Alcohol Consumption and Carotid Artery Structure in Older French Adults
The Three-City Study

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Background and Purpose—Several epidemiological studies have suggested a U-shaped association between alcohol consumption and cardiovascular risk. However, the modifications of vascular structure associated with alcohol consumption are largely unknown.

Methods—The study population sample comprised 6216 subjects (3780 women and 2436 men) aged 65 years or older who were recruited from 3 French cities (Bordeaux, Dijon, and Montpellier, which are located in the 3 principal wine-growing regions). Usual alcohol consumption was assessed by a standardized questionnaire. Carotid ultrasound examination included measurements (at sites free of plaques) of intima-media thickness (IMT) at the common carotid arteries (CCA), CCA–lumen diameter, and assessment of atherosclerotic plaques in the extracranial carotid arteries.

Results—Neither CCA–IMT nor carotid plaques were associated with alcohol consumption categories in the overall population. Weak and marginal positive associations were observed between categories of alcohol consumption and carotid plaques in men (P=0.02 for linear trend). CCA–lumen diameter was positively and independently associated with alcohol consumption in overall population and in men and in women. Similar results were found between alcohol consumption and carotid measurements in subjects free of cardiovascular disease (90.1% of the population).

Conclusions—This very large population sample of French older adults shows no marked relationships of alcohol consumption with atherosclerosis. The positive association of alcohol intake with carotid arterial diameter may reflect the ability of alcohol to maintain adaptive enlargement to preserve lumen area. (Stroke. 2004;35:2770-2775.)

Key Words: alcohol ● atherosclerosis ● carotid arteries ● epidemiology

Accumulated results from several prospective studies suggest that moderate alcohol drinkers have a lower risk of mortality, coronary artery disease, and stroke.1,2 This is further supported by the observation that the French population has one of the highest alcohol intakes in the world, whereas cardiovascular mortality rates are lower than in most other developed countries.3

The modifications of vascular structure associated with alcohol consumption remain unclear. Recent technological advances in high-resolution B-mode carotid ultrasonography have enabled us to evaluate directly minimal peripheral arterial wall or structure abnormalities (intima-media thickness [IMT], lumen diameter, and focal atherosclerotic plaques).4–6 The few studies that have directly examined the association between alcohol consumption and arterial structural modifications have yielded inconsistent findings.7–11 However, most of these studies may be limited by the use of carotid IMT as the only marker of vascular alterations and, to our knowledge, only one previous study has focused on the association of alcohol consumption with carotid atherosclerosis in elderly individuals who are at greater risk for cardiovascular disease.11

In this population-based cross-sectional study of 6216 subjects aged 65 years and older, we report the associations of carotid structure assessed by B-mode ultrasound with reported alcohol consumption.

Materials and Methods
The design of the Three-City Study, an ongoing longitudinal study aiming to evaluate the risk of dementia and cognitive impairment attributable to vascular factors, has been reported elsewhere.12 Briefly, between 1999 and 2001, 9294 subjects (3649 men and 5645 women), aged 65 years and older, and noninstitutionalized were recruited from the electoral rolls of 3 French cities, ie, Bordeaux, Dijon, and Montpellier. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre.
and each participant signed an informed consent. The first step of the sampling procedure was to select administrative districts. Eligible inhabitants of the selected districts were then invited to participate in the study. The acceptance rate was 37%.

The practical organization of the different components of the data collection varied slightly between centers. In Bordeaux and Dijon, participants were first examined at home (interview, cognitive testing). They were then invited to the study examination center (a community medical center in Dijon and a mobile center in a specially equipped vehicle in Bordeaux) for completing the other parts of the study protocol; those who refused or were unable to visit the center had a second visit at home. In Montpellier, all subjects were asked to attend a half-day examination at a research clinic established within the regional neurology hospital.

