

Association of Alcohol Consumption With Brain Volume in the Framingham Study

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Background: While adults who drink low to moderate amounts of alcohol have lower rates of cardiovascular disease than other adults, the effect of alcohol on the brain is less clear. There is evidence that drinking large amounts of alcohol is related to brain atrophy. It is uncertain what the effects of low to moderate consumption might be.

Objective: To determine whether consumption of smaller amounts of alcohol negatively affects brain volume or is protective in reducing the well-documented age-related decline in brain volume.

Design: Total cerebral brain volume (TCBV) was computed, correcting for head size. Multivariate linear regression models were used to evaluate the association between 5 categories of alcohol consumption (abstainers, former drinkers, low, moderate, high) and TCBV, adjusting for age, sex, education, height, body mass index (calculated as weight in kilograms divided by height in meters squared), and the Framingham Stroke Risk Profile. Pairwise comparisons were also conducted between the alcohol consumption groups.

Participants: A total of 1839 subjects from the Framingham Offspring Study who had magnetic resonance imaging of the brain between 1999 and 2001.

Results: Most participants reported low alcohol consumption, and men were more likely than women to be moderate or heavy drinkers. There was a significant negative linear relationship between alcohol consumption and TCBV ($r = -0.25$; $P < .001$). This relationship was modified by sex, with alcohol consumption having a stronger association with TCBV in women than in men ($r = -0.29$ vs -0.20).

Conclusions: In contrast to studies on cardiovascular disease, this study found that moderate alcohol consumption was not protective against normal age-related differences in total brain volume. Rather, the more alcohol consumed, the smaller the total brain volume.

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ANY STUDIES HAVE considered the costs and benefits of alcohol consumption in diverse populations. Moderate alcohol consumption has frequently been reported to have a beneficial effect on cardiovascular disease (CVD).¹⁻³ Because the brain is perfused by the cardiovascular system, moderate alcohol consumption may attenuate age-related decline in brain volume.

It is recognized that brain volume declines with age⁴ at an estimated rate of 1.9% per decade,⁵ while white matter lesions (WMH) increase with age.⁶ In addition, decline in brain volume and increase in WMH accompany the progression of dementia^{7,8} and cognitive deficits.⁹ Lower brain volumes and larger WMH are also observed in persons with higher cardiovascular risk.^{5,10}

Excess alcohol consumption has often been correlated with decline in cognition and can lead to Korsakoff syndrome.¹¹ Yet moderate alcohol consumption has been associated with improved cognitive functioning,¹²⁻¹⁴ a lower risk of Alzheimer disease (AD),¹⁵ and less severe WMH,^{16,17} although one study found no protective effect of moderate alcohol intake on cerebral infarction.¹⁸

The effect of alcohol on brain volume and WMH, however, has not been examined in a community-based sample that is free of clinically evident neurological disease. This cross-sectional study tested the hypothesis that low or moderate alcohol consumption was associated with larger brain volume and less WMH when compared with no drinking or high levels of alcohol consumption in a sample of community-dwelling adults.

Table 1. Distribution of Alcohol Consumption in the Total Sample, Men, and Women^a

| | Total, No. | No. (%) | |
|-----------------------|---------------|-------------|-------------|
| | | Men | Women |
| Participants | 1839 | 861 (46.81) | 978 (53.18) |
| Alcohol consumption | | | |
| Abstainers | 71 | 23 (2.67) | 48 (4.91) |
| Former drinkers | 545 | 217 (25.20) | 328 (33.54) |
| Low ^b | 762 | 326 (37.86) | 436 (44.58) |
| Moderate ^c | 276 | 163 (18.93) | 113 (11.55) |
| High ^d | 185 | 132 (15.33) | 53 (5.42) |

^aSample size is 1839 participants from the Framingham Offspring Cohort.

^bDefined as 1 to 7 drinks per week.

^cDefined as 8 to 14 drinks per week.

^dDefined as more than 14 drinks per week.

