Alcohol Consumption and Subclinical Findings on Magnetic Resonance Imaging of the Brain in Older Adults

The Cardiovascular Health Study

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Background and Purpose—Subclinical findings on MRI of the brain are associated with poorer cognitive and neurological function among older adults. We sought to determine how alcohol consumption is related to these findings.

Methods—As part of the Cardiovascular Health Study, 3660 adults aged 65 years and older underwent MRI of the brain from 1992 to 1994. We excluded 284 participants with a confirmed history of cerebrovascular disease. We assessed self-reported intake of beer, wine, and liquor at the annual clinic visit closest to the date of the MRI and grouped participants into 6 categories: abstainers, former drinkers, <1 drink weekly, 1 to <7 drinks weekly, 7 to <15 drinks weekly, and ≥15 drinks weekly. Neuroradiologists assessed white matter grade, infarcts, ventricular size, and sulcal size in a standardized and blinded manner. We used multivariate regression to control for sociodemographic and clinical characteristics.

Results—We found a U-shaped relationship between alcohol consumption and white matter abnormalities. Compared with abstainers, individuals consuming 1 to <7 drinks had an OR of 0.68, and those consuming ≥15 drinks weekly had an OR of 0.95 (p for quadratic term = 0.01). Heavier alcohol consumption was associated with a lower prevalence of infarcts (OR for ≥15 drinks weekly relative to abstainers 0.59; P for trend = 0.004), but larger ventricular size (OR for ≥15 drinks weekly relative to abstainers 1.32; P for trend = 0.006) and sulcal size (OR for ≥15 drinks weekly relative to abstainers 1.53; P for trend = 0.007).

Conclusions—Moderate alcohol consumption is associated with a lower prevalence of white matter abnormalities and infarcts, thought to be of vascular origin, but with a dose-dependent higher prevalence of brain atrophy on MRI among older adults. The extent to which these competing associations influence overall brain function will require further study.

(Stroke. 2001;32:1939-1946.)

Key Words: alcohol drinking • aged • atrophy • brain infarction • magnetic resonance imaging

Subclinical findings on MRI of the brain, such as white matter changes, infarcts, and enlarged ventricles or sulci, are common, particularly among older individuals.¹,² These lesions may have great prognostic importance.³,⁴ For example, in the Cardiovascular Health Study (CHS), white matter grade, infarcts, and ventricular size are all associated with poorer neurological and cognitive function in cross-sectional analyses.⁵-⁷ And infarcts and larger ventricular volume are both associated with greater declines in cognitive function over time.⁸

Although some cardiovascular risk factors, such as hypertension, age, and subclinical atherosclerosis, have been associated with MRI findings of the brain,⁹-¹¹ not all cardiovascular risk factors share this association.¹¹,¹² Whether moderate alcohol consumption, which is associated with a lower risk of cardiovascular disease in the elderly,¹³,¹⁴ is also associated with subclinical MRI findings is not known. Paradoxically, moderate and heavy alcohol consumption have rather different effects on cerebral vasculature, structure, and function. Studies of alcoholic individuals have consistently shown brain atrophy on MRI,¹⁵-¹⁸ and heavy alcohol use is associated with an increased risk of cerebral infarction.¹⁹-²¹ In contrast, moderate alcohol consumption is associated with a lower risk of ischemic stroke¹⁹-²² and better cognitive performance.²³

To determine the relationship of alcohol consumption to MRI findings among older adults, we studied the cross-sectional association of alcohol consumption with white...
matter abnormalities, infarcts, and measures of atrophy in the CHS, a longitudinal, population-based study of individuals aged 65 years and older. We hypothesized that moderate alcohol consumption would be associated with a lower prevalence of white matter changes and infarcts than either abstention or heavy drinking and that ventricular and sulcal size would be positively related to alcohol consumption.

**Subjects and Methods**

**Study Population and Design**

The CHS is a prospective, longitudinal study of 5888 men and women aged $\geq$65 years who were randomly selected from Medicare eligibility lists in 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 participants were recruited and examined; in 1992 and 1993, an additional 687 black participants were recruited and examined. 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. The baseline examination included standardized medical history questionnaires, physical examination, resting electrocardiography, spirometry, and laboratory examination. Follow-up contact occurred every 6 months, alternating between telephone calls and clinic visits.

