstainers).

**Discussion**

In a cross-sectional analysis of a population-based study of older adults free of established cardiovascular disease, we found that consumption of 1 to 6 drinks per week was associated with less carotid atherosclerosis and consumption of 14 or more drinks was associated with greater atherosclerosis. This finding was present in men and women and in both common and internal carotid arteries. HDL and hypertension both seemed to mediate the effects of alcohol intake to some degree.
Our results are consistent with studies from Bruneck and Kuopio, where carotid IMT seemed to be highest among subgroups of CHS Participants, According to usual Baseline Alcohol Consumption.

<table>
<thead>
<tr>
<th>Subgroups of CHS Participants</th>
<th>No CVD</th>
<th>Confirmed CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Former</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite†</td>
<td>466</td>
<td>194</td>
</tr>
<tr>
<td>Internal†</td>
<td>1279</td>
<td>149</td>
</tr>
<tr>
<td>Common†</td>
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<tr>
<td>Women</td>
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<tr>
<td>Composite</td>
<td>2256</td>
<td>1148</td>
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<tr>
<td>Internal</td>
<td></td>
<td></td>
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<tr>
<td>Common</td>
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<tr>
<td>ApoE4-negative, n</td>
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<td>215</td>
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<tr>
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<tr>
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<tr>
<td>ApoE4-positive, n</td>
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<tr>
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<td>398</td>
<td>84</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed CVD, n</td>
<td>661</td>
<td>194</td>
</tr>
</tbody>
</table>

*p values are from analyses that model alcohol categories as linear/quadratic terms, respectively.
†Analyses adjusted for age, sex, race, current smoking, former smoking, marital status, education, income, diabetes, body mass index, leisure-time physical activity, and hormone replacement therapy.

The few other studies that have assessed alcohol intake and carotid atherosclerosis have come to conflicting conclusions. Our results are consistent with studies from Bruneck and Kuopio,7–9 where carotid IMT seemed to be highest among the heaviest drinkers. We also confirmed the inverse cross-sectional association of moderate drinking and carotid IMT documented in the Bruneck Study,7 a finding that was not observed in the ARIC study.6 Investigators from the National...
Heart, Lung, and Blood Institute (NHLBI) Family Heart Study\textsuperscript{21} found no significant trend between alcohol intake and prevalence of carotid artery lesions, with odds ratios of 0.8 (95\% CI, 0.5 to 1.5) and 1.1 (95\% CI, 0.4 to 2.8) among consumers of 1 to 12 g and >24 g of alcohol per day, respectively.

We found an apparent interaction of alcohol use with apoE4 status on carotid atherosclerosis, at least for moderate drinking. In this study, apoE4-positive moderate drinkers had higher average internal carotid IMT values than abstainers but apoE4-negative participants did not. Other studies also suggest that moderate drinking may have adverse effects on apoE4-positive adults. For example, the Epidemiology of Vascular Aging study reported that moderate alcohol intake was inversely associated with cognitive deterioration in subjects without an apoE4 allele but positively associated with cognitive deterioration among apoE4 carriers,\textsuperscript{22} a finding that parallels results on alcohol use and dementia from CHS.\textsuperscript{12} Alcohol use also interacts with apoE genotype in its effects on blood pressure and LDL level.\textsuperscript{11,23,24} The NHLBI Family Heart Study did not find a statistically significant interaction of alcohol use with apoE genotype on carotid atherosclerosis but was limited to 544 subjects and wide confidence intervals, and their findings generally went in the same direction as in our study.\textsuperscript{21}

Although not studied here, variation in genes associated with alcohol metabolism, HDL metabolism, and inflammation may also modify the apparent vascular effects of alcohol intake. In the Physicians’ Health Study,\textsuperscript{25} moderately drinking men homozygous for the $\gamma$-1 allele in alcohol dehydrogenase 1C (associated with faster oxidation of alcohols) had an odds ratio for myocardial infarction of 0.62 compared with nondrinking men with the same genotype. In contrast, moderate drinkers homozygous for the $\gamma$-2 allele had an odds ratio of 0.14. The ECTIM (Etude Cas-Temoins de l’Infarctus du Myocarde) Study Group found that homozygotes for the AA genotype of the cholesteryl ester transfer protein $\beta$-4 polymorphism had a stronger association of alcohol intake with HDL levels and, at least among heavy drinkers, a lower risk of myocardial infarction than carriers of the C allele.\textsuperscript{26} In a recent population-based study of 1000 German adults,\textsuperscript{27} alcohol consumption had a J-shaped relation with carotid IMT levels in the overall cohort. However, consumers of >45 g of alcohol per day who were homozygous for the CC genotype of the interleukin-6–174 polymorphism had much higher levels of interleukin-6, higher common carotid IMT levels, and a greater prevalence of carotid plaque than did other heavy drinkers.