Medical History and Standard Biological Procedures

Data were collected during a face-to-face interview using a standardized questionnaire administered by trained psychologists or nurses. Information about demographic background, occupation, medical history, drug use, and personal habits such as alcohol consumption and cigarette consumption were collected. Blood pressure was measured twice with a digital electronic tensiometer (model M4; Omron) and the average of the 2 measurements was used in the statistical analyses.

Centralized measurements of biological parameters were performed. Hypertension, hypercholesterolemia, and diabetes were defined as previously reported. The presence of cardiovascular disease was defined by self-reported history of hospitalized myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, and/or stroke.

Alcohol Consumption Assessment

Participants reported their usual alcohol consumption per week of wine, beer, and 4 classes of aperitif and distilled alcoholic (liquor), and the amount of alcohol consumed (in grams per day) was calculated by multiplying the consumption of each beverage by its ethanol content, summing all beverages and dividing by 7. We categorized daily ethanol intake in grams into 6 categories: none, former drinkers, 0.1 to 12 (<1 drink), 12.1 to 24 (1 to 2 drinks), 24.1 to 36 (>2 to 3 drinks), and >36 grams or more (>3 drinks). Participants were asked whether they changed their usual pattern of consumption and, if so, whether they have increased or decreased their consumption.

Ultrasoundography

The carotid ultrasound methods use a scanning protocol common to the 3 field centers, and central reading of ultrasound studies according to a standardized protocol. The ultrasound examination of the carotid arteries was only proposed to participants younger than age 85 who were able to come to the examination centers. Because of the cost of the examinations, ultrasound examination also was not proposed to persons included during the last 4 months of the baseline period because of the cost of the examinations, ultrasound examination also was not proposed to persons included during the last 4 months of the baseline period. Overall, 73.7% of the participants younger than age 85 years (n=6631) had carotid ultrasound measures. As expected, compared with subjects who did not undergo ultrasound examinations, subjects who were able to come to examination centers and who underwent ultrasound examinations had lower means of age (73.5±4.9 versus 74.5±5.1 years; P<0.001), body mass index (25.6±4.2 versus 25.9±4.0 kg/m²; P=0.01), systolic blood pressure (145.2±21.1 versus 151.0±23.0 mm Hg; P<0.001), and total cholesterol (5.77±0.97 versus 5.96±1.03 mmol/L; P<0.01). They had slightly higher mean of daily alcohol consumption (12.8±14.7 versus 12.1±14.4 g/d; P=0.053).

Ultrasound examinations that were similar to those applied in the EVA Study were performed by sonographic technicians. The B-mode system (Ultramark 9 High Definition Imaging) with a 5- to 10-MHz sounded was used at each of the 3 centers. All ultrasound images were transferred to a computer system (IoTEC) and digitized into 640X580 peak cells with 256 gray levels. They were stored on CD-ROMs that were sent to the reference center weekly. The IMT was measured at a site free of any discrete plaques along a 10-mm-long segment of the far wall of the CCA and measured as the distance between the lumen–intima interface and the media–adventitia interface using an automated edge detection algorithm. A mean of 6 measurements was automatically performed on each image and on each side. Lumen diameter was defined as the average of the distances between the 2 leading edges of far wall and near wall lumen–intima interfaces along at least 0.5 cm of length using a computerized validated program.

Reproducibility Study

A reproducibility study was conducted. One hundred fourteen subjects underwent 2 ultrasound examinations performed blindly by 2 different sonographers during the same visit. The mean absolute difference and correlation coefficient between repeated examinations of CCA–IMT were, respectively, 0.06 mm and 0.71. For lumen diameter, they were, respectively, 0.16 mm and 0.91. For carotid plaque, the Kappa coefficient for agreement between the 2 examinations was 0.78.

