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Alcohol Consumption, Brain Amyloid- β Deposition, and Brain Structural Integrity Among Older Adults Free of Dementia

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Abstract

Background: Light to moderate alcohol consumption has been variably associated with lower or higher risk of dementia, but effects on Alzheimer's disease pathology are less clear.

Objective: We determined whether late-life alcohol consumption was associated with Alzheimer's disease pathology among older adults.

Methods: We assessed the associations of alcohol consumption self-reported in 2000–2002 with brain amyloid- β deposition on PET scans, and white matter lesion and hippocampal volume on MRIs measured 7–9 years later in 189 participants of the Ginkgo Evaluation of Memory Study (age 75–87 years at baseline) who were free of clinical dementia, using multivariable-adjusted and inverse probability-weighted robust linear regression models.

Results: Alcohol consumption was not statistically significantly associated with amyloid- β deposition (standardized uptake value ratio difference per drink: -0.013 [95% CI: $-0.027, 0.002$]).

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SUPPLEMENTARY MATERIAL

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Both non-drinkers and participants consuming 1 drink(s)/week had higher white matter lesion volume (% intracranial volume) than did the reference group of those consuming <1 drink/week (differences: 0.25 % [95%CI: 0.01, 0.50]; 0.26 % [95%CI: 0.02, 0.50]). The association of alcohol consumption and hippocampal volume was modified by age ($p = 0.02$). Among participants younger than 77 years, participants consuming 1–7 drinks/week had larger hippocampal volume compared with participants consuming <1 drink/week.

Conclusions: Alcohol consumption was not statistically significantly associated with amyloid- β deposition 7–9 years later. Non-drinking and greater alcohol consumption were associated with higher white matter lesion volume compared with drinking <1 drink/week. Moderate drinking was associated with higher hippocampal volume in younger individuals. Given the selective nature of this population and adverse health effects of excessive alcohol consumption, these findings warrant further investigation, but cannot be translated into clinical recommendations.

Keywords

Alcohol; brain amyloid- β ; epidemiology; hippocampal volume; white matter lesions

INTRODUCTION

Alzheimer's disease (AD) is the fifth leading cause of mortality in Americans aged 65 years or older [1]. In 2018, an estimated 50 million people were living with AD and other dementias, and by 2030, this number is expected to increase to 82 million [2]. Given the high prevalence of dementia, the identification of modifiable risk factors or factors that prevent or delay the onset of dementia is of great value.

Alcohol is a globally consumed beverage [3] and light-to-moderate alcohol consumption, defined as up to one drink per day for women and up to two drinks per day for men, tends to be associated with lower risk of cardiovascular disease [4], a major risk factor for dementia [5]. On the other hand, excessive alcohol consumption cost the U.S. an estimated \$250 billion in 2010, with the majority of estimated costs attributable to binge drinking, defined as four drinks or more per occasion for women and five drinks or more per occasion for men [6]. Furthermore, chronic heavy alcohol consumption, defined as eight drinks or more per week for women and 15 drinks or more for men, is an established risk factor for a number of neurological complications, including Wernicke's encephalopathy, Korsakoff's syndrome, and alcohol-related dementia [7, 8]. However, the effects of light-to-moderate alcohol intake on the brain are less clear [9–11].

Some studies have suggested that alcohol consumption even in moderate amounts has been linked to adverse brain outcomes including lower hippocampal volume, lower grey matter density, and lower white matter integrity [12–14]. In contrast, other studies have found potentially beneficial associations of light-to-moderate alcohol intake with brain structural integrity and function [14–17]. Little is known about the association of moderate alcohol consumption and brain amyloid- β deposition. Analysis of autopsy cohorts have revealed no difference in brain amyloid- β aggregation comparing individuals with alcohol abuse to non-drinkers [18]. Thus, the association of light-to-moderate alcohol consumption and brain

structural integrity remains uncertain, as are the role of potential modifiers of this association such as apolipoprotein E (*APOE*) genotype [16].