**Alcohol Consumption**

At each clinic visit, participants were asked their usual frequency of consumption of alcoholic beverages (daily, weekly, monthly, yearly, or rarely/never). Participants then reported the usual number of 12-ounce cans or bottles of beer, 6-ounce glasses of wine, and shots of liquor that they drank on each occasion. The number of drinks and frequency of use of beer, wine, and liquor use were determined individually. In primary analyses, we used the alcohol questionnaire from the annual clinic visit closest to the date of the MRI examination. In secondary analyses, we restricted our analyses to the 2345 participants whose categorical alcohol consumption did not change between the baseline visit and the visit closest to the MRI examination.

At baseline, participants reported whether they had changed their pattern of consumption during the past 5 years and whether they had ever regularly consumed 5 or more drinks daily. Participants who reported current abstention but responded yes to either of these questions were classified as former drinkers, as were individuals who reported consumption of any alcohol at baseline but no alcohol consumption at the clinic visit closest to the MRI examination.

We categorized participants into categories according to weekly ethanol consumption as follows: none, former, $<1$ drink weekly, 1 to 7 drinks weekly, 7 to $<15$ drinks weekly, and $\geq15$ drinks weekly. For logistic regression analyses, we used abstainers without former use as the reference category.

**TABLE 1. Characteristics of 3376 CHS Participants Free of Stroke or Transient Ischemic Attack Who Underwent Cranial MRI, According to Usual Alcohol Consumption**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None</th>
<th>Former</th>
<th>$&lt;1$</th>
<th>1 to $&lt;7$</th>
<th>7 to $&lt;15$</th>
<th>$\geq15$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1294</td>
<td>511</td>
<td>606</td>
<td>525</td>
<td>304</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>75.1</td>
<td>75.1</td>
<td>75.0</td>
<td>74.6</td>
<td>75.6</td>
<td>74.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Female</td>
<td>70.9%</td>
<td>55.2%</td>
<td>63.9%</td>
<td>46.1%</td>
<td>46.7%</td>
<td>28.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>23.9%</td>
<td>7.4%</td>
<td>12.4%</td>
<td>12.4%</td>
<td>7.2%</td>
<td>9.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Married</td>
<td>62.9%</td>
<td>69.5%</td>
<td>66.5%</td>
<td>72.2%</td>
<td>77.3%</td>
<td>74.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7.3%</td>
<td>10.6%</td>
<td>9.4%</td>
<td>10.5%</td>
<td>11.5%</td>
<td>16.2%</td>
<td>0.005</td>
</tr>
<tr>
<td>Former smoker</td>
<td>32.8%</td>
<td>51.9%</td>
<td>47.2%</td>
<td>56.4%</td>
<td>59.9%</td>
<td>69.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weekly drinks, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.5</td>
<td>1.9</td>
<td>6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wine</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.7</td>
<td>3.3</td>
<td>4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liquor</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.9</td>
<td>4.9</td>
<td>10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61.6%</td>
<td>56.4%</td>
<td>52.0%</td>
<td>49.3%</td>
<td>56.6%</td>
<td>64.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0</td>
<td>26.1</td>
<td>26.6</td>
<td>26.0</td>
<td>25.2</td>
<td>26.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.9%</td>
<td>13.7%</td>
<td>11.2%</td>
<td>9.0%</td>
<td>6.6%</td>
<td>10.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalence of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4.9%</td>
<td>6.5%</td>
<td>3.3%</td>
<td>2.5%</td>
<td>2.0%</td>
<td>4.4%</td>
<td>0.005</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.9%</td>
<td>2.9%</td>
<td>3.0%</td>
<td>3.4%</td>
<td>3.3%</td>
<td>2.2%</td>
<td>0.37</td>
</tr>
<tr>
<td>Energy expended in leisure physical activities, kcal</td>
<td>1320</td>
<td>1553</td>
<td>1518</td>
<td>1851</td>
<td>1788</td>
<td>1914</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Some vocational school or college</td>
<td>31.7%</td>
<td>41.9%</td>
<td>53.3%</td>
<td>58.7%</td>
<td>66.5%</td>
<td>66.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Income $\geq$16 000</td>
<td>48.3%</td>
<td>60.5%</td>
<td>65.6%</td>
<td>73.6%</td>
<td>79.4%</td>
<td>75.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>211.4</td>
<td>205.5</td>
<td>209.9</td>
<td>203.8</td>
<td>207.9</td>
<td>204.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>52.9</td>
<td>52.3</td>
<td>53.6</td>
<td>54.4</td>
<td>57.5</td>
<td>60.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>147.5</td>
<td>146.6</td>
<td>141.0</td>
<td>130.2</td>
<td>125.7</td>
<td>128.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>330.0</td>
<td>326.5</td>
<td>327.3</td>
<td>313.8</td>
<td>306.7</td>
<td>307.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$P$ values for binary variables derived from $\chi^2$ tests and continuous variables from ANOVA. Mean values are shown for continuous variables.
MRI Examination
A total of 3660 CHS participants completed an MRI examination between 1992 and 1994. Reasons for not completing an MRI included death (n=411), lack of an appropriately timed visit (n=244), contraindication to MRI (n=277), refusal (n=596), inability to complete the scan (n=467), technical difficulties (n=48), and other (n=185). We excluded participants with a confirmed history of cerebrovascular disease (transient ischemic attack or stroke) at any time prior to the MRI examination (n=284), leaving 3376 participants eligible for analysis. The CHS participants who completed an MRI examination were generally healthier than those participants who did not. On average, they were younger and more likely to be white, married, normotensive, nondiabetic, and free of coronary heart disease or stroke. In addition, participants who completed an MRI examination consumed a mean of 2.6 drinks per week, compared with 2.2 drinks per week among participants who did not complete an examination (P=0.008).

