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Longitudinal alcohol-related brain changes in older adults: The Sydney Memory and Ageing Study

Louise Mewton[1] | Rachel Visontay[1] | Gerard Hughes[2] | Catherine Browning[2] | Wei Wen[2] | Anya Topiwala[3] | Brian Draper[2] | John D. Crawford[2] | Henry Brodaty[2] | Perminder S. Sachdev[2]

[1]The Matilda Centre for Mental Health and Substance Use, Faculty of Medicine and Health, University of Sydney, Sydney, Australia

[2]Centre for Healthy Brain Ageing, Faculty of Medicine and Health, University of New South Wales, Sydney, Australia

[3]Nuffield Department Population Health, Big Data Institute, University of Oxford, Oxford, UK

Correspondence
Louise Mewton, The Matilda Centre for Mental Health and Substance Use, Faculty of Medicine and Health, University of Sydney, Sydney, Australia.
Email: louise.mewton@sydney.edu.au

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Abstract

Increases in harmful drinking among older adults indicate the need for a more thorough understanding of the relationship between later-life alcohol use and brain health. The current study investigated the relationships between alcohol use and progressive grey and white matter changes in older adults using longitudinal data. A total of 530 participants (aged 70 to 90 years; 46.0% male) were included. Brain outcomes assessed over 6 years included total grey and white matter volume, as well as volume of the hippocampus, thalamus, amygdala, corpus callosum, orbitofrontal cortex and insula. White matter integrity was also investigated. Average alcohol use across the study period was the main exposure of interest. Past-year binge drinking and reduction in drinking from pre-baseline were additional exposures of interest. Within the context of low-level average drinking (averaging 11.7 g per day), higher average amount of alcohol consumed was associated with less atrophy in the left ($B = 7.50$, pFDR = 0.010) and right ($B = 5.98$, pFDR = 0.004) thalamus. Past-year binge-drinking was associated with poorer white matter integrity ($B = -0.013$, pFDR = 0.024). Consuming alcohol more heavily in the past was associated with greater atrophy in anterior ($B = -12.73$, pFDR = 0.048) and posterior ($B = -17.88$, pFDR = 0.004) callosal volumes over time. Across alcohol exposures and neuroimaging markers, no other relationships were statistically significant. Within the context of low-level drinking, very few relationships between alcohol use and brain macrostructure were identified. Meanwhile, heavier drinking was negatively associated with white matter integrity.

KEYWORDS
ageing, alcohol use, epidemiology, longitudinal neuroimaging, neurodegeneration

1 | INTRODUCTION

Globally, 1.34 billion people consume alcohol in harmful amounts, with alcohol use accounting for 1.78 million deaths in 2020.[1] Midlife alcohol use disorders have recently been identified as a key modifiable risk factor for all-cause dementia,[2] whereas midlife alcohol use in excess of national guidelines has been recognised as a critical target for dementia prevention efforts in the most recent report from the *Lancet Commission*

for Dementia Prevention, Intervention and Care.[3] The extent to which later-life alcohol use is associated with brain health, however, is contentious. Recent increases in the number of older adults consuming alcohol in harmful patterns,[4,5] as well as our ageing population, indicate that a more thorough understanding of the impact of later-life alcohol use on brain health should be a public health priority.

Although moderate alcohol use (≤3 drinks/day) in midlife have been positively associated with some indicators of brain health, such as larger white matter volume[6] and better white matter integrity,[7] other studies have demonstrated robust negative impacts of midlife alcohol use on brain outcomes. In the Whitehall II Study, for example, moderate alcohol use in middle age was associated with hippocampal atrophy and impaired white matter microstructure in the corpus callosum 30 years later.[8] Similarly, studies using large-scale data from the UK Biobank (ages 40–69 years) have indicated that alcohol use is negatively associated with global brain volume measures, regional grey matter volumes, white matter microstructure and functional connectivity in a dose–response relationship.[9–11] These findings are consistent with another recent cross-sectional study that showed that alcohol use in middle-aged adults (ages 39–45 years) was associated with smaller total brain volume in a dose–response manner.[12] Overall, alcohol use in midlife appears detrimental to brain health both in the short and long terms.

The evidence for the relationship between alcohol use and brain health in samples restricted to older adults (i.e., aged over 60 years) is more contradictory. Protective effects of alcohol use have been identified, including a dose–response relationship between alcohol use and larger grey matter volume in older adults[13] and older men specifically.[14,15] Moderate alcohol use (≤3 drinks/day) in later life has also been associated with larger grey matter volumes in subcortical brain regions, including the hippocampus and amygdala, as well as less severe white matter lesions and brain infarcts.[16–18] In contrast, negative dose–response relationships between alcohol use and white matter volume have been identified in older adults in the general population.[14,15] Later-life alcohol use has also been linearly associated with other indicators of brain atrophy, including larger lateral ventricles[14] and less volume in the corpus callosum.[19] Summarising the existing literature, it appears that in later life, alcohol use may be associated with larger grey matter volumes but impairments in white matter, although inconsistencies and null effects are common.

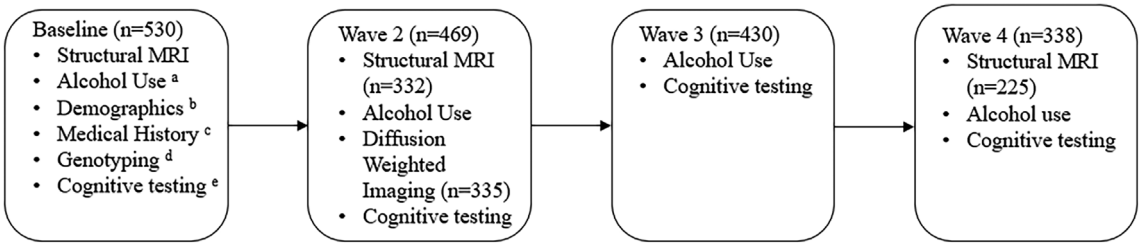
The inconsistencies in prior research investigating the relationship between alcohol use and brain health may be explained by the reliance on cross-sectional data. Cross-sectional designs are unable to properly investigate the directionality of effects, including the possibility that it is changes in brain health that are causing changes in alcohol use. A limited number of previous studies have been based on prospective data,[8,9,17] where alcohol use has been assessed some years prior to the neuroimaging assessment, thereby providing some evidence for directionality of effects. However, in analysing a single neuroimaging assessment per individual, these studies have still been limited in their ability to establish that alcohol use precedes changes in brain health, rather than brain changes preceding changes in alcohol use.

Using three waves of neuroimaging data (totalling 1087 scans) and four waves of alcohol use data prospectively collected over 6 years (Figure 1), the current study investigated the dose–response relationships between alcohol use and progressive grey and white matter changes in 530 non-demented older adults (aged 70–90 years at baseline).[20] Analyses were also conducted to examine whether there are any relationships between heavier (i.e., 'binge') drinking and progressive changes in brain health. Finally, analyses were conducted to examine whether reducing drinking from pre-baseline was associated with progressive changes in brain health in later life.

2 | METHOD

2.1 | Study design and participants

Participants were recruited as part of the Sydney MAS, a longitudinal study of community-dwelling individuals aged 70 to 90 years who were randomly recruited through the electoral roll from the Eastern Suburbs of Sydney, New South Wales.[20] The MAS began in 2005 with the primary objective of examining the clinical characteristics and prevalence of mild cognitive impairment and related syndromes in non-demented older Australians and determining the rate of change in cognitive function over time. Of the 8914 individuals who were invited, 1772 responded affirmatively to a letter of recruitment and were assessed for eligibility, of whom 1037 participants underwent baseline assessment. Those who participated in the study did not



[a] Measured by the Alcohol Use Disorder Identification Test (AUDIT)
[b] Age, sex, non-English speaking background status, years of education
[c] Smoking, hypertension, diabetes, stroke/TIA
[d] Apolipoprotein E carrier status
[e] Attention processing speed, executive functioning, language, visuospatial, verbal memory, and memory domains

FIGURE 1 Participant flow and summary of data used in the current study from the Sydney Memory and Ageing Study.

differ from those who did not participate in terms of age and sex (see Supporting Information for more details).

Inclusion criteria included the ability to speak and write in English. Exclusion criteria included a known diagnosis of dementia, a Mini-Mental State Examination (MMSE) score of <24 (age and education adjusted) or a diagnosis of dementia after comprehensive assessment. Other exclusion criteria included psychotic symptoms, a diagnosis of schizophrenia, bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy or any medical or psychological conditions that may have prevented a potential participant from completing assessments.

Of the 1037 participants in the study, 530 (51.1%) were included in the neuroimaging study. Figure 1 presents the participant flow through the study and data collection protocols. Data on sociodemographics, health and lifestyle (including alcohol use) were measured over a follow-up period of 6 years, at approximately 2-year intervals (four waves of data). Structural MRI (sMRI) was conducted at study baseline, Wave 2 and Wave 4 of the study (three waves of data) using similar acquisition parameters at each time point. Diffusion-weighted MRI (dMRI) was also conducted at Wave 2 and Wave 4 of the study (two waves of data) using different acquisition parameters. Given the loss to follow-up at Wave 4 and the use of different parameters that precluded the examination of longitudinal dMRI data, only Wave 2 dMRI data are reported here. Written, informed consent was obtained from all participants, and the study was approved by the University of New South Wales Human Ethics Review Committee (HC 05037, 09382, 1432).

2.2 | Outcomes

Based on previous studies[8–10,15,21] examining the alcohol–brain relationship, we focused on total grey matter volume and total white matter volume, as well as specific regions of interest (ROIs), namely, the hippocampus, thalamus, amygdala, corpus callosum, orbitofrontal cortex and insula. Outcomes related to white matter integrity were volume of deep and periventricular WMH, as well as whole brain difference in distribution functions (DDF as acquired via dMRI[22]) and peak skeletonised mean diffusivity (PSMD as acquired by dMRI[23]). As with previous studies using MAS data, WMH volume was log transformed to obtain a normal distribution. Within each wave, outliers (>3 standard deviations from the mean) in outcome measurements were winsorised. At baseline, 281 of the 530 scans were acquired using a Philips 3 T Intera Quasar scanner. The remaining baseline scans and all follow-up scans were acquired on a Philips 3 T Achieva Quasar Dual scanner. Further details on image acquisition and processing are included in the Supporting Information.

2.3 | Main exposure

The main exposure variable was average grams per day of ethanol, derived from past year AUDIT-C[24] quantity and frequency questions across all four waves of data, as derived previously using this cohort.[25]

2.4 | Additional exposures of interest

Analyses were also conducted to examine whether reporting of past-year binge drinking (6+ drinks/occasion as queried by the AUDIT-C; dichotomous yes/no) at baseline was associated with longitudinal brain outcomes. As an indicator of earlier life drinking, participants were also asked whether they had consumed alcohol more heavily in the past. Those who reported drinking more heavily in the past were compared with those who did not (dichotomous yes/no).

2.5 | Covariates

Covariates were entered into models sequentially beginning with a model controlling for baseline age, sex, age-by-sex interactions, scanner type and *z*-transformed intracranial volume, as well as alcohol use as the exposure of interest. Analyses were then conducted which additionally controlled for demographic and other clinical confounders, including non-English speaking background status, smoking (never/former/current), years of education, *APOE*ε4 status (determined via genotyping; ε4 carrier/non-carrier), hypertension