The association of alcohol use and carotid IMT seemed to be mediated in part by both HDL and hypertension. Other studies have suggested that HDL levels mediate the lower risk of coronary heart disease among moderate drinkers to a substantial degree,\textsuperscript{2,28} although some animal models of atherosclerosis suggest that other mechanisms are more important.\textsuperscript{29} The apparent mediating effect of hypertension is consistent with the somewhat stronger association of alcohol use with common carotid IMT than internal carotid IMT in this study, because the former is more strongly related to blood pressure in CHS.\textsuperscript{14} Other cohort studies have found a lower incidence of hypertension among light drinkers,\textsuperscript{30,31} but this finding has not been explored extensively in older populations.

Although we found some differences in carotid IMT according to beverage type, we did not find a particular benefit associated with wine consumption. This result is consistent with 2 meta-analyses that found no difference in the relation of alcohol use to coronary heart disease according to beverage type.\textsuperscript{32,33} Given the results of binge drinking reported from Kuopio,\textsuperscript{9} the positive association of liquor consumption with carotid atherosclerosis could relate to a specific drinking pattern among liquor drinkers, but we could not directly assess this hypothesis in our analyses.

**Study Limitations**

The CHS has both strengths and limitations. CHS participants represent a relatively healthy group of older adults, given the CHS eligibility criteria and selective participation in CHS. Thus, our results are most readily generalized to older adults in similar health. Although we cannot extrapolate our findings to other populations without additional research, we have no inherent reason to believe that our results would differ in other populations.

As with any observational study, unevenly distributed characteristics could lead us to overestimate or underestimate the true effect of alcohol consumption, although the range of covariates available in CHS is substantially more robust than in many other studies. In our analyses, the inverse cross-sectional association of alcohol use with atherosclerosis persisted after adjustment for a variety of sociodemographic and clinical characteristics. Although we cannot exclude the possibility of uncontrolled or residual confounding, any remaining confounder would need to be strongly associated with both alcohol use and carotid atherosclerosis and generally unrelated to the factors included in our models.

We relied on self-reported alcohol consumption assessed by a standardized questionnaire, a technique that has been validated in other settings.\textsuperscript{34} In a review of errors in assessment of alcohol use in the elderly, Herzog\textsuperscript{35} concluded that such errors are no worse in surveys of older adults than in surveys of the general population. Also, the age-, sex-, and race-adjusted correlation of baseline alcohol intake with HDL levels among the 5802 CHS participants with available data were 0.23 ($P<0.001$), virtually identical to the correlation found in other representative studies.\textsuperscript{36} Thus, the actual amount of alcohol consumed by CHS participants may differ somewhat from that reported here, but the rank order of participants according to alcohol use is unlikely to be greatly affected.

We did not have detailed information on drinking patterns in this study. The use of a measure of average alcohol use may obscure differences between regular and episodic alcohol intake, although binge drinking rates decline with age among adults in the United States.\textsuperscript{37}

**Conclusions**

In conclusion, in this study of older adults free of established cardiovascular disease, we found that consumption of 1 to 6 drinks per week was associated with less-prevalent carotid...
atherosclerosis but consumption of 14 or more drinks was associated with greater atherosclerosis. This finding is consistent with previous studies in other populations, but additional prospective data on alcohol use and progression of atherosclerosis are needed. Although results from epidemiological studies like CHS should be extrapolated to clinical care with caution, our results do provide support for American Geriatrics Society guidelines38 that advise older adults who drink alcohol to consume no more than 1 drink per day.

Acknowledgments

CHS is conducted and supported by the NHLBI in collaboration with the Cardiovascular Health Study Investigators. This manuscript has been reviewed by CHS and by NHLBI for scientific content and consistency of data interpretation with previous CHS publications; significant comments were incorporated before submission for publication.

The research reported in this article was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01-HC-15103 from the NHLBI and grant K23-AA-00299 from the National Institute on Alcohol Abuse and Alcoholism. Participating CHS investigators and institutions: Steering Committee: Curt D. Furberg, MD, PhD, Wake Forest University School of Medicine. NHLBI Project Office: Jean Olson, MD, MPH. Johns Hopkins University: John EC Reading Center: Pentti M. Rautaharju, MD, PhD. University of California, Davis: John Gardin, MD. Georgetown Medical Center—ECG Reading Center: Pemti M. Rautaharju, MD, PhD. University of California, Davis; John Robbins, MD, MHS, Johns Hopkins University: Linda P. Fried, MD, MPH. Johns Hopkins University—MRI Reading Center: Nick Bryan, MD, PhD, Norman J. Beauchamp, MD. University of Pittsburgh: Lewis H. Kuller, MD, DrPH. University of California, Irvine—Echocardiography Reading Center (baseline): Julius M. Gardin, MD. Georgetown Medical Center—Echocardiography Reading Center (follow-up): John S. Gottdiener, MD. New England Medical Center, Boston—Ultrasound Reading Center: Daniel H. O’Leary, MD. University of Vermont—Central Blood Analysis Laboratory: Russell P. Tracy, PhD. University of Arizona, Tucson—Pulmonary Reading Center: Paul Enright, MD. Retinal Reading Center—University of Wisconsin: Ronald Klein, MD. University of Washington—Coordinating Center: Richard A. Kronmal, PhD.

References


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Arterioscler Thromb Vasc Biol. 2003;23:2252-2259; originally published online October 16, 2003;
doi: 10.1161/01.ATV.0000101183.58453.39
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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