Noncontrast MRI imaging was performed in a standard fashion, including standard sagittal T1-weighted, spin-density, and T2-weighted images, all with 5-mm thickness and no interslice gaps. Neuroradiologists rated the MRI examinations at a single reading center without clinical information provided.

We quantified MRI findings in a standardized manner, as previously described. Grades for white matter, ventricles, and sulci were scored from 0 to 9, based on comparison to templates. Infarcts were defined as areas of abnormal signal intensity at least 3 mm in size in a vascular distribution that lacked mass effect. Grading for all of these measures has been shown to be reliable. Consistent with previous CHS analyses, we also categorized the MRI parameters as follows: for white matter grade, 0; for infarcts, 0, 1, 2, 3, 4; for ventricular and sulcal size, 0, 1, 2, 3, 4, 5.

Other Covariates
We defined diabetes as a fasting blood sugar ≥126 mg/dL or the use of antidiabetic medication. We defined hypertension as an average random zero 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. Apo E genotype testing was performed as described. We defined orthostatic hypotension as a difference in standing systolic blood pressure ≥20 mm Hg or diastolic blood pressure ≥10 mm Hg on change from supine to standing position, or an inability to tolerate standing procedures due to lightheadedness.

Statistical Methods
We tested univariate associations with continuous variables with ANOVA and binary variables with χ2 tests. We used multivariate regression to adjust for factors that could confound the relationship between alcohol consumption and MRI findings. These factors were age, race, sex, educational attainment, income, marital status, current smoking, former smoking, diabetes, body mass index, total cholesterol, atrial fibrillation, history of congestive heart failure, and kilocalories expended in daily activities. Because high-density lipoprotein cholesterol (HDL), fibrinogen, hypertension, and orthostatic hypotension may be plausible mediators of the effect of alcohol consumption, we used logistic regression analyses using ordinal (polytomous) logistic regression. We tested for linear trend by treating the categories of alcohol consumption as a continuous variable, excluding former drinkers. We used SAS, release 6.12 (SAS Institute, Inc) for all analyses.

Results
Table 1 shows the sociodemographic and clinical characteristics of the CHS participants who completed an MRI examination, according to usual alcohol consumption. Consistent with previous epidemiological studies of alcohol consumption, heavier alcohol consumption was more common among participants who were male, white, married, current or former smokers, and more physically active. The relationships of alcohol consumption to hypertension, diabetes, and congestive heart failure were U shaped. Body-mass index, triglyceride levels, and fibrinogen levels were lower among individuals who consumed more alcohol.