Statistical Analyses

Standard procedures from the Statistical Analysis System (SAS) were used for statistical analyses. Ultrasound parameters used in this report were CCA–IMT, lumen diameter, and carotid plaques. Differences in cardiovascular risk factors and in ultrasound parameters according to alcohol consumption categories were adjusted for gender and tested by analysis of covariance for quantitative variables and by Mantel–Haenszel χ² test for qualitative variables. Multivariate associations between alcohol consumption categories and ultrasound parameters were tested using analysis of covariance and multiple logistic regressions. To test the linear trends of associations between alcohol consumption and ultrasound parameters, the categories of alcohol consumption were treated as a continuous variable, excluding former drinkers. To test the quadratic trend, the linear trend variable was squared. Of the 6631 participants who had ultrasound examinations, 415 were excluded from the statistical analyses because of missing data on alcohol consumption and/or one or more of the ultrasound measurements, giving a final sample of 6216 subjects. There were no statistical significant differences between subjects who were included in the analyses and those who were excluded for the studied cardiovascular risk factors.

Results

Mean levels of alcohol consumption were 12.8 g/d (median 9.6, standard deviation, 14.7 g/d); 86.8% of alcohol consumption was wine, 31.1% beer, and 10.1% liquor. The main clinical characteristics of the study population according to alcohol consumption categories are presented in Table 1. Smoking habits, total cholesterol, and high-density lipoprotein cholesterol were positively associated with alcohol consumption.
Alcohol consumption was not associated with CCA–IMT in sex-adjusted and multivariate-adjusted analyses (Table 2). Adding quadratic terms did not modify these results. When CCA–IMT values were divided into 3 or 4 categories according to sex-specific tertile or quartile values, similar patterns of results were observed confirming the lack of an association between CCA–IMT and alcohol consumption.

CCA–lumen diameter was positively associated with alcohol consumption (Table 2). Multivariate adjustment for potential cardiovascular risk factors (including high-density lipoprotein cholesterol) did not alter these findings (Table 2). When CCA–IMT and/or carotid plaques were added to the multivariate models, the associations of alcohol consumption with CCA–lumen diameter remained significant. In addition, substitution of weight and height for body mass index in the multivariate models did not alter the results (data not shown).

No association between alcohol consumption and carotid plaques was observed. Multivariate analyses confirmed these findings (Table 2).

When analyses were separately performed according to sex, the lack of association between alcohol consumption and CCA–IMT and the positive association between alcohol consumption and CCA–lumen diameter were confirmed in men and in women (Table 3). For carotid plaques, weak positive associations with categories of alcohol consumption were observed in men (Table 3), and the interaction term to test the differential associations of alcohol consumption with plaques according to gender was statistically significant (P=0.02).

This was not the case for CCA–IMT (P=0.23) and CCA–lumen diameter (P=0.34).

When all analyses were limited to subjects without cardiovascular disease (n=5602) or to those with stable alcohol consumption (n=3850), similar results to those observed in the whole population were found (data available from the authors).

### Discussion

In this large-scale study conducted in older adults, we found no significant association of alcohol consumption with common carotid IMT and carotid plaques (in women) and a modest association between alcohol consumption and carotid plaques in men. The magnitude of the latter association may be of little biological importance. Common carotid lumen diameter was positively associated with alcohol consumption independently of major known cardiovascular risk factors.

