Alcohol Intake and Cerebral Abnormalities on Magnetic Resonance Imaging in a Community-Based Population of Middle-Aged Adults

The Atherosclerosis Risk in Communities (ARIC) Study

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Background and Purpose—Although the risks associated with heavy drinking for increased stroke and neurodegenerative changes are well established, the effects on the brain of low to moderate alcohol intake are unclear. Subclinical cerebral abnormalities identified on MRI have been associated with neurocognitive decline and incident stroke. We examined the associations of alcohol intake with MRI-defined cerebral abnormalities in a middle-aged, population-based cohort.

Methods—During 1993–1994, a total of 1909 middle-aged adults (40% men and 49% blacks) from 2 communities in the Atherosclerosis Risk in Communities (ARIC) Study (Forsyth County, North Carolina, and Jackson, Miss) underwent a cerebral MRI examination. Trained neuroradiologists coded the images for the presence of infarction and the extent (10-point scale) of white matter lesions, ventricular size, and sulcal size.

Results—In logistic regression analyses, there was no association between alcohol intake and the presence of MRI infarction. In linear regression analyses, alcohol intake was not associated with white matter grade. However, intake of each additional alcoholic drink per week was associated with a 0.01 grade greater ventricular size (P=0.03) and a 0.009 grade greater sulcal size (P=0.02) after adjustment for age, sex, race, body mass index, smoking, income, sports index, and diabetes. The positive associations of alcohol intake with ventricular and sulcal size were consistent across sex and race subgroups.

Conclusions—A protective effect of low to moderate alcohol intake on cerebral infarction was not found; moreover, increased alcohol intake was associated with brain atrophy. (Stroke. 2004;35:16-21.)

Key Words: alcohol drinking • atrophy • cerebral infarction • magnetic resonance imaging
sectional analyses in a large sample of community-based, middle-aged adults. We hypothesized that moderate alcohol intake may be inversely associated with infarction and white matter lesions on MRI but positively associated with brain atrophy in middle-aged adults.

Subjects and Methods

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective, community-based study designed to investigate the etiology and natural history of atherosclerosis. A probability sample of 15,792 participants, aged 45 to 64 years, was selected from 4 US communities. With 1987–1989 as the baseline, follow-up examinations were conducted approximately every 3 years. Among participants who were alive at each follow-up examination, the return rate was 93% for the second examination (1990–1992) and 86% for the third examination (1993–1995). The ARIC Study was approved by the institutional review board of each participating institution, and the participants gave informed consent.

A total of 2821 participants, aged ≥55 years, were randomly selected from 2 ARIC communities (Forsyth County, North Carolina, and Jackson, Miss) for cerebral MRI examination during the first 2 years of the third examination (average 5.8 years after baseline, ranging from 5.5 to 7.7 years). After the exclusion of 4% of participants who were ineligible for the MRI examination (mostly people in occupations with exposure to metal fragments) and 23% of participants who declined the MRI examination, 1935 participants underwent a cerebral MRI in 1993–1995. After further exclusion of participants with missing information on alcohol intake or MRI examination, the sample size for the present analysis was 1909 (22% white men, 18% black men, 29% white women, and 32% black women). The baseline characteristics of those who were ineligible or declined the MRI examination were similar to those who were included in the present analysis (data not shown).

General Electric (General Electric Medical Systems) or Picker (Picker Medical Systems) 1.5-T MR scanners were used for the MRI examination. The scanning angle was parallel to the anterior commissure–posterior commissure line. The scans were sent to the MRI Reading Center (Johns Hopkins Hospital, Baltimore, Md) on magnetic tapes or optical disks and read by trained and certified neuroradiologists. The readers were masked with regard to the participants’ clinical information. MRI infarction was defined as at least 1 lesion ≥3 mm, hypointense on axial T2-weighted and T2-weighted (repetition time [TR] 3000 [≥2500] ms, echo time [TE] 30/100 [<35/75] ms, 5 mm, 0 gap) scans and hypointense on T1-weighted (TR 500 [400–600] ms, TE 20 [<35] ms, 5 mm, 0 gap) scans. Proton density scans were used to determine the extent of white matter lesions (periventricular and subcortical), ventricular size, and sulcal size. Each abnormality was graded with the use of a semiquantitative, 10-point scale (from 0, indicating no abnormality, to 9, indicating severe abnormality) by visual comparison with studies in a standardized reference atlas. Interreader and intrareader agreement rates for MRI infarction were 79% and 82%, respectively. The reliability of white matter, ventricular, and sulcal grading was also good and was consistent with results previously reported for the CHS, using the identical coding protocol.