Table 2 demonstrates the association of alcohol consumption with MRI findings. For white matter grade, the association was U shaped, with a white matter score among individuals consuming 1 to <7 drinks per week approximately 0.2 grades lower than that among abstainers or individuals consuming ≥15 drinks per week. For infarcts, we found an inverse relationship, with the lowest prevalence of lesions among the individuals consuming ≥15 drinks weekly (OR relative to abstainers 0.57; 95% CI 0.36 to 0.90). For both ventricular and sulcal size, measures of brain atrophy, the association was linear, with scores approximately 0.2 grades larger among the heaviest drinkers relative to long-term abstainers (but not former drinkers). These relationships were changed little by controlling for demographic and clinical characteristics.

Figure 1. MRI findings of the brain among CHS participants free of a confirmed history of cerebrovascular disease, according to usual alcohol consumption. ORs derived from ordinal regression models, controlling for age, race, sex, educational attainment, income, marital status, current smoking, former smoking, diabetes, body mass index, total cholesterol, atrial fibrillation, history of congestive heart failure, and energy expended in leisure activities. Abstainers were the reference group for all comparisons, and former drinkers were excluded.
Previous studies have generally found U- or J-shaped relationships between alcohol consumption and symptomatic ischemic stroke, with the highest risk among heavy drinkers. Although we found an inverse relationship to the...
prevalence of infarcts in this study, the heaviest drinkers we studied (≥15 drinks weekly) would have been classified as moderate drinkers in other studies. Thus, alcohol consumption may have similar associations with subclinical and symptomatic cerebral infarctions.

Both white matter abnormalities and infarcts may reflect deficiencies in cerebral blood flow. Chronic or recurrent occlusion of the long, penetrating corticofugal arteries may be responsible for white matter abnormalities. Infarcts likely result from occlusion of small penetrating branches of large cerebral arteries, such as the lenticulostriate or thalamoperforating arteries. In both cases, alcohol consumption could conceivably lower the risk of arterial occlusion, whether by lowering the likelihood of hypertension (particularly for white matter changes) or raising HDL concentrations (which accounted for as much as 27% of the association of alcohol consumption with infarcts in some models). Changes in platelet function (which we did not measure in this study) could also explain a possible relationship of alcohol consumption to cerebral arterial occlusion, although the lower fibrinogen levels seen among drinkers do not appear to play a significant role.

We found that ventricular and sulcal size were both larger with greater alcohol consumption. Although the difference in these measures was modest between abstainers and light drinkers, the association was linear, suggesting that alcohol consumption may contribute to brain atrophy even at low levels of consumption. Many studies associate heavy drinking with smaller cortical size, particularly in the frontal lobe, but the relationship between alcohol consumption and brain atrophy at lower levels of intake has not been extensively investigated. Given the consistency of our findings across 2 measures of atrophy and in all subgroups we studied, alcohol consumption may lower brain volume in a dose-dependent manner, with no safe threshold of consumption. However, such brain shrinkage may be at least partly reversible during abstinence.

As suggested by Figure 1, alcohol consumption has a complex mix of associations with cerebral findings on MRI examination, including a U-shaped association with white matter lesions, a positive association with brain atrophy, and an inverse association with infarcts. We would expect some of these associations to be beneficial and others detrimental. In this report, we cannot ascertain how they interact to influence overall brain function. For now, we merely speculate that the lower white matter grade and lower prevalence of subclinical infarcts seen among moderate drinkers could be associated with better cognitive function, while the greater brain atrophy and higher white matter grade found among heavier drinkers could be associated with cognitive dysfunc-
tion. If these speculations are correct, they could explain the J-shaped relationship between alcohol consumption and cognitive performance suggested from results of some other studies.\textsuperscript{35–37} Regardless of the mechanisms involved, the actual balance of effects of alcohol consumption in any given individual cannot be assessed with the population-level data.