Few large studies have specifically evaluated the effects of regular alcohol intake on large artery structure and conflicting results have been reported.7–11 In the ARIC Study of 45- to 64-year-old subjects with considerable proportions of non-drinkers (from 29% to 78% according to gender and ethnicity) and drinkers of less than once per week (from 44% to 80% among drinkers), no cross-sectional association between current alcohol consumption and carotid IMT was observed.7 The Bruneck Study, conducted in adults and older subjects (n=919) with very high alcohol consumption (57 g/d in men and 25.9 g/d in women), showed J-shaped cross-sectional and
longitudinal relationships of alcohol consumption with carotid atherosclerosis determined by the presence (incidence) of plaques and stenosis.5,9
To the best of our knowledge, only the Cardiovascular Health Study (CHS) has specifically reported the association of alcohol use with carotid atherosclerosis in the elderly.11 Relative to older subjects who abstain from alcohol, consumption of 1 to 6 drinks per week had an inverse association with carotid IMT, whereas consumption of ≥14 drinks had a positive association. The discrepancy of these results with ours is difficult to explain. Two-fifths of the subjects were nondrinkers, and beer and liquor were the predominant types of alcoholic beverages consumed by the CHS population.11 However, we do not think that types of alcoholic beverages can explain the discrepancy because accumulated findings support the hypothesis that the beverage most widely consumed by a given population is the one most likely to be inversely associated with the risk of myocardial infarction and stroke in that population.1,16 Nevertheless, the inconsistency in the results provided by the different studies may suggest that the effects of alcohol consumption on carotid atherosclerosis, if they exist, are modest.
In our study, common carotid lumen diameter increased with increasing alcohol consumption, independently of classical cardiovascular risk factors. These findings extend those of 2 other population-based studies.4,17 Arterial enlargement

### TABLE 2. Associations of Daily Alcohol Consumption Categories With Common Carotid Intima-Media Thickness (mm), Lumen Diameter (mm), and Prevalence of Carotid Plaques

<table>
<thead>
<tr>
<th>Categories of Daily Alcohol Consumption</th>
<th>None</th>
<th>Former</th>
<th>≤1 Drink</th>
<th>&gt;1–2 Drinks</th>
<th>&gt;2–3 Drinks</th>
<th>&gt;3 Drinks</th>
<th>p*</th>
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<td>CCA-IMT</td>
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<tr>
<td>Multivariate-adjusted†</td>
<td>0.72±0.004</td>
<td>0.73±0.01</td>
<td>0.71±0.02</td>
<td>0.71±0.03</td>
<td>0.73±0.006</td>
<td>0.72±0.005</td>
<td>0.28</td>
<td>0.39</td>
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<td>Multivariate-adjusted‡</td>
<td>0.73±0.005</td>
<td>0.74±0.01</td>
<td>0.73±0.004</td>
<td>0.73±0.005</td>
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<td>Multivariate-adjusted†</td>
<td>6.27±0.02</td>
<td>6.23±0.05</td>
<td>6.27±0.01</td>
<td>6.32±0.02</td>
<td>6.40±0.04</td>
<td>6.46±0.03</td>
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<td>&lt;0.0001</td>
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<td>Multivariate-adjusted‡</td>
<td>6.35±0.03</td>
<td>6.31±0.06</td>
<td>6.37±0.02</td>
<td>6.41±0.03</td>
<td>6.49±0.04</td>
<td>6.54±0.04</td>
<td>&lt;0.0001</td>
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<td>Carotid plaques</td>
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<tr>
<td>Multivariate-adjusted**</td>
<td>47.6</td>
<td>43.1</td>
<td>45.3</td>
<td>45.5</td>
<td>48.4</td>
<td>47.7</td>
<td>0.17</td>
<td>0.54</td>
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<td>OR</td>
<td>(0.54–1.12)</td>
<td>(0.81–1.11)</td>
<td>(0.78–1.14)</td>
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<td>(0.90–1.50)</td>
<td>(0.07</td>
<td>0.08</td>
<td>0.12</td>
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OR indicates odds ratios.
*P for difference was calculated by analysis of covariance using all categories of alcohol consumption; P for linear trend (and quadratic trend) was calculated after excluding former drinkers by analysis of covariance using the categories of alcohol consumption as a continuous variable (and squared the linear trend variable for quadratic trend).†Mean ± standard error of mean.
‡Adjusted for age, sex, center, body mass index, smoking habits, hypertension, diabetes, hypercholesterolemia, HDL cholesterol, and presence of cardiovascular disease.