On the basis of participants’ self-reports at baseline, alcohol intake was categorized into never, former, and current drinking. Among current drinkers, the number of usual drinks (4 oz wine, 12 oz beer, or 1.5 oz liquor) per week was assessed. In the present analysis, participants were categorized into 5 categories: never drinkers, former drinkers, occasional drinkers (<1 drink per week), low drinkers (≥1 drink per week but <7 drinks per week), and moderate drinkers (≥7 drinks per week). Because only 99 current drinkers consumed ≥14 drinks per week (mean, 25 drinks per week), they were assigned into the moderate drinking category rather than a separate heavy drinking group.

The total combined family income from all sources for 12 months before baseline was categorized into 8 categories ranging from <$5000 to >$50,000. A sports index was scored on the basis of frequency and intensity of activities reported at baseline from 1 (low) to 5 (high). Cigarette years of smoking was defined as the average number of cigarettes per day times the number of years smoked at baseline. The methods for determining plasma total cholesterol, HDL cholesterol, and fibrinogen concentrations have been described elsewhere. Hypertension at baseline was defined as diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg or current use of antihypertensive medication. Coronary heart disease at the third examination was based on ECG, medical history, and history of coronary procedures. Diabetes at the third examination was defined as a blood glucose level ≥126 mg/dL after ≥8 hours of fasting or a blood glucose level ≥200 mg/dL among the few participants who were not fasting, self-reported diabetes, or current use of medication for diabetes. Clinical stroke at the third examination was defined as a self-reported, physician-diagnosed stroke.

Analysis

Means and proportions of the characteristics of the participants in the various alcohol intake categories were compared with the use of ANCOVA and logistic regression analysis, with adjustment for age, sex, and race. Logistic regression analysis was used to assess the association of alcohol intake categories with MRI infarction, after adjustment for demographic factors (age, sex, and race), body mass index, smoking status, cigarette years of smoking, income, sports index, and diabetes. To avoid overadjustment, coronary heart disease was not adjusted for in the analysis because coronary heart disease may be in the causal pathway between alcohol intake (protective effect) and MRI infarction. Multiple linear regression analysis was used to assess the associations of the amount of alcohol intake with white matter, ventricular, and sulcal grades, all as continuous variables, after the exclusion of former drinkers. SAS software (SAS Institute) was used for the statistical analyses.

Results

More men than women and more whites than blacks reported alcohol intake (Table 1). Never drinkers had the lowest and moderate drinkers had the highest proportion of current smokers, while former drinkers had the highest proportion of former smokers. Among current smokers, current and former drinkers smoked more cigarettes than never drinkers. Current drinkers were more physically active and had higher family income compared with former and never drinkers. Low and moderate drinkers had a better plasma lipid profile compared with the other categories. Coronary heart disease and diabetes were more prevalent among former drinkers than among never or current drinkers. There was a U-shaped association between the level of alcohol intake and clinical stroke. In general, the level of alcohol intake was positively associated with ventricular and sulcal size, but no consistent association was seen with MRI infarction or white matter grade.

Compared with never drinkers, former drinkers and moderate drinkers had higher odds (only marginally significant for moderate drinkers) of MRI infarction in unadjusted analyses (Table 2). These associations were attenuated after adjustment for demographic factors, body mass index, smoking, income, sports index, and diabetes. Excluding participants with clinical stroke (n=82) further attenuated the associations. There was no risk or protection of MRI infarction associated with occasional drinking and low drinking.

Logistic regression analyses evaluating the association of alcohol intake with MRI infarction were further stratified by sex or race and adjusted for demographic factors, body mass...
index, smoking, income, sports index, diabetes, race, and sex, respectively (Figure 1). Among all subgroups, there was no statistically significant association of alcohol intake and MRI infarction.

While no linear association of alcohol intake with white matter grade was seen, both ventricular and sulcal size increased significantly with increasing amounts of alcohol intake, with or without adjustment of other covariates