METHODS

SUBJECTS

The Framingham Offspring cohort, begun in 1971, included children from the original Framingham Heart Study cohort and their spouses (n=5124) aged 33 to 88 years during the study. Study participants had had 7 health examinations every 4 to 8 years for the past 30 years. Participants at examination 7 (n=3539; 1999-2001) were invited to have a magnetic resonance image (MRI) of the brain; 1886 participants were imaged through August 2001. Major reasons for not being imaged were residence out of state, medical contraindications for MRI such as pacemakers, and claustrophobia. An additional 47 participants were excluded for prevalent stroke, dementia, or other neurological disorder, resulting in a sample of 1839 respondents without stroke or dementia. Unpublished data find that those who did not have a brain MRI were older and had a higher risk of cardiovascular disease, suggesting that our findings are a conservative estimate of the relationship between alcohol consumption and brain volume.

MEASUREMENT OF TOTAL BRAIN VOLUME

The total (parenchymal) brain volume (TBV) and WMH volumes were corrected for total cranial volume (TCV); the resulting measures are TCBV=(TBV/TCV) × 100 and WMHV=(WMH/TCV) × 100, as described by DeCarli et al,⁴ where TCBV indicates total cerebral brain volume; WMHV, white matter lesion volume.

MEASUREMENT OF ALCOHOL CONSUMPTION

Participants reported at examination 7 the number of alcoholic drinks per week (beer, white wine, red wine, or liquor) they consumed during the past month. Alcohol consumption was recorded as a continuous variable and participants were classified into 1 of 5 categories that have been used in other studies^{14,17,18}: abstainers, former drinkers (drinkers based on their drinking status at earlier examinations), low (1-7 drinks per week), moderate (8-14 drinks per week), and high (> 14 drinks per week).

COVARIATES

Covariates obtained at examination 7 included age (in years), sex, education (categorized as [1] fourth grade or less, [2] fifth

through seventh grade, [3] high school or some college, and [4] college graduate), height, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and Framingham Stroke Risk Profile (FSRP, an estimate of the 10-year risk of stroke on a scale of 0 to 1 based on age, sex, systolic blood pressure, antihypertensive therapy, diabetes, smoking status, history of CVD, and the presence of atrial fibrillation and left ventricular hypertrophy¹⁹).

STATISTICAL ANALYSIS

The mean TCBV and WMHV were calculated for each of the 5 alcohol consumption groups and the means were compared using an analysis of covariance with pairwise comparisons ($\alpha=.0125$ for each pairwise comparison). Means were tested for a linear trend across alcohol consumption groups at a level of significance of $\alpha=0.5$. The initial model included all covariates; those covariates that did not contribute significantly to the model were eliminated 1 at a time, provided that their exclusion did not alter the β coefficient for the alcohol consumption term and that they were not clinically important. Sex was assessed as an effect modifier to determine whether the association between amount of alcohol consumption and TCBV and WMH differed between men and women. Analyses were performed using SAS version 8.2 (SAS Inc, Cary, North Carolina).

RESULTS

The sample included 1839 participants aged 33 to 88 years (mean [SD] age, 60.64 [9.42] years). There were 861 men and 978 women. As shown in **Table 1**, most participants reported consuming 1 to 7 drinks per week, followed by former drinkers. While women were more likely than men to be abstainers, former drinkers, or those who drink 1 to 7 drinks per week, men were more likely to report moderate or high alcohol consumption.

For the total sample, the mean (SD) TCBV was 77.40% (3.41%) for men (range, 64.89%-85.52%) and 78.35% (2.94%) (range, 67.84%-85.85%) for women.

The covariates for each group were evaluated separately for women and men (**Table 2**). Among women, amount of alcohol consumption was significantly associated with each covariate (age, sex, BMI, and FSRP score), but among men, alcohol consumption was associated only with FSRP score. Notably, women who consumed moderate amounts of alcohol had the lowest BMI, most education, and lowest FSRP scores, while men who drank low amounts had the lowest FSRP scores.

ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND TCBV AND WMHV IN THE TOTAL SAMPLE

In unadjusted analyses, participants who had low alcohol consumption had slightly larger TCBV compared with the other groups. However, when adjusted for covariates (age, sex, education, BMI, and FSRP score), there was a significant negative linear association between the amount of alcohol consumed and TCBV (β coefficient, -0.25; $P<.01$) (**Figure 1**). This slope of -0.25 is slightly larger than the average decline in brain volume per year with aging. From the pairwise comparisons be-

Table 2. Comparison of Means (SD) of Covariates Within Categories of Alcohol Consumption^a

| | Mean (SD) | | | | | |
|------------------------|-------------|-----------------|------------------|-----------------------|-------------------|---------|
| Covariates | Abstainers | Former Drinkers | Low ^b | Moderate ^c | High ^d | P Value |
| Women | | | | | | |
| Age, y | 62.9 (10.1) | 62.2 (9.4) | 59.5 (9.6) | 59.4 (8.6) | 58.9 (8.2) | <.001 |
| BMI | 28.3 (7.3) | 28.1 (6.3) | 27.1 (5.4) | 25.8 (4.4) | 26.9 (5.6) | .004 |
| Height, in | 63 (2.3) | 63.2 (2.5) | 63.6 (2.5) | 63.8 (2.2) | 64.2 (2.1) | .008 |
| Education ^a | 2.5 (0.9) | 2.7 (0.9) | 3.0 (0.9) | 3.1 (0.9) | 3.0 (0.9) | <.001 |
| FSRP score | 0.05 (0.06) | 0.05 (0.06) | 0.04 (0.05) | 0.04 (0.04) | 0.05 (0.05) | <.001 |
| Men | | | | | | |
| Age, y | 63.2 (9.5) | 61.6 (10.1) | 60.1 (9.1) | 60.8 (9.8) | 60.5 (8.5) | .29 |
| BMI | 27.9 (3.4) | 28.9 (4.9) | 28.4 (4.1) | 28.2 (3.6) | 28.8 (4.7) | .47 |
| Height, in | 68.4 (2.0) | 68.8 (2.5) | 68.8 (2.7) | 69.0 (2.4) | 68.8 (2.7) | .86 |
| Education ^a | 3 (1) | 2.9 (1.0) | 3.2 (0.9) | 3.1 (1.0) | 3.1 (0.9) | .04 |
| FSRP score | 0.10 (0.07) | 0.11 (0.08) | 0.08 (0.06) | 0.09 (0.08) | 0.10 (0.08) | .04 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FSRP, Framingham Stroke Risk Profile.

^aSample is 1839 men and women in the Framingham Offspring Cohort.

^bDefined as 1 to 7 drinks per week.

^cDefined as 7 to 14 drinks per week.

^dDefined as more than 14 drinks per week.

^eDefined as 1 through 4 where 1 indicates fourth grade or less, 2, fifth through seventh grade; 3, high school or some college; 4, college graduate.

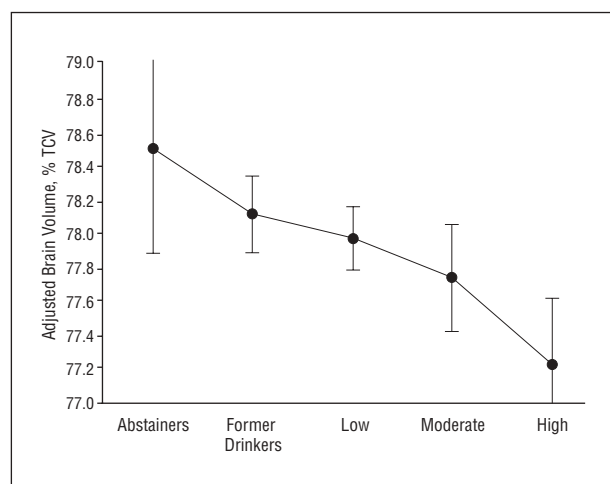


Figure 1. Mean total cranial brain volume, including confidence intervals illustrated as error bars, adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and Framingham Stroke Risk Profile (slope = -0.25 ; $P < .01$; $R^2 = 0.96$). TCV indicates total cranial volume; low, 1 to 7 drinks per week; moderate, 8 to 14 drinks per week; and high, more than 14 drinks per week.