Given the widespread use of alcohol, which is frequent even into older age, the clear risks and costs of its overuse, and the uncertain balance of risks and benefits of moderate use, the urgent need for investigations relating moderate alcohol intake to brain structural integrity is unmistakable. Improved understanding of the intimate relationship between light-to-moderate alcohol consumption and brain imaging biomarkers is ultimately expected to point toward new modifiable behavioral strategies for the prevention of neurodegeneration. Therefore, we investigated the associations of alcohol consumption with brain amyloid- β deposition assessed by PET scans, and hippocampal volume, and white matter lesions detected on magnetic resonance imaging (MRI) in participants of the Ginkgo Evaluation of Memory (GEM) imaging study who remained dementia-free throughout the trial. We hypothesize that light-to-moderate late life alcohol intake is associated with lower amyloid- β deposition, lower white matter lesion volume, and higher hippocampal volume.

MATERIALS AND METHODS

Study population and design

The GEM Study was a multi-center, placebo-controlled, randomized double-blind clinical trial ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00010803) Identifier: [NCT00010803](https://clinicaltrials.gov/ct2/show/study/NCT00010803)), conducted from 2000 to 2008, evaluating the effect of *Ginkgo biloba* for the prevention of dementia in 3,069 older adults [19, 20]. Primary exclusion criteria for GEM were dementia, abnormal laboratory values, and disabling medical conditions. Recruitment strategies were community-based and approaches to recruitment utilized mailing lists, on-site visits at retirement centers, nursing homes, churches, community centers, and health fairs, newspaper ads, radio, television, magazines, posters, and press releases [20].

The present study included a subsample of 197 participants (of the GEM Study from the Pittsburgh, Pennsylvania site) who were free of clinical dementia at study closure (2008) and underwent PET scans for amyloid- β deposition and magnetic resonance imaging in 2009, approximately 10 ± 3 months after GEM closeout. Study participants and their proxies provided written informed consent. The Institutional Review Board of the University of Pittsburgh, Pennsylvania approved the study. Entry criteria for the GEM study excluded individuals who would be unable, in the judgement of study staff, to complete the trial, including those with a known history of excessive alcohol use. We excluded three participants for technical problems with positron emission tomography (PET) imaging, three participants with dementia diagnosis between 2008 and imaging and two participants with no information on alcohol consumption, leaving 189 participants of the initial GEM imaging study in the final analysis.

Alcohol consumption

Participants reported frequency of beer, wine, and liquor consumption per week, and they also reported the usual number of 12-ounce cans/bottles of beer, 6-ounce glasses of wine, and shots of liquor consumed on each occasion at the baseline visit (2000–2002).

Participants were categorized according to their weekly alcohol consumption as follows: non-drinker, less than 1 drink/week, 1 to seven drinks/week, more than seven to 14 drinks/week, and more than 14 drinks/week. We were unable to separate former drinkers and lifelong abstainers included in the non-drinker category. Thus, participants consuming less than 1 drink/week were set as the reference group, as suggested by Shaper et al. [21].

Neuroimaging

Neuroradiologists quantified amyloid- β deposition on PET scans, and hippocampal and white matter lesion volume on brain MRI scans as described previously [22]. We used the ratio of the averaged Pittsburgh Compound B (PiB) retention per voxel in 5 bilateral brain regions-of-interest (anterior cingulate gyrus, frontal cortex, lateral temporal cortex, parietal cortex, and precuneus cortex) to the PiB retention per voxel in the cerebellum reference region, the standardized uptake value ratio (SUVR) as a continuous measure of brain amyloid- β deposition.