<table>
<thead>
<tr>
<th></th>
<th>Never (n=742)</th>
<th>Former (n=342)</th>
<th>Occasional (n=297)</th>
<th>Low (n=318)</th>
<th>Moderate (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* y</td>
<td>57</td>
<td>57</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Male,† %</td>
<td>21</td>
<td>54</td>
<td>35</td>
<td>49</td>
<td>76</td>
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<tr>
<td>Black,‡ %</td>
<td>64</td>
<td>58</td>
<td>22</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28</td>
<td>28</td>
<td>27</td>
<td>27</td>
<td>26</td>
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<td>Current smoking, %</td>
<td>12</td>
<td>27</td>
<td>24</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>Former smoking, %</td>
<td>22</td>
<td>43</td>
<td>29</td>
<td>32</td>
<td>29</td>
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<tr>
<td>Cigarette years of smoking§</td>
<td>456</td>
<td>728</td>
<td>606</td>
<td>571</td>
<td>764</td>
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<td>Sports index</td>
<td>2.3</td>
<td>2.2</td>
<td>2.5</td>
<td>2.5</td>
<td>2.4</td>
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<tr>
<td>Family income (≥$16 000), %</td>
<td>69</td>
<td>62</td>
<td>76</td>
<td>71</td>
<td>72</td>
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<tr>
<td>Cholesterol, mmol/L</td>
<td>5.42</td>
<td>5.35</td>
<td>5.50</td>
<td>5.36</td>
<td>5.49</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.34</td>
<td>1.38</td>
<td>1.40</td>
<td>1.50</td>
<td>1.67</td>
</tr>
<tr>
<td>Fibrinogen, μmol/L</td>
<td>9.0</td>
<td>9.2</td>
<td>8.9</td>
<td>8.9</td>
<td>8.6</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>43</td>
<td>44</td>
<td>39</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>Coronary heart disease,</td>
<td></td>
<td></td>
<td>6.2</td>
<td>8.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Clinical stroke,</td>
<td></td>
<td></td>
<td>5.3</td>
<td>4.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19</td>
<td>23</td>
<td>17</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>MRI infarction,</td>
<td></td>
<td></td>
<td>11</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>White matter grade</td>
<td>1.40</td>
<td>1.56</td>
<td>1.39</td>
<td>1.38</td>
<td>1.46</td>
</tr>
<tr>
<td>Ventricular grade</td>
<td>2.45</td>
<td>2.48</td>
<td>2.42</td>
<td>2.54</td>
<td>2.60</td>
</tr>
<tr>
<td>Sulcal grade</td>
<td>2.08</td>
<td>2.05</td>
<td>2.09</td>
<td>2.18</td>
<td>2.30</td>
</tr>
</tbody>
</table>

*Adjusted only for sex and race.
†Adjusted only for age and race.
‡Adjusted only for age and sex.
§Includes only current smokers.
||Also adjusted for smoking status and cigarette years of smoking.

### TABLE 2. Logistic Regression Analyses of the Baseline Alcohol Intake on MRI Infarction in 1993–1995

<table>
<thead>
<tr>
<th></th>
<th>Never (n=742)</th>
<th>Former (n=342)</th>
<th>Occasional (n=297)</th>
<th>Low (n=318)</th>
<th>Moderate (n=210)</th>
</tr>
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<tr>
<td>Odds Ratio 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Model 1*</td>
<td>1</td>
<td>1.60</td>
<td>0.98</td>
<td>0.76</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td>1.1, 2.3</td>
<td>0.6, 1.5</td>
<td>0.5, 1.2</td>
<td>0.9, 2.3</td>
<td></td>
</tr>
<tr>
<td>Model 2†</td>
<td>1</td>
<td>1.38</td>
<td>1.40</td>
<td>1.02</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>0.9, 2.1</td>
<td>0.8, 2.3</td>
<td>0.6, 1.7</td>
<td>0.8, 2.5</td>
<td></td>
</tr>
<tr>
<td>Model 3‡</td>
<td>1</td>
<td>1.35</td>
<td>1.21</td>
<td>1.02</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>0.9, 2.1</td>
<td>0.7, 2.1</td>
<td>0.6, 1.7</td>
<td>0.6, 2.2</td>
<td></td>
</tr>
</tbody>
</table>

* Unadjusted (including 1909 participants).
†Adjusting for age, sex, race, body mass index, smoking status, cigarette years of smoking, income, sports index, and diabetes (excluding 206 participants due to missing information on income, cigarette years of smoking, and diabetes).
‡Excluding those with clinical stroke (n=82); adjusting for age, sex, race, body mass index, smoking status, cigarette years of smoking, income, sports index, and diabetes (further excluding 200 participants due to missing information).
Adjusted means of white matter, ventricular, and sulcal grades were calculated by sex and race, respectively, for each category of alcohol intake (Figure 2). There were no consistent differences in white matter grade between current drinkers and never drinkers across sex and race subgroups. In general, both ventricular and sulcal size increased with increasing alcohol intake among men, women, whites, and blacks. The distribution of adjusted mean ventricular size among subgroups corresponded to that for sulcal size. Excluding those with MRI infarction reduced the white matter, ventricular, and sulcal grades, but the aforementioned patterns remained.

Adding systolic and diastolic blood pressure, antihypertensive medication, fibrinogen, and total and HDL cholesterol to the models or excluding those consuming ≥14 drinks per week did not change the results substantially. Likewise, using the average alcohol intake from all 3 examinations (the baseline and 2 follow-up examinations) or using the maximum alcohol intake from the 3 examinations, instead of the baseline alcohol intake, produced similar results. However, when the alcohol intake at the third examination was used, the association of alcohol intake with ventricular and sulcal size showed a similar pattern but was not statistically significant.