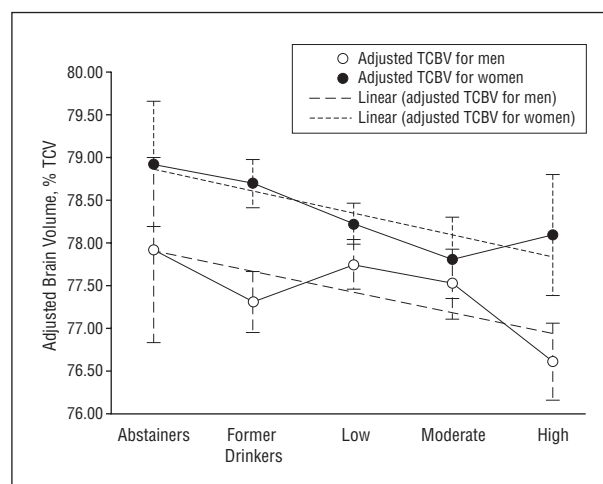


Figure 2. Mean values for total cranial brain volume, including confidence intervals illustrated by error bars, for men (slope = -0.20 ; $P = .02$) and women (slope = -0.25 ; $P = .02$), adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and Framingham Stroke Risk Profile. TCV indicates total cranial volume; low, 1 to 7 drinks per week; moderate, 8 to 14 drinks per week; and high, more than 15 drinks per week.

tween groups, moderate drinkers had significantly smaller TCBV than former drinkers ($P = .03$), and participants who consumed more than 14 drinks per week had significantly smaller TCBV than the other groups (high drinkers vs abstainers, $P < .01$; vs former, $P < .01$; vs low, $P < .01$; vs moderate, $P = .04$). By contrast, there was no significant association between alcohol consumption and WMH.

ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND TCBV BY SEX

In sex-specific analyses, adjusted mean TCBV was higher for women than men in every category of alcohol consumption (**Figure 2**). Moreover, the linear regression

curve for the association between alcohol consumption and TCBV was steeper for women than for men. The interaction between drinking and sex on TCBV was significant ($P < .01$).

Among women, greater amount of alcohol consumed was significantly associated with smaller TCBV in multivariable analyses ($P = .02$). From the pairwise comparisons, adjusted mean TCBV only differed significantly between women who were abstainers and moderate drinkers ($P = .01$), former and low drinkers ($P = .01$), and former and moderate drinkers ($P < .01$). Among men, alcohol consumption was also significantly associated with smaller TCBV ($P = .02$), but while the trend was in the same direction as for women, the overall association was somewhat weaker (β coefficient, -0.20 for men vs -0.29

for women). Adjusted mean TCBV only differed significantly between men who were high drinkers and each of the other alcohol consumption categories (abstainers, $P=.03$; former, $P=.02$; low, $P<.01$; moderate, $P<.01$) (Figure 2).

To verify that there was no protective effect of alcohol on TCBV, the low consumption group was contrasted with all of the other alcohol consumption groups for both women and men and no significant difference was found for either sex ($P=.07$ and $.39$ for women and men, respectively). In addition, there was no quadratic relationship between alcohol consumption and TCBV for men ($P=.31$).

COMMENT

This study found no protective effects of alcohol in reducing the normal age-related differences in brain volume in the Framingham Offspring Cohort. Instead, higher levels of alcohol consumption were consistently associated with smaller brain volume after adjusting for covariates. This association was modified by the participants' sex, with women showing larger TCBV than men at every level of alcohol consumption and a steeper negative slope in the line relating alcohol consumption and TCBV. However, the direction of this relationship was the same for both sexes and the magnitude of the differences between sexes was small. We also found no significant correlation between alcohol consumption and WMHV.