### TABLE 3. Multivariate* Associations of Daily Alcohol Consumption Categories With Common Carotid Intima-Media Thickness (mm), Lumen Diameter (mm), and Prevalence of Carotid Plaques

<table>
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*Adjusted for age, center, body mass index, smoking habits, hypertension, diabetes, hypercholesterolemia, HDL cholesterol, hormonal replacement therapy (in women), and presence of cardiovascular disease.
†Mean ± standard error of mean.
‡Odds ratios (95% confidence interval).
is considered an adaptive response of the arterial wall to atherosclerosis. Ultrasonographic studies have also suggested that compensatory enlargement of the carotid arteries might occur in response to arterial wall thickening and plaque progression.\textsuperscript{17,18} When we added CCA–IMT and/or carotid plaques in the multivariate analyses, the associations between alcohol consumption and CCA–lumen diameter remained significant, suggesting that the differences in arterial dimensions according to alcohol consumption categories are independent of atherosclerosis.

The mechanisms, which may link alcohol intake to carotid enlargement, are largely unknown. Blood flow and wall shear stress are the major determinants of vascular lumen diameter.\textsuperscript{19,20} Adaptive changes in arterial diameter produced by changes in blood flow or shear stress are in part endothelium-dependent.\textsuperscript{19} Because ethanol and nonalcoholic components of alcoholic beverages have possible favorable effect on endothelium (reducing intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin expression of vascular endothelium, as well as monocyte adhesion),\textsuperscript{22} these adaptive changes in arterial diameter may be preserved with aging in subjects with increasing alcohol intake. Alcohol (particularly red wine) could also enhance nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells, leading to vasoprotective impact.\textsuperscript{23,24} Other possible mechanisms of the vasodilator effects of alcohol may be that ethanol can potentiate contractions mediated by the noradrenergic component of sympathetic nerves that play a role in maintaining vascular tone and regulation of blood flow.\textsuperscript{25} All these potential mechanisms may suggest the ability of alcohol to maintain adaptive arterial enlargement preserving lumen area. However, our findings obtained from a cross-sectional study should be confirmed by longitudinal studies.

Our population consisted of an elderly population who were able to come to the study examination centers. This may explain the differences in cardiovascular risk factors between participants who had ultrasound examinations and those who had not. This fact and the potential effects of selective survival, as well as self-selection biases leading to an underrepresentation of persons in poor health, should be considered as a methodological limitation of the study. We assessed the effects on carotid structure of average amounts of alcohol consumed rather than drinking habits. The Kuopio Ischemic Heart Disease Risk Factor Study showed that binge-drinking men with heavy alcohol consumption have the greatest progression of carotid atherosclerosis.\textsuperscript{10} However, binge-drinking habits are uncommon in France. Analyses were conducted adjusting for major known cardiovascular risk factors. The potential confounding effects of unknown and, to a lesser extent, unmeasured factors could not be ruled out, although these factors would need to be strongly associated with both alcohol and carotid structure.\textsuperscript{11} Self-reported current usual alcohol consumption was assessed by a standardized questionnaire. Nondifferential and differential measurement errors (because of underreporting consumption, especially by heavy drinkers, and recall bias in older subjects) might also have occurred. Because alcohol drinking is socially accepted in France, we think that error measurements of alcohol would not be higher that those occurring in other comparable population-based studies. In addition, the associations of alcohol intake with smoking habits and high-density lipoprotein cholesterol were virtually equivalent to those found in other studies,\textsuperscript{11} suggesting that alcohol intake of our study is reasonably valid.

In conclusion, this very large population sample of older adults showed no marked relationships of alcohol consumption with CCA–IMT and carotid plaques. The results also suggest that alcohol intake and carotid arterial diameter are positively associated, independently of conventional cardiovascular risk factors. The potential ability of alcohol to maintain adaptive enlargement to preserve lumen area should be investigated in longitudinal studies.

**Acknowledgments**

The 3C Study is mainly supported by the Fondation pour la Recherche Médicale and the Sanofi-Synthélabo Company.

**References**


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Stroke. 2004;35:2770-2775; originally published online October 28, 2004; doi: 10.1161/01.STR.0000147968.48379.c3

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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