The CHS has its strengths but some limitations as well. The CHS participants who underwent MRI examination represent a relatively healthy group of older adults, given the CHS eligibility criteria and selective participation in CHS and its MRI component. Thus, our results are most readily generalized to older adults in similar health, and further research is needed to extend these findings to other populations. Importantly, the MRI findings studied here are particularly prevalent in older individuals, and a similar study among younger people would require a sample size even larger than that of the CHS.

In this cross-sectional analysis, some individuals may have changed their alcohol intake in response to illnesses that predisposed them to MRI findings like those we studied. However, the participants we studied were a relatively healthy subgroup of older adults free of known cerebrovascular disease, we repeated our analyses restricted to individuals with stable alcohol consumption, and we separated former drinkers from long-term abstainers. Moreover, we detected patterns of associations that would be little changed by exclusion of abstainers.

As with any observational study, the associations we observed could be related, at least in part, to differences between drinkers and nondrinkers other than their level of alcohol consumption. However, controlling for a wide variety of demographic, socioeconomic, and clinical factors did not materially change our results. To have produced the associations regarding alcohol consumption in this study, which has been validated in other epidemiological investigations\textsuperscript{38} but may have introduced some error into our analyses. Although such error is unlikely to have altered the rank order of CHS participants, the levels of alcohol consumption we report may differ from the actual number of drinks consumed by these individuals. Because CHS participants included few heavy drinkers, we also had limited power to determine how heavy alcohol consumption relates to MRI findings, although its association with brain atrophy is well established.\textsuperscript{33,34}

In conclusion, in this study of older adults, alcohol consumption was associated with white matter abnormalities, infarcts, and measures of brain atrophy on MRI examination of the brain. White matter abnormalities and infarcts, which may have a vascular origin, were lower among moderate drinkers, but measures of brain atrophy were higher with greater alcohol consumption. Given the complex relationship of alcohol consumption with these MRI findings, recommendations regarding alcohol consumption among older adults must await additional research to assess the overall effects of alcohol intake on cognitive function and quality of life.

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Editorial Comment

Alcohol Consumption and the Risk of Silent Brain Infarcts and Stroke

Heavy drinking—both chronic alcoholism and binge drinking—has long been assumed to increase the risk of stroke.1–3 However, the role of alcohol consumption in general as an independent risk factor for stroke has been questioned,4 and case-control reports emphasize that whereas heavy alcohol intake increases the risk of stroke, regular light-to-moderate drinking decreases stroke risk.5–8 Large prospective studies found that although heavy drinking is associated with an increased risk of stroke, this is largely mediated through blood pressure,7 and light-to-moderate drinking has a protective effect against ischemic stroke both in women and men.8,9

There are several factors that can distort the results of such studies. The selection of the control group might influence the conclusions in case-control studies.10 The reliability of the self-reported amount of consumed alcohol is another critical issue. In a large, prospective cohort study, serum concentration of gamma-glutamyl transferase—a biological marker of marked alcohol consumption—was associated with the risk of total and ischemic strokes in both genders, but self-reported alcohol drinking was not associated with any type of stroke.11

Subcortical silent brain infarctions were found to be risk factors for clinical stroke, and such white matter lesions were associated with alcohol consumption of >58 g/d.12 The role of alcohol consumption is controversial in MRI-detectable lacunar infarcts: symptomatic lesions were related to alcohol consumption,13 whereas alcohol intake was not associated with asymptomatic lacunar infarcts.14

The study of Mukamal et al compares MRI findings to the reported amount of alcohol consumption in a practically healthy elderly population. From the data and the figures, it seems that abstainers have 50% higher risk for harboring at least 1 asymptomatic brain infarct than moderate-to-heavy drinkers, and moderate-to-heavy drinkers have somewhat larger ventricles and wider sulci than abstainers. Reading the article of Mukamal et al, probably most people would choose to drink at least 15 drinks a week rather than be abstinent to get the benefit of a marked reduction in the risk of infarcts for the price of a small increase in atrophy, especially if we consider that another report from the same study found that the atrophy group performed better than expected on cogni-
tive and motor tasks. As the authors correctly state, 15 drinks per week is the limit of moderate and not heavy alcohol consumption. Considering the other studies mentioned above, it would be worth identifying study participants with really heavy alcohol consumption and reanalyzing the data including this group, after which the implicit suggestion of the paper might (or might not!) change.

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References
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