Our results are consistent with 2 recent studies in smaller samples. In a study of 405 Japanese men, both global and regional gray matter volumes were negatively correlated with lifetime alcohol intake.²⁰ In another sample of 385 adults aged 60 to 64 years, greater alcohol consumption was associated with more brain atrophy.²¹ Neither of these studies found beneficial effects of low to moderate alcohol consumption.

Two other studies related alcohol consumption to ventricular and sulcal size.^{17,18} It is noteworthy that both studies found increasing ventricular sizes with increasing amounts of alcohol consumed. These findings are consistent with our results because ventricular size is an inverse measure of brain atrophy.

Our finding that sex modified the association between alcohol consumption and brain volume could be related to biological factors. Alcohol is absorbed more rapidly in women than in men, and in general women are more vulnerable to the effects of alcohol than men. Women, on average, are smaller than men and have less blood to dilute the alcohol. Results from this study suggest that alcohol also has a greater negative effect on brain volume in women than in men. In our sample, twice as many men as women reported high alcohol consumption and more men also reported moderate alcohol consumption, which may suggest a behavioral rather than a biological explanation for these findings.

Our hypothesis was based on many observations of a J-shaped association between amount of alcohol consumption and CVD. However, our results indicate that there is no neuroprotective effect of alcohol on neurons.

This study had several limitations. It was restricted to TBV, while regional brain areas have not yet been considered independently. Because some of the alcohol consumption groups contained few participants, statistical power was low for some analyses. Additionally, the Framingham Offspring cohort is predominantly of European origin and the mean educational level is high, thus these results may not be generalizable to other racial and economic groups. Finally, only about 50% of the sample had MRI scans; however this participation rate is found for all of the Framingham Heart Study articles and is consistent with most other MRI studies.^{17,22,23}

Another potential limitation is the difficulty of distinguishing the effects of alcohol consumption from those of age on TCBV. Age is a normally accompanied by smaller brain volume⁴ and is inextricably linked to many of the other covariates, especially BMI and FSRP score.

Use of self-reported data to determine the quantity of alcohol consumed is also a concern because participants are likely to underreport their true drinking pattern.²⁴ However, underreporting of alcohol consumption would most likely have resulted in an underestimate of the association,²⁵ suggesting that the true association between alcohol consumption and brain volume would be even larger than the one observed.

Finally, these results were observed in cross-sectional data. Thus, we cannot relate alcohol consumption to decline in brain volume. Prospective analyses of this association would be important to establish the temporal relationship between alcohol consumption and brain volume.

Nonetheless, this study has many strengths. It included MRIs performed on more than 1800 Framingham Study participants without clinical dementia or stroke. These volumetric MRI data were examined after adjusting for a wealth of baseline data on cardiovascular risk. Finally, the MRI readers were blinded to participants' demographic and clinical data.

The public health effect of this study gives a clear message about the possible dangers of drinking alcohol. While there are many reports of the beneficial effects of moderate alcohol consumption, these reports are often accompanied by concerns that the data not be interpreted as encouraging drinking. Prospective longitudinal studies are needed to confirm these results as well as to determine whether there are any functional consequences associated with increasing alcohol consumption. This study suggests that, unlike the associations with CVD, alcohol consumption does not have any protective effect on brain volume.

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Author Contributions: Ms Paul had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Paul, Fredman, and Seshadri. *Acquisition of data:* Au, Seshadri, DeCarli, and Wolf. *Analysis and interpretation of data:* Paul, Au, Fredman, Mas-

saro, Seshadri, and Wolf. *Drafting of the manuscript*: Paul, Seshadri, and DeCarli. *Critical revision of the manuscript for important intellectual content*: Au, Fredman, Massaro, Seshadri, and Wolf. *Statistical analysis*: Paul, Fredman, and Massaro. *Obtained funding*: Wolf. *Administrative, technical, and material support*: Wolf. *Study supervision*: Au and DeCarli.

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Announcement

Online Submission and Peer Review System Available. The *Archives of Neurology* editorial office has introduced an online manuscript submission and peer review system developed by eJournalPress that will serve the needs of authors, reviewers, and editors. The new system went live on November 14, 2005. See <http://archneur.ama-assn.org> for more detailed information.