Discussion

In contrast to the CHS, which demonstrated an inverse association of moderate alcohol intake with MRI cerebral infarction and white matter lesions in older adults, the present study showed that alcohol intake was not associated with MRI infarction or white matter lesions in middle-aged adults. A recent Scottish study suggests that socioeconomic and lifestyle factors may explain the inverse association of low and moderate alcohol intake with clinical stroke. However, after adjustment for socioeconomic and lifestyle factors, the CHS still showed inverse associations of moderate alcohol intake with MRI infarction and white matter lesions. One explanation may be that a protective effect of alcohol is most pronounced among persons at increased risk for atherosclerosis. Alternatively, the susceptible segment of the moderate drinking population may either succumb or cease moderate drinking before they reach older age. Thus, while socioeconomic and lifestyle factors may explain a part of the inverse association, other explanations, such as a different pathogenesis or differences in drinking behaviors between non-Hispanic whites and blacks and suggest that alcohol intake contributes to brain atrophy in a dose-response fashion. What the present study showed is that alcohol intake contributes to brain atrophy in a dose-response fashion. What the present study showed is that alcohol intake contributes to brain atrophy in a dose-response fashion.

Excluding those with MRI infarction and white matter lesions in older adults, the present study showed a positive association between alcohol intake and brain atrophy. In accordance with the CHS, the results presented here showed associations that were consistent among men, women, whites, and blacks and suggest that alcohol intake contributes to brain atrophy in a dose-response fashion. What the present study shows is that alcohol intake contributes to brain atrophy in a dose-response fashion.

In accordance with the CHS, the present study found a positive association between alcohol intake and brain atrophy. As in the results from the analyses in the older participants in the CHS, the results presented here showed associations that were consistent among men, women, whites, and blacks and suggest that alcohol intake contributes to brain atrophy in a dose-response fashion. What the present study adds to existing evidence is that the process might begin earlier in life than was suggested by the CHS. Moreover, the fact that the patterns did not change after excluding those with MRI infarction implies that the association is not due to compensatory ventricular enlargement or gyral atrophy secondary to infarction alone. While chronic alcohol abuse has been associated with loss of brain volume, especially in the

**TABLE 3. Linear Regression Analyses of the Baseline Alcohol Intake on White Matter, Ventricular, and Sulcal Grades (a Higher Grade Reflecting Greater Abnormality) in 1993–1995, Excluding Former Drinkers**

<table>
<thead>
<tr>
<th>White Matter Grade</th>
<th>Ventricular Grade</th>
<th>Sulcal Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta^* ) ( P )</td>
<td>( \beta^* ) ( P )</td>
<td>( \beta^* ) ( P )</td>
</tr>
<tr>
<td>Model 1†</td>
<td>0.008</td>
<td>0.06</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>0.004</td>
<td>0.36</td>
</tr>
<tr>
<td>Model 3§</td>
<td>0.004</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Indicates the increase in grade for each increase in drink per week.
†Unadjusted (including 1567 participants).
‡ Adjusting for age, sex, race, body mass index, smoking status, cigarette years of smoking, income, sports index, and diabetes (excluding 167 participants due to missing information on income, cigarette years of smoking, and diabetes)
§ Excluding those with MRI infarction (n=236); adjusting for age, sex, race, body mass index, smoking status, cigarette years of smoking, income, sports index, and diabetes (further excluding 138 participants due to missing information).
Frontal lobes, the results from the CHS and the present study further suggest that even moderate alcohol intake is associated with brain atrophy. Brain atrophy may be associated with lower cognition and upper and lower extremity function. However, the clinical significance of the small reduction of brain volume associated with moderate alcohol drinking observed in the present study is unknown.

The mechanisms underlying the association of alcohol intake with brain atrophy are unclear. Alcohol may contribute to atrophy directly, through adverse effects on neurons or cell constituents, or indirectly, for example, through hypertension or cardiac arrhythmias leading to reduced cerebral blood flow. However, brain atrophy and related neurological deficits induced by chronic alcohol abuse may be partially reversible through sustained abstinence.

The participants in the present study may not fully represent the general population of middle-aged adults because of selective participation in the MRI procedure. However, consistent results for atrophic brain changes across subgroups support the internal validity of the present study. When concurrent alcohol information was used, the association of alcohol intake with brain atrophy was attenuated. The possible explanation is that brain atrophy may progress gradually over time, and some drinkers may have quit because of alcohol-induced conditions. Because only 1 MRI measurement was available, an incidence-prevalence bias could have affected the results. If persons with MRI infarction among never drinkers were more likely to have died than those among moderate drinkers, any protective effect of moderate drinking could have been attenuated. However, this bias is less likely to have contributed significantly to the results in these middle-aged adults than in older adults.

In conclusion, the present study does not support the hypothesis that low and moderate alcohol intake is protective against cerebral abnormalities detected on MRI in middle-aged adults. Furthermore, alcohol intake was consistently and positively associated with brain atrophy.

Acknowledgments

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References

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