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# Neuroimaging-Derived Predicted Brain Age and Alcohol Use Among Community-Dwelling Older Adults

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## Abstract

**Objectives:** Observational studies have suggested that moderate alcohol use is associated with reduced risk of dementia. However, the nature of this association is not understood. We investigated whether light to moderate alcohol use may be associated with slower brain aging, among a cohort of older community-dwelling adults using a biomarker of brain age based on structural neuroimaging measures.

**Design:** Cross-sectional observational study.

**Participants.—**Well-characterized members of a longitudinal cohort study who underwent neuroimaging. We categorized the 163 participants (mean age 76.7 ±7.7, 60% women) into current

non-drinkers, light drinkers (1–7 drinks/week) moderate drinkers (>7–14 drinks/week), or heavier drinkers (>14 drinks/week).

**Measurements.—**We calculated brain-predicted age using structural MRIs processed with the BrainAgeR program, and calculated the difference between brain-predicted age and chronological age (brain-predicted age difference, or brain-PAD). We used analysis of variance to determine if brain-PAD differed across alcohol groups, controlling for potential confounders.

**Results:** Brain-PAD differed across alcohol groups ($F_{(3, 150)}=4.02$; $p=0.009$) with heavier drinkers showing older brain-PAD than light drinkers (by about 6 years). Brain-PAD did not differ across light, moderate, and non-drinkers. Similar results were obtained after adjusting for potentially mediating health-related measures, and after excluding individuals with a history of heavier drinking.

**Discussion:** Among this sample of healthy older adults, consumption of more than 14 drinks/week was associated with a biomarker of advanced brain aging. Light and moderate drinking was not associated with slower brain aging relative to non-drinking.

### Keywords

Ethanol; Aging; Imaging; Dementia; MRI

## Introduction

Prevalence of alcohol use has been increasing, particularly among older adults [1]. According to a National Poll on Healthy Aging conducted in 2021, two in three adults aged 50–80 reported drinking alcohol at least occasionally in the past year [2]. Among those who drank, 77% reported drinking 1 or 2 alcoholic beverages on days in which they consumed alcohol, while 23% reported consuming 3 or more drinks - an amount that is above the U.S. Department of Health and Human Services' guidelines for reducing morbidity and mortality risks associated with alcohol use [3].

Light and moderate alcohol use has been associated with better cognitive function among older adults and reduced risk of developing dementia [4–6]. In contrast to the large body of literature showing cardioprotective associations of light to moderate alcohol use [7–9], associations of moderate alcohol use with neuroimaging measures of brain health have been mixed. In high doses, alcohol is neurotoxic, and numerous studies have documented a widespread reduction in brain gray and white matter volume among heavy drinkers and those with alcohol use disorders [10–12]. Associations of light or moderate alcohol use with neuroimaging measures of brain health are less consistent. Some studies have reported reduced total or regional brain volumes with even light amounts of alcohol intake [13–16] whereas others have reported larger total or regional brain volumes [19] among moderate drinkers than non-drinkers [20]. Still others observed no associations between alcohol use and brain volumes or atrophy rates among moderate drinkers [10, 17, 18].

Alcohol associations with brain aging may be better observed by examining associations with the overall pattern of changes in brain structure with aging, rather than by examining total brain volume or volumes in specific regions. Machine learning methods have been

applied to structural neuroimaging data to take into account spatial patterns of age-related volume differences across brain gray and white matter to create a biomarker of brain aging [21–23]. These biomarkers of brain aging have been validated in studies showing that older brain-predicted age compared to chronological age (brain-predicted age difference, or brain-PAD) is associated with earlier mortality, higher chronic disease burden, and lower scores on cognitive and physical function tests. In contrast, younger brain-PAD has been associated with higher levels of education and greater physical activity [24–26]. We recently reported that older brain-PAD was observed among drinkers compared with non-drinkers [27], while others have reported Increasing brain-PAD with increasing alcohol intake [13, 28, 29], with larger effect sizes observed at higher amounts of alcohol consumption. However, these studies have primarily examined younger or middle-aged adults. It is possible that associations may differ among older adults who tend to consume lower amounts of alcohol than younger adults and who experience a higher rate of brain volume loss with age.

Here, we examine brain-PAD by amount of alcohol use among a longitudinal cohort of community-dwelling older adults who had alcohol use assessed repeatedly over a 22-year period. Because these participants are at an age where substantial age-related atrophy is likely to have occurred [30], subtle protective associations of light to moderate drinking may be more apparent than among studies of younger adults. Thus, we hypothesized that light drinkers would show younger brain-PAD relative to non-drinkers whereas heavier drinkers would show older brain-PAD.

## Methods

### Participants

The study sample comprised participants from the Rancho Bernardo Study of Healthy Aging (RBS). The RBS is a community-based longitudinal cohort study, initiated in 1972–1974, when 82% of adult residents of the Rancho Bernardo community, aged 30–79, enrolled in a study of heart disease risk factors [31]. The Rancho Bernardo community was primarily white and middle-upper middle class at time of study inception. Participants have been followed ever since with periodic research clinic visits. The current study examined participants who attended the most recent study visit, the 12th visit, occurring in 2014–2016. Locally-dwelling participants who participated in one or more prior research clinic visits were invited to participate if they had no implanted medical devices inconsistent with MRI, and no history of stroke, neurological disease, or treatment for alcohol use disorder. A total of 221 participants enrolled in this visit. Of these, 47 did not undergo imaging due to contraindications for MRI (e.g., potential for implanted ferromagnetic material; claustrophobia; inability to lay still in the scanner) or to unwillingness to be scanned. Of the 166 participants who underwent imaging, data from 3 participants were excluded due to brain abnormalities related to prior head injury (n=2) or severe white matter disease (n=1). The final sample thus comprised 163 participants (60% women, age 56–97, mean age 76.7 (±7.7) years). This study was conducted under oversight of the University of California San Diego Institutional Review Board and all participants provided written informed consent.

### Alcohol use

Participants were surveyed about alcohol use through self-report questionnaires at most study visits. Alcohol use reported at the 12th visit, at the time of MRI acquisition, is used here to categorize participants by current drinking status. Participants were asked whether they had ever consumed an alcoholic beverage, and if so, whether they had consumed an alcoholic beverage in the past 12 months. Those who reported alcohol intake in the past year were asked to indicate the number of alcoholic drinks consumed during a typical week, with separate questions asking about beer, wine, hard liquor, and liqueur consumption. One drink was defined as one 12 oz can/bottle of beer, 5 oz glass of wine, or beverage containing 1.5 oz of hard liquor. Participants were categorized as current non-drinkers (no drinks during an average week), light drinkers (1–7 drinks in an average week), moderate drinkers (8–14 drinks per week) or heavy drinkers (>14 drinks per week). In secondary analyses, we further divided the non-drinking group into never drinkers (those who indicated no lifetime alcohol intake, and who reported no alcohol intake in prior study visits), former drinkers (those who reported prior alcohol intake but no intake in the past year), and occasional drinkers (those who indicated some alcohol intake during the past year but not during an average week). We also examined data collected in prior research visits to determine prior history of heavier drinking (i.e., >14 drinks in an average week).

### MRI Data Acquisition

Neuroimaging data were acquired on a 3.0 Tesla Discovery 750 scanner (GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased array head coil at the University of California, San Diego Center for Functional MRI. The MRI sequence included a three-plane localizer and a sagittal 3D fast spoiled gradient echo T1-weighted volume optimized for maximum gray/white matter contrast (TE=3.2 ms, TR=8.1 ms, inversion time=600 ms, flip angle=8°, FOV=24 cm, frequency=256, phase=192, voxel size=1×1×1.2 mm, scan time 8:27).

### Predicted Brain Age Calculation

To calculate predicted brain age from T1-weighted MRI data, we used the predicted brain age model developed by Cole [21, 26, 32]. This model applies an algorithm developed using Guassian Processes Regression, implemented using the kernlab package in R [33], to relate voxel-based MRI features to chronological age. The model was trained on a sample of 3377 healthy adults aged 18–92, from multiple publicly available data sets, and tested on a sample of 857 healthy adults from the same datasets, aged 18–90 years.

As previously described [34], we used SPM12 to segment and normalize the T1-weighted MRI scans prior to using the Rnifti package in R to create vectors with mutually exclusive grey matter, white matter and cerebrospinal fluid tissue compartments. We then used the R Kernlab package to quantify the 435 variables found by Cole to best predict chronological age, and obtained the predicted age score. Visual quality control was conducted using FSL [35]. Brain-PAD scores were calculated by subtracting chronological age from the predicted age. Positive scores reflect an older predicted age than actual age.

## Covariates

Demographic characteristics and health behaviors assessed using a self-reported questionnaire administered at visit 12 were included as covariates. Demographic measures included age, sex (female/male), years of education (categorized as ≤12; 13–15; 16; or ≥17 years), and marital status (currently married/not married). Participants were asked whether they currently or ever smoked cigarettes (yes/no). They were also asked if they exercised or labored at least three times per week (yes/no). We included performance on the Modified Mini-Mental State Test (3MS) as a measure of global cognitive function [36] and score on the Beck Depression Inventory (BDI) as a measure of depressed mood [37]. Because >97% of the sample are non-Hispanic White, race/ethnicity was not included as a covariate.

Participants were weighed and measured by a study technician; BMI was calculated using participants' weight and age. Systolic (SBP) and diastolic blood pressure (DBP) were measured twice at rest, with participants in a seated position. Participants were considered hypertensive if they had SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, used anti-hypertensive medications, or reported diagnosis of hypertension from a physician. Diabetes was defined as self-reported physician diagnosis or use of diabetes medications. Number of co-morbidities was determined by a count of self-report of doctor diagnosis of heart attack, congestive heart failure, angina, arterial fibrillation, transient ischemic attack, obstructive pulmonary disease, asthma, liver disease, kidney disease, thyroid disorders, osteoporosis. Hypertension and diabetes, as defined above, were also included in the count of total number of comorbidities. Number of co-morbidities was categorized into 0, 1 and 2 or more.

## Statistical analyses

To examine how closely brain-predicted age matched chronological age, and whether there was systematic bias in brain-age estimation, we conducted Pearson correlations between brain-predicted age and chronological age, and between brain-PAD and chronological age. To determine whether participant characteristics differed across drinking groups, we performed analyses of variance (ANOVAs) for continuous measures, and Pearson's $\chi^2$ or Fisher Freeman-Halton Exact tests for categorical measures. We used ANOVAs to examine whether brain PAD varied across the four alcohol groups (non-drinkers, light drinkers, moderate drinkers, and heavier drinkers). We began with a minimally adjusted model, adjusting for sex only. Next, we added potential confounders including education, smoking status, marital status, physical activity, cognitive function and depressed mood. We then additionally adjusted for potential mediators including BMI, diabetes, hypertension, and number of comorbidities. We consider the confounder-adjusted model to be our primary outcome. When significant results were obtained in the ANOVA for alcohol group, we compared each drinking group to the light drinking group in post-hoc pairwise comparisons, with Bonferroni correction for multiple comparisons.

In exploratory analyses, we examined whether associations differed by sex, by including an interaction term for sex and alcohol group. We also examined whether history of heavier drinking may have influenced the results, by excluding individuals from the former, light, and moderate drinking groups who reported consuming more than 14 drinks in an average week on any of the prior 5 study visits (spanning a 22-year period). Finally, we explored

heterogeneity within the non-drinker group by dividing this group into subgroups of never drinkers, former drinkers, and occasional drinkers, as described above. Analyses were conducted in SPSS (version 28); two-sided p values are reported; p values < .05 were considered significant.

## Results

Participant demographics by alcohol group are presented in Table 1. Most participants (69%) consumed alcohol during an average week, with light alcohol drinking (7 or fewer drinks per week) being the most prevalent (47.2%). Less than 10% of the sample were heavier drinkers (> 14 alcoholic drinks in an average week: range 16–29 drinks, mean 22 drinks per week). Individuals who consumed alcohol at this level tended to be younger than other groups and somewhat more likely to be men. Non-drinkers were least likely to have ever smoked and had lower 3MS scores than drinkers. Wine was the most frequently consumed beverage (consumed by 75% of current drinkers), followed by spirits, beer, and liqueur (28%, 20% and 5% respectively).

Participants and non-participants (those who attended visit 12 but were excluded due to missing or unusable imaging data) did not differ in alcohol intake. Nor did they differ in education, smoking status, physical activity, BMI, BDI, diabetes status, or number of co-morbidities (see Supplemental Table S1). Participants were younger (76.7 ±7.7 vs. 79.7 ±9.0 years) more likely to be female (60% vs. 43%), less likely to have hypertension (62% vs. 82%), and had higher 3MS scores (95.0 ±5.7 vs. 92.3 ±8.2) than non-participants.

Brain-predicted age was highly correlated with actual age ($r = 0.71$; $p =001$), suggesting good model fit to the current sample. Brain-PAD was not correlated with age ($r = -0.05$; $p = 0.51$) indicating that there was no systematic bias in brain age estimation.

Figure 1 shows brain PAD as a function of alcohol group, after adjustment for potential confounders. Table 2 shows the results from the minimally adjusted model, the model adjusting for potential confounders and the model adjusting for potential mediators. In all models, there were significant differences in brain-PAD across alcohol groups. Post-hoc pairwise comparisons, using the light-drinking group as the reference group, showed that heavier drinkers had significantly older appearing brains (by about 6 years) than light drinkers. Non-drinkers and moderate drinkers showed no significant differences in brain-PAD compared to light drinkers in any model. Results did not differ by sex (sex by alcohol group interaction ($F(1,3) = 0.94$; $p = 0.42$)

Patterns of alcohol intake over the 22-year follow-up were relatively stable, with correlations ranging from 0.64 to 0.90 between total number of drinks reported in an average week between the current visit and the 5 prior visits. All but two participants who reported heavier drinking in the current visit also reported heavier drinking in at least one prior visit. Approximately one third of the participants in the moderate drinking group reported heavier drinking in a prior visit, while only 3 current light drinkers and 1 current non-drinker reported prior heavier drinking. Excluding those with history of prior heavy drinking from all but the current heavy drinking group, yielded comparable results, with heavier drinkers

continuing to show significantly older brain-PAD than light drinkers, with no significant differences between light drinkers and non-drinkers or moderate drinkers (see Table 2).

Although group sizes were small, we explored heterogeneity within the non-drinker group by dividing it into 3 separate groups of never drinkers, former drinkers, and occasional drinkers (Table 3). Occasional drinkers were somewhat younger than former and never drinkers; never drinkers were less likely to have hypertension than former and occasional drinkers but more likely to have 2 or more comorbidities. Never drinkers and occasional drinkers showed younger brain-PAD while former drinkers showed older brain-PAD. With adjustment for potential confounders (sex, education, age, smoking, physical activity, marital status, cognitive status and depressed mood) significant differences across the six groups were observed (F(5, 148) = 2.89; p=.016), with the heavier drinking group showing significantly higher brain-PAD relative to light drinkers; none of the three non-drinking groups differed from light drinkers (See Figure 2).

## Discussion

Among this cohort of older, community-dwelling adults, we found that heavier drinking (i.e., >14 drinks during a week) was associated with a biological marker of advanced brain age. Structural neuroimaging measures indicated that the brains of heavier drinkers appeared to be about 6 years older than those of light drinkers. Lower amounts of alcohol intake were not associated with advanced brain aging. We found no evidence for a protective association of light drinking on brain age: brain-PAD did not differ between light drinkers and non-drinkers.

The finding that heavier drinkers showed evidence of accelerated brain aging is consistent with the large number of studies that have found heavier drinking to be associated with widespread reductions in brain gray and white matter volumes [10–12], as well as with studies showing the heavier drinking is associated with advanced brain aging [13, 14, 28, 29]. Our finding that light, moderate, and non-drinkers did not differ in brain-PAD is consistent with some prior studies that have observed no differences in brain volumes or atrophy rates between light or moderate drinkers and non-drinkers [10, 18]. It is also generally consistent with results of a study among UK Biobank participants which found no difference in a biomarker of brain aging among those who did not drink and those who drank with any frequency less than daily [38]. However, our results are in contrast with studies that have reported that any amount of alcohol use is associated with accelerated brain aging. These studies have tended to examine alcohol as a binary measure of drinker/non-drinker [27] or examined slopes of differences in brain measures by amount of alcohol intake [14, 15, 28, 29]. In either case, results can be strongly influenced by heavier drinkers in the sample and results may differ among samples with fewer heavy drinkers. For example, a recent study indicated that associations of alcohol with advanced brain aging were smaller when the sample excluded heavier drinkers [13].

Our results are also in contrast with the few studies that have reported beneficial associations of light or moderate drinking with structural neuroimaging measures. In one study of middle-aged adults, men showed positive associations of alcohol intake for some regional

grey matter volumes, but negative associations for white matter volumes; whereas alcohol intake was not associated with gray or white matter volumes in women [20]. Our sample comprised more women than men, and our measure of brain aging incorporates both grey and white matter volumes. In a study of older adults of similar age to our cohort by Gu et al. [19], higher total brain volume was observed among drinkers than non-drinkers, with associations primarily observed among wine drinkers. Although we lacked power to differentiate associations with brain aging by type of alcohol consumed, our sample comprised primarily wine drinkers. The study by Gu et al. [19] compared drinkers to an undifferentiated group of non-drinkers. Because non-drinkers may have quit drinking for health-related reasons, inclusion of former drinkers in the comparison group may inflate estimates of beneficial associations of alcohol use. Our non-drinking group contained more infrequent drinkers than former drinkers, and although our sample sizes are too small to draw firm conclusion, former drinkers showed somewhat older brain-PAD than all other groups except heavy drinkers. Studies with higher proportion of former drinkers in non-drinking comparison groups may be thus be more likely to observe protective associations among light or moderate drinkers relative to non-drinkers than those who include more never drinkers or infrequent drinkers in non-drinker comparison groups.

A strength of this study is the repeated assessment of alcohol use over time, which allowed us to differentiate never drinkers from former drinkers. Reported amounts of alcohol intake were relatively stable over the 22-year follow-up period, consistent with our prior report on the larger RBS cohort [39]. In secondary analyses, we excluded the few participants from non-drinking, light-drinking and moderate-drinking groups who had a history of heavier drinking to determine whether this may have masked any protective associations of light or moderate drinking on brain-PAD, but results were unchanged.

Limitations of our study include the relatively small sample size and homogeneity of the cohort with regard to race/ethnicity and socioeconomic status. Participants were white, and middle to upper class. While this limits confounding due to differences in these measures, results may not generalize to other populations. Although we observed no differences in associations between men and women, this must be viewed with caution given our relatively small sample size with few women in the heavy drinking group. As is common for epidemiological studies, alcohol was assessed via self-report and therefore may be susceptible to social acceptability bias. We also did not take into account binge drinking, which may have affected results, and is an important variable to consider in future studies. It is also important to note the correlational nature of this cross-sectional study. Although chronic heavy alcohol use and extreme levels of alcohol intake causes neuronal injury [11], and thus there is biological plausibility for a causal role of heavy drinking on accelerated brain aging, the association may not necessarily reflect an adverse effect of alcohol. Recent results from a Mendelian Randomization study in UK Biobank participants found no evidence for a causal association between higher alcohol use and advanced brain aging, but reported suggestive evidence of reverse causation, because the genetic instrument was more closely related to brain volume than to alcohol use [29]. It is also possible that uncontrolled confounding variables, including comorbidities that were not measured or included, may underlie the observed association of heavier alcohol use with older-appearing brain structure.

Our study adds to the literature by focusing on a cohort of community-dwelling older adults, the majority of whom (88%) were aged 70 or older. Given the growing prevalence of alcohol use among older adults it is important to understand the associations of alcohol use with brain health specifically in this population. Our results may be reassuring in showing that among generally healthy older adults, drinking in moderation (equivalent of up to 2 drinks per day) is not associated with evidence of accelerated brain aging. However, our results may be of concern for the estimated 23% of older adults who consume alcohol at heavier levels [2], who may be at risk for greater age-related neurodegeneration.

In summary, among this sample of healthy older adults, consuming alcohol above recommended guidelines of no more than two alcoholic drinks per day (equivalent to >14 drinks per week) was associated with a biomarker of advanced brain aging. Drinking within recommended guidelines was not associated with premature brain aging, but nor was it associated with slower brain aging. Thus, this study did not find evidence that light or moderate alcohol use is protective against age-related changes in brain structure.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

## Data Sharing Statement

Data from the Rancho Bernardo Study of Healthy Aging is available at https://knit.ucsd.edu/ranchobernardostudy/.

Imaging data is available via request to the corresponding author.

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**What is the primary question addressed by this study?**

Is light to moderate alcohol use associated with biomarker of slower brain aging among older community dwelling adults?

**What is the main finding of this study?**

Heavier drinkers, those drinking more than 2 drinks per day, showed older than expected predicted brain age; those drinking less did not show younger than expected predicted brain age relative to non-drinkers.

**What is the meaning of the finding?**

Light and moderate alcohol use does not appear to be protective against age-related structural changes in the brain, but heavier alcohol use is associated with evidence of greater neurodegeneration with age.

**Figure 1.**
Estimated marginal means of brain-predicted age difference (Brain-PAD) by alcohol group, adjusting for sex, education, smoking, physical activity, marital status, cognitive function, and depressed mood. Brain-PAD is calculated as brain-predicted age minus chronological age; thus higher Brain-PAD indicates older-appearing brain. Error bars represent 95% confidence intervals. Only heavier drinkers differed significantly from the light drinker reference group.

**Figure 2.**
Estimated marginal means of brain-predicted age difference (Brain-PAD) by alcohol group, adjusting for sex, education, smoking, physical activity, marital status, cognitive function, and depressed mood, with non-drinkers separated into former drinkers, never drinkers and occasional (less than weekly) drinkers. Error bars represent the 95% confidence intervals. Only heavier drinkers differed significantly from the light drinker reference group
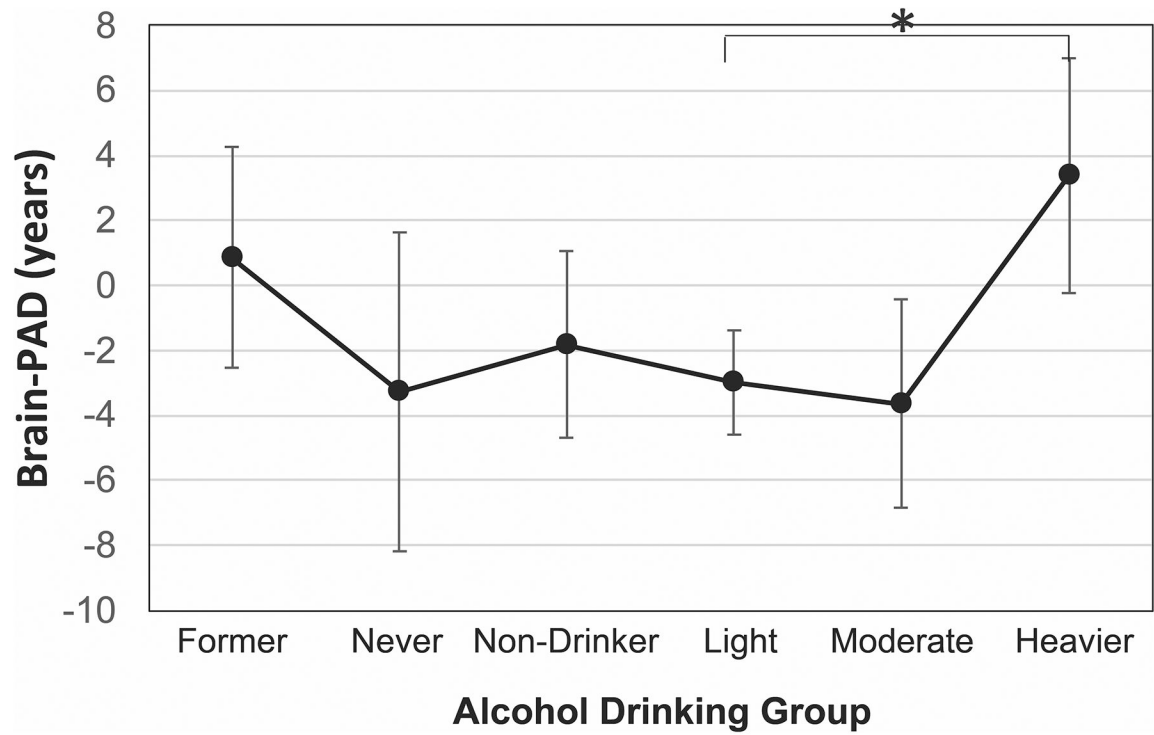
**Table 1:**

Participant characteristics by drinking group. Values are n (%) unless otherwise indicated.

| | Non-Drinker N=50 (30.7%) | Light N=77 (47.2%) | Moderate N=20 (12.3%) | Heavier N=16 (9.8%) | Statistic |
|---|---|---|---|---|---|
| Gender | | | | | $\chi^2(3)= 6.23$; p=0.10 |
| Men | 19 (38.0) | 28 (36.4) | 7 (35) | 11 (68.8) | |
| Women | 31 (62.0) | 49 (63.6) | 13 (65) | 5 (31.3) | |
| Age, mean (SD) | 77.7 (6.4) | 77.0 (7.9) | 76.5 (8.4) | 71.8 (8.3) | $F(3,159)=2.76$; p=0.05 |
| Education (years) | | | | | Fisher Exact test p=0.18 |
| 12 | 9 (18.0) | 15 (19.5) | 2 (10.0) | 5 (31.3) | |
| 13–15 | 17 (34.0) | 27 (35.1) | 3 (15.0) | 2 (12.5) | |
| 16 | 19 (38.0) | 21 (27.3) | 12 (60.0) | 6 (37.5) | |
| 17 | 5 (10.0) | 14 (18.2) | 3 (15.0) | 3 (18.8) | |
| Married | 35 (70) | 60 (77.9) | 14 (70.0) | 15 (93.8) | $\chi^2(3)= 4.31$; p=0.23 |
| Ever Smoker | 14 (28.0) | 32 (41.6) | 13 (65.0) | 11 (68.8) | $\chi^2(3)=12.94$; p=0.01 |
| Physically Active | 31 (62.0) | 57 (74.0) | 17 (85.0) | 14 (87.5) | $\chi^2(3)=6.28$; p=0.10 |
| BMI, mean (SD) | 26.8 (4.9) | 25.9 (3.6) | 24.7 (3.4) | 27.0 (3.9) | $F(3,156)=1.53$; p=0.21 |
| Hypertension | 30 (60.0) | 46 (59.7) | 11 (55.0) | 10 (62.5) | $\chi^2(3)=0.10$; p=0.98 |
| Diabetes | 12 (24.0) | 26 (33.8) | 2 (10.0) | 5 (31.3) | $\chi^2(3)= 5.0$; p = 0.17 |
| Comorbidities | | | | | $\chi^2(6)=8.10$; p=0.23 |
| 0 | 9 (18.0) | 11 (14.3) | 8 (40.0) | 4 (25.0) | |
| 1 | 13 (26.0) | 27 (35.1) | 5 (25.0) | 5 (31.3) | |
| >1 | 28 (56.0) | 39 (50.6) | 7 (35.0) | 7 (43.8) | |
| 3MS, mean (SD) | 93.8 (5.4) | 95.4 (3.6) | 96.6 (2.2) | 94.5 (3.8) | $F(3,159) = 2.68$; p =0.05 |
| BDI, mean (SD) | 4.9 (4.1) | 4.3 (3.8) | 4.3 (3.5) | 3.1 (3.7) | $F(3,157) = 0.95$; p =0.42 |
| Brain-PAD | −1.5 (6.2) | −3.0 (7.3) | −2.6 (7.4) | 3.4 (7.8) | |

BMI = body mass index; Brain-PAD = brain predicted age difference; calculated by subtracting chronological age from predicted age from chronological age; higher values indicated older than expected predicted brain age.

**Table 2.**

Comparison of brain-PAD by alcohol group. For post-hoc comparisons values are mean difference, in years, between light drinkers and other drinking groups, 95% confidence intervals.

| Model | Statistic | Post-Hoc Comparison Relative to Light Drinkers | | |
|---|---|---|---|---|
| | | Non-Drinker | Moderate Drinker | Heavier Drinker |
| A. Minimally Adjusted | F(3,158)=3.28; p=0.023 | −1.43 (−3.94 – 1.10) | −0.40 (−3.88 – 3.08) | −6.07 (−9.95 – −2.19)[*] |
| B. Confounder Adjusted | F(3, 150)=4.02; p=0.009 | −1.85 (−4.45 – 0.74) | 0.70 (−2.87 – 4.28) | −6.37 (−10.33 – −2.42)[*] |
| C. Mediator-Adjusted | F(3,141)=3.7; p=0 .014 | −1.50 (−4.11 – 1.11) | −0.34 (−4.00 – 3.31) | −6.40 (−10.29 – −2.51)[*] |
| D. Excluding prior heavy drinking | F(3, 139) = 3.42; p=.019 | −1.62 (−4.28 – 1.05) | −0.05 (−4.38 – 4.29) | −6.29 (−10.30 – −2.28)[*] |

Model A: adjusted for sex; Model B: Model A + education, marital status, physical activity, smoking, cognitive function and depressed mood. Model C: Model B+ BMI, diabetes, hypertension, and number of comorbidities. Model D: Model B, excluding individuals from light, moderate and non-drinker groups who had a history of heavier drinking.

[*] Bonferroni corrected p value < .01; all other comparisons non-significant at Bonferroni corrected p-values > 0.05.

**Table 3:**

Participant characteristics among non-drinking subgroups. Values are n (%) unless otherwise indicated.

| | Never Drinker n=9 | Former Drinker n=17 | Occasional Drinker N=24 | Statistic* |
|---|---|---|---|---|
| Gender | | | | $\chi^2(2)= 1.55$; p=0.46 |
| Men | 4 (44.4) | 8 (47.1) | 7 (29.2) | |
| Women | 5 (55.6) | 9 (52.9) | 17 (70.8) | |
| Age, mean (SD) | 79.7 (6.5) | 79.1 (7.6) | 76.0 (5.0) | $F(2,47)=1.73$; p=0.19 |
| Education (years) | | | | Fisher Exact test p=0.20 |
| 12 | 1 (11.1) | 5 (29.4) | 3 (12.5) | |
| 13–15 | 3 (33.3) | 3 (17.6) | 11 (45.8) | |
| 16 | 3 (33.3) | 8 (47.1) | 8 (33.3) | |
| 17 | 2 (22.2) | 1 (5.9) | 2 (8.3) | |
| Married | 9 (100.0) | 16 (94.1) | 21 (87.5) | $\chi^2(2)= 1.55$; p=0.46 |
| Ever Smoker | 1 (11.1) | 6 (35.3) | 7 (29.2) | $\chi^2(2)= 1.74$; p=0.42 |
| Physically Active | 6 (66.7) | 9 (52.9) | 16 (66.7) | $\chi^2(2)= 0.90$; p=0.64 |
| BMI, mean (SD) | 25.5 (6.2) | 27.0 (4.7) | 27.1 (4.6) | $F(2,46)=0.32$; p=0.71 |
| Hypertension | 0 (0.0) | 9 (52.9) | 12 (50.0) | $\chi^2(2)= 7.14$; p=0.03 |
| Diabetes | 3 (33.3) | 3 (17.6) | 6 (25.0) | $\chi^2(2)= 0.82$; p=0.66 |
| 3MS, mean (SD) | 89.3 (9.3) | 94.7 (4.2) | 94.9 (3.2) | $F(2,47)=4.24$; p=0.02 |
| BDI, mean (SD) | 3.4 (3.1) | 5.4 (4.1) | 5.2 (4.4) | $F(2,47)=0.74$; p=0.48 |
| Comorbidities | | | | Fisher Exact Test p=0.03 |
| 0 | 0 (0.0) | 2 (22.2) | 7 (29.2) | |
| 1 | 0 (0.0) | 6 (46.2) | 7 (29.2) | |
| >1 | 9 (100) | 9 (32.1) | 10 (41.7) | |
| Brain-PAD | −4.50 (5.70) | 0.66 (5.83) | −1.98 (6.20) | |

BMI = body mass index; Brain-PAD = brain predicted age difference; calculated by subtracting chronological age from predicted age from chronological age; higher values indicated older than expected predicted brain age.