Hippocampal and white matter lesion volume were quantified on brain MRI scans using automatic segmentation software (FMRIB's Automated Segmentation Tool, University of Oxford) [23] as previously described [24]. We used continuous measures of hippocampal and white matter lesion volume (as a percentage of intracranial volume; $ICV \times 100$). MRIs were obtained on a 1.5-T scanner (GE Health-care, Waukesha, WI) and standard head coil, with fluid-attenuated inversion recovery and 5 ms echo time and 25 ms repetition time. A T1-weighted volumetric spoiled gradient recalled (SPGR) sequence was obtained (0.937×0.937 mm) in sagittal (slice thickness = 1.2 mm/0 mm interslice) or coronal plane (slice thickness = 1.5 mm/0 mm interslice). Voxel-based brain morphometry was performed with the sagittal SPGR MRI acquisition protocol. White matter volumes were quantified with automatic segmentation software (FMRIB's Automated Segmentation Tool [23], University of Oxford) using T1 weighted images in native anatomical space [24]. The T2-weighted fluid-attenuated inversion recovery images were used to quantify white matter lesion volume using a fuzzy-connectedness algorithm. Intracranial volume was computed with an advanced option (- A) of the Brain Extraction Tool. An atlas-based automated labeling pathway segmentation technique was applied to compute hippocampal volumes using a fully deformable registration procedure to assess preselected regions of interest [25]. Anatomical regions of interest originated from the automated anatomical labeling atlas [26]. The Montreal Neurological Institute Colin 27 average reference brain was transformed to fit each individual's recorded image.

Other covariates

The median time between the screening and baseline visits was 22 days (Q5, Q95; 9, 68 days). At the screening visit, trained technicians assessed age, sex, years of education, and race/ethnicity. Participants self-reported information on smoking status and the frequency of walking for exercise or pleasure at the baseline examination. Trained technicians measured body weight, height, and blood pressure and assessed history of heart disease (heart attack, angina pectoris, stroke, transient ischemic attack, heart failure, atrial fibrillation, deep vein thrombosis, coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker implant, and defibrillator implant) and diabetes in interviews. We coded missing

information of history of diabetes in two participants as no history of diabetes. Participants brought all prescribed medications and over-the-counter drugs to the clinic visit. The Center for Epidemiologic Studies-Depression Scale was used to assess depression. The degree of social interaction was quantified based on information obtained on how often participants engaged in playing cards and visiting with others (in other's homes or their own). We categorized social activity as not active (never/<1 time/month), somewhat active (1–3 times/month), and socially active (≥1 times/week). We pre-specified social interaction as a potential confounder because both higher and lower degrees of social integration have been related to greater alcohol consumption [27].

Participants underwent phlebotomy at the screening visit. Assessments included Apolipoprotein E (*APOE*) genotyping at the University of Pittsburgh from isolated DNA. Frozen plasma samples, stored at the GEM study blood repository at the National Cell Repository for Alzheimer's Disease and Related Dementias (NCRAD) at Indiana University, Indiana, were shipped on dry ice to the lipid laboratory of the Harvard T. H. Chan School, Boston, Massachusetts of Public Health for measurements of apoA-I in whole plasma using sandwich ELISA (Academy Biomedical Company Inc, Houston, Texas).

MCI was diagnosed when participants scored ≥10th percentile for age and education on at least two tests of the neuropsychological battery (using the Cardiovascular Health Study population as a reference population) and when participants had a Clinical Dementia Rating global score of 0.5. The neuropsychological battery of 10 cognitive tests covered the following domains: memory, construction, language, attention/psychomotor speed, executive function, and premorbid intellectual functioning [28, 29].

Statistical analysis

Given the effects of alcohol on high-density lipoprotein (HDL) concentrations in experimental studies [30], we validated self-reported alcohol consumption by assessing the sex-adjusted correlation of apoA-I, the main protein component of HDL-cholesterol, with the number of drinks consumed per week, as described previously [31].

To account for selection bias because of attrition prior to brain imaging, we used inverse probability weighting. We fit a logistic regression model for being uncensored using the following covariates: age, sex, race/ethnicity (white, non-white), education (years), social activity (never/<1 time/month, 1–3 times/month, ≥1 times/week), frequency of walking for exercise or pleasure (never/<1 time/month, 1–3 times/month, ≥1 times/week), smoking status (never, former, and current smoker, missing), body mass index (kg/m²), lipid-lowering medication use (former, current, or never-use), history of cardiovascular disease, systolic blood pressure, antihypertensive medication use, history of diabetes, Center for Epidemiologic Studies-Depression Scale (continuous), and treatment assignment (placebo, *Ginkgo biloba*). We assessed the associations of alcohol consumption self-reported in 2000–2002 with amyloid-β deposition, hippocampal volume, and white matter lesion volume measured 7–9 years later in robust linear regression models using stabilized inverse probability weights for the conditional probability of being uncensored. We initially adjusted for age, sex, and race/ethnicity (white, non-white). Subsequent analyses also controlled for education (years), social activity (never/<1 time/month, 1–3 times/month, ≥1 times/week),

frequency of walking for exercise or pleasure (never/<1 time/month, 1–3 times/month, 1 times/week), smoking status (never, former, and current smoker, missing), body mass index (kg/m^2), lipid-lowering medication use (former, current, or never-use), history of cardiovascular disease, systolic blood pressure, antihypertensive medication use, history of diabetes, Center for Epidemiologic Studies-Depression Scale (continuous) and treatment assignment (placebo, *Ginkgo biloba*). For plotting purposes, Kernel-weighted local polynomial smoothing (one degree of freedom, alternative Epanechnikov kernel, bandwidth 7 for amyloid- β deposition, bandwidth 4 for hippocampal volume, and white matter lesion volume) was performed among drinkers. In sensitivity analyses, we repeated the analysis without inverse probability weights. Additional adjustment for cerebellar PiB did not alter our findings on amyloid.

To test whether observed associations varied by age, sex, treatment assignment (placebo, *Ginkgo biloba*), or *APOE* $\epsilon 4$ carrier status (yes or no, excluding participants with missing information), their separate interaction terms were included as covariates. We performed stratified analyses in the event of statistically significant interaction. To test linear trends, we used alcohol consumption as a simple continuous variable, winsorizing all values >97.5 percentile to be set at the 97.5th percentile. All statistical tests were two-tailed and *p*-values below 0.05 were considered statistically significant.

We used the squared linear trend variable to test for quadratic trend. We performed all analyses using STATA version 12.1 (Stata Corp., College Station, TX).

RESULTS

Table 1 and Supplementary Table 1 show the characteristics of the GEM imaging study participants at baseline (age 75 to 87 years) and study closure based on usual alcohol consumption at baseline. Heavier alcohol consumption was less common among women. A total of 18 participants had MCI at baseline, primarily participants with the fewest alcoholic drinks per week. A total of 102 participants (54%) had high amyloid- β deposition and 32 participants were *APOE* $\epsilon 4$ carriers (all heterozygotes). Amyloid- β deposition was not significantly correlated with hippocampal volume (age-and sex-adjusted correlation coefficient, $r = -0.13$, $p = 0.09$) or white matter lesion volume ($r = -0.07$, $p = 0.39$), and hippocampal volume was not significantly correlated with white matter lesion volume ($r = 0.02$, $p = 0.83$).

Greater alcohol consumption was associated with higher apoA-I concentrations ($r = 0.25$, $p = 0.001$, $N = 187$) at baseline and neuroimaging assessment ($r = 0.21$, $p = 0.007$, $N = 174$) to the expected extent [32]. Table 2 and Supplementary Figure 1 demonstrate the association of alcohol consumption with neuroimaging parameters. Alcohol consumption was not statistically significantly associated with amyloid- β deposition in the brain in basic or fully adjusted models modeling alcohol intake as a continuous or categorical variable (*p* for linear trend = 0.09; difference in SUVR/drink: -0.013 [95% CI: -0.027 , 0.002]).

We did not observe a linear association between white matter lesion volume and alcohol intake, modelling alcohol as a continuous variable. Rather, the association of alcohol

consumption and white matter lesion volume was approximately V-shaped in basic and fully adjusted models, such that non-drinkers and combined participants consuming 1 or more drinks/week had statistically significantly higher white matter lesion volume than did the reference group of those consuming <1 drink/week (differences in white matter lesion volume: 0.25 % ICV [95% CI: 0.01, 0.50] and 0.26 % ICV [95% CI: 0.02, 0.50, respectively]).

Out of the three neuroimaging outcomes studied, we observed a tendency for effect modification only for the association of alcohol consumption with hippocampal volume by age (p for interaction = 0.02). Further stratification by median age showed that participants younger than 77 years consuming 1–7 drinks/week had statistically significantly higher hippocampal volume than similarly aged participants consuming less than 1 drink/week in fully adjusted models (Fig. 1), but not for ages over 77 years. The associations of alcohol consumption with amyloid- β deposition, white matter lesion volume, or hippocampal volume were not modified by sex, treatment assignment (placebo, *Ginkgo biloba*), or *APOE* genotype (all p for interaction > 0.05). Analyses without inverse probability weighting largely confirmed the main findings, albeit with narrower confidence intervals and a significant effect on amyloid- β (Supplementary Table 2).

DISCUSSION

In elderly participants without clinical dementia, late-life alcohol consumption had complex associations with findings on brain imaging. Amyloid- β deposition was not statistically significantly associated with alcohol consumption assessed 7–9 years earlier across the levels observed in this cohort. At the same time, non-drinking and greater alcohol consumption were associated with higher white matter lesion volume when compared with drinking less than 1 drink/week. Among participants aged less than 77 years, those consuming 1 to 7 drinks/week had statistically significantly higher hippocampal volume compared with participants consuming alcohol in amounts less than 1 drink per week.

To our knowledge, this is the first study assessing the association of light-to-moderate alcohol consumption and amyloid- β deposition quantified on PET scans in humans. Aho et al. found no difference in the amount of amyloid- β deposited in postmortem brain samples between 54 heavy drinkers and 54 age- and gender-matched non-drinkers compared with light-to-moderate drinkers [18]. However, the study might not have been sufficiently powered to detect difference in amyloid- β deposition. Similarly, we found that alcohol intake was not associated with amyloid- β deposition in the brain. In contrast, evidence from *in vitro* experiments suggested that alcohol prevented the formation of amyloid- β dimers [33]. If alcohol inhibited amyloid- β accumulation in the brain, higher amyloid- β levels could be transported out of the nervous system. In support of this concept, in a small study of 35 individuals aged 62 years or older, greater alcohol intake was associated with higher amyloid- β_{1-40} in the circulation [34]. Given the selective nature of this study population and the adverse health effects of excessive alcohol consumption, further studies of alcohol consumption in relation to circulatory and cerebral amyloid- β concentrations and tau pathology are required to clarify the role of alcohol intake in AD pathology and its possible mechanisms.

Previous studies on moderate alcohol consumption and markers of brain structural integrity were mainly cross-sectional and yielded inconsistent results. Four studies showed no association between alcohol consumption and the extent of white matter lesions [13, 15, 35, 36]. Some evidence suggested higher white matter lesion volume and less white matter integrity with increasing alcohol consumption [12, 37]. We found a U-shaped association between alcohol intake and the extent of white matter lesions, indicating that low levels of alcohol are associated with less leukoaraiosis than are non-drinking or moderate-heavy drinking. Our results were in general agreement with the Rotterdam Study and the Cardiovascular Health Study (CHS) where both studies found a U-shaped association between alcohol intake and the extent of white matter lesions [14, 16]. However, the Rotterdam Study and CHS found the lowest white matter lesion volume among the moderate drinkers, whereas light-drinkers had the lowest white matter lesion volume in the GEM imaging subset. The younger age distributions of the Rotterdam Study and CHS could explain the difference. Aging might increase the susceptibility of detrimental effects for low-to-moderate amounts of alcohol. Moreover, alcohol intake declines with age. If white matter lesion volume was determined by life-long alcohol consumption, the nadir of the U-shaped pattern could be expected to shift toward lower amounts of alcohol among older individuals. Indeed, in men, lifetime alcohol intake has been shown to be more closely related to white matter density than current alcohol intake [38].

The association of alcohol consumption and hippocampal volume has been studied to a lesser extent. Similar to our findings of higher hippocampal volume in moderate drinkers compared with light drinkers, moderate late-life alcohol consumption was related to higher hippocampal volume in the Framingham Heart Study Offspring Cohort [39]. These findings provide some reassurance that drinking within recommended limits is not associated with lower hippocampal volume. In contrast, in the Whitehall II Imaging sub-study, greater alcohol consumption was associated with higher odds of hippocampal atrophy late in life [12] but was unrelated to hippocampal volume in the Personality & Total Health Through Life Project [40]. Demyelination and reductions in axonal integrity and dendritic processes have been suggested as mechanisms linking heavy alcohol consumption to higher white matter lesion volume and lower hippocampal volume [41–43]. Experimental animal studies suggest that moderate alcohol intake induces neurogenesis and cell proliferation in the hippocampus compared with abstinence. The latter effect might preserve hippocampal volume [44]. Prospective studies with repeated measures of brain volume and particularly hippocampal volume are clearly needed to clarify these inconsistencies.

The strength of this study is the detailed assessment of clinical information using standardized protocols among elderly participants without dementia. We used a statistical parametric mapping software to estimate intracranial volume, which has shown good accuracy compared to manual segmentation [45]. However, there were some limitations. The nature of this sample of elderly individuals limits the generalizability to populations aged less than 75 years. We used inverse probability weighting to account for the fact that our analysis was limited to dementia-free survivors and to maximize applicability of our findings to the original GEM cohort. We were unable to study the risks associated with heavy drinking. Given our finding that alcohol intake within recommended limits was associated with higher white matter lesion volume and the lack of clear evidence of safety for amyloid-

β deposition and hippocampal volume, further research is necessary to clarify these associations. Further prospective studies are warranted to investigate the association of lifetime alcohol consumption with repeated neuroimaging biomarkers in populations with different racial and ethnic composition and different educational backgrounds. Given our current results, study of the association of moderate alcohol intake with other neuroimaging biomarkers, including such as gray matter volume and density, is warranted. Only few studies have assessed if the association of alcohol intake with neuroimaging biomarkers differs by *APOE* genotype. One study found similar associations between alcohol intake and brain imaging biomarkers among participants with and without the *APOE* $\epsilon 4$ allele [16]. Den Heijer et al. reported an inverse association between alcohol consumption and hippocampal volume among persons with the *APOE* $\epsilon 4$ allele [14]. Although we did not find evidence for effect modification by *APOE* genotype, the sample size of our study was too small to draw firm conclusions about interactions by *APOE* genotype. In addition, our analysis was limited to self-reported alcohol consumption, although we observed the expected association of alcohol intake with apoA-I values in the present analysis [46]. Alcohol increases apoA-I concentrations in experimental studies among humans that show that the concentration of apoA-I increased by 0.3 mg/dl per each additional gram increase in alcohol consumption [30]. The degree of correlation of apoA-I with the self-reported number of alcoholic drinks argues for the validity of the self-reported alcohol intake. Furthermore, we had no information on previous drinking habits and no information on neuroimaging biomarkers at the time of alcohol assessment with which to evaluate changes in neuroimaging biomarkers. Long-term cohort studies have shown that mid-life drinking habits showed a J- or U- shaped relation with mild cognitive impairment or dementia later in life [47, 48]. However, further studies on life-time drinking habits and the chronic and cumulative effects of alcohol consumption are warranted in populations with genetic susceptibility or comorbidity.

In conclusion, in elderly participants without clinical dementia, none of the drinking groups was consistently associated with an optimal brain imaging profile across the three outcomes studied. Late-life alcohol consumption was not statistically significantly associated with late-life amyloid- β deposition 7–9 years later. Non-drinking and greater alcohol consumption were both associated with higher white matter lesion volume compared with rare drinking. Among participants aged less than 77 years, participants consuming 1–7 drinks/week had statistically significantly higher hippocampal volume compared with participants consuming alcohol in amounts less than 1 drink per week. Given the selective nature of this study population that is likely enriched for individuals resilient for dementia and the adverse health effects of excessive alcohol consumption, these findings warrant further investigation and at present cannot be directly translated into clinical recommendations. Studies of modifiable risk factors that prevent or delay the onset of functional or structural brain alterations can be of value for dementia prevention trials or targeted public health prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Mean differences in hippocampal volume according to usual alcohol consumption. Mean differences in hippocampal volume (% intracranial volume $\times$ 100, error bars indicate 95% confidence intervals) in participants of the Ginkgo Evaluation of Memory Imaging study ($n = 169$) according to usual alcohol consumption stratified by median age (77 years). Mean differences were adjusted for sex, age, and race/ethnicity, education, social activity, frequency of walking for exercise or pleasure, smoking status, body mass index, lipid-lowering medication use, history of cardiovascular disease, systolic blood pressure, antihypertensive medication use, history of diabetes, Center for Epidemiologic Studies-Depression Scale, and treatment assignment.

Table 1
Baseline characteristics (2000–2002) of 189 participants of the GEM imaging study based on usual alcohol consumption

Characteristics ^a	Non-drinker	Weekly Number of Alcoholic Drinks			
		0.1–0.9	1.0–7.0	7.1–14.0	>14
No. of participants	72	26	49	24	18
Age, y	78 (75, 83)	79 (75, 84)	76 (75, 80)	77 (75, 84)	76 (75, 81)
Female, n (%)	36 (50)	12 (46)	18 (37)	10 (42)	2 (11)
Race, white, n (%)	68 (94)	25 (96)	49 (100)	23 (96)	18 (100)
Education, y	12 (10, 18)	14 (12, 18)	16 (12, 20)	16 (12, 19)	16 (12, 20)
Engagement in social activity					
Never or <1 time/month	5 (7)	2 (8)	3 (6)	2 (8)	0 (0)
1–3 times/month	26 (36)	8 (31)	17 (35)	11 (46)	8 (44)
1 times/week	41 (57)	16 (62)	29 (59)	11 (46)	10 (56)
Walking for exercise or pleasure					
Never or <1 time/month	13 (18)	2 (8)	8 (16)	2 (8)	2 (11)
1–3 times/month	7 (10)	3 (12)	2 (4)	6 (25)	4 (22)
1 times/week	52 (72)	21 (81)	39 (80)	16 (67)	12 (67)
Body mass index, kg/m ²	27 (20, 34)	27 (21, 35)	26 (22, 32)	27 (23, 31)	28 (23, 33)
Smoking status, n (%) ^b					
Never	41 (58)	9 (35)	16 (33)	8 (33)	4 (22)
Former	28 (39)	15 (58)	31 (65)	16 (67)	13 (72)
Current	2 (3)	2 (8)	1 (2)	0 (0)	1 (6)
History of cardiovascular disease, n (%)	18 (25)	5 (19)	13 (27)	10 (42)	3 (17)
Systolic blood pressure, mmHg	130 (107, 177)	134 (105, 159)	129 (107, 163)	136 (89, 159)	126 (91, 161)
Antihypertensive medication use, n (%)	34 (47)	9 (35)	23 (47)	12 (50)	6 (33)
Lipid-lowering medication use, n (%)	15 (21)	9 (35)	10 (20)	5 (21)	2 (11)
History of diabetes, n (%)	5 (7)	1 (4)	1 (2)	0 (0)	3 (17)
Depression score	2 (0, 11)	3 (0, 6)	1 (0, 11)	2 (0, 7)	2 (0, 7)
Mild cognitive impairment, n (%)	10 (14)	5 (19)	2 (4)	1 (4)	0 (0)
Randomized to <i>Ginkgo biloba</i> , n (%)	34 (47)	15 (58)	30 (61)	7 (29)	8 (44)
<i>APOE</i> ε4 allele carrier ^c , n (%)	12 (19)	4 (21)	11 (27)	3 (16)	2 (13)

Characteristics ^a	Weekly Number of Alcoholic Drinks				
	Non-drinker	0.1–0.9	1.0–7.0	7.1–14.0	>14
Neuroimaging in 2009					
Amyloid- β deposition, SUVR	1.7 (1.2, 2.7)	1.6 (1.3, 2.7)	1.6 (1.2, 2.5)	1.9 (1.3, 2.6)	1.4 (0.8, 2.6)
High amyloid- β deposition [SUVR 1.57], n (%)	42 (58)	13 (50)	26 (53)	16 (67)	5 (28)
ICV, d cm ³	1790 (1468, 2077)	1793 (1561, 2036)	1811 (1545, 2141)	1818 (1617, 2157)	1978 (1635, 2313)
White matter lesion volume, d mm ³	159 (47, 450)	120 (46, 266)	134 (45, 287)	132 (60, 385)	109 (31, 381)
Hippocampal volume, d cm ³	4.4 (3.6, 5.3)	4.5 (3.9, 5.6)	4.9 (3.7, 5.7)	4.6 (3.1, 6.0)	5.0 (3.8, 5.4)
White matter lesion volume, d % ICV $\times$ 100	0.9 (0.3, 2.5)	0.7 (0.2, 1.5)	0.7 (0.2, 1.6)	0.7 (0.3, 2.1)	0.6 (0.2, 1.9)
Hippocampal volume, d % ICV $\times$ 100	25 (20, 30)	26 (21, 29)	27 (22, 32)	25 (18, 33)	25 (21, 27)

APOE, Apolipoprotein E gene. ICV, intracranial volume. SUVR, standardized uptake value ratio.

^aData are expressed as median (Q5; Q95) unless otherwise indicated.

^bN = 187.

^cN = 158.

^dN = 169.

Table 2

Inverse probability weighted mean difference (95% CI) in amyloid- β deposition, hippocampal volume, and white matter lesion volume in 2009 according to usual alcohol consumption in 2000 to 2002 in 189 participants of the GEM imaging study

	Mean difference (95% CI) by weekly number of drinks					Continuous per drink	<i>p</i> for linear trend (quadratic) ^a
	Non-drinker	0.1–0.9	1.0–7.0	7.1–14.0	>14		
Amyloid-β deposition, SUVR, <i>n</i> = 189							
Basic model ^b	0.06 (–0.22, 0.34)	0	–0.07 (–0.35, 0.22)	0.18 (–0.15, 0.52)	–0.15 (–0.54, 0.24)	–0.005 (–0.021, 0.012)	0.58 (0.10)
Full model ^c	0.07 (–0.20, 0.34)	0	–0.13 (–0.40, 0.14)	0.03 (–0.28, 0.34)	–0.24 (–0.61, 0.12)	–0.013 (–0.027, 0.002)	0.09 (0.40)
White matter lesion volume, % ICV × 100, <i>n</i> = 169							
Basic model ^b	0.29 (0.03, 0.55)	0	0.20 (–0.11, 0.50)	0.29 (–0.04, 0.62)	0.30 (–0.14, 0.74)	0.01 (–0.01, 0.03)	0.37 (0.49)
Full model ^c	0.25 (0.01, 0.50)	0	0.20 (–0.10, 0.50)	0.32 (–0.03, 0.67)	0.31 (0.01, 0.62)	0.015 (–0.004, 0.034)	0.13 (0.27)
Hippocampal volume, %ICV × 100, <i>n</i> = 169							
Basic model ^b	–0.70 (–2.10, 0.70)	0	0.46 (–1.08, 2.01)	–1.44 (–3.81, 0.93)	–0.68 (–2.26, 0.90)	–0.07 (–0.19, 0.06)	0.32 (0.90)
Full model ^c	–0.57 (–2.06, 0.92)	0	0.58 (–1.15, 2.31)	–0.80 (–3.39, 1.78)	–0.24 (–2.20, 1.73)	–0.03 (–0.15, 0.10)	0.38 (0.96)

ICV, intracranial volume. SUVR, standardized uptake value ratio.

^a All values > 97.5 percentile set to the 97.5th percentile.

^b Adjusted for sex, age, and race/ethnicity.

^c Additionally adjusted for education, social activity, frequency of walking for exercise or pleasure, smoking status, body mass index, lipid-lowering medication use, history of cardiovascular disease, systolic blood pressure, antihypertensive medication use, history of diabetes, Center for Epidemiologic Studies-Depression Scale, and treatment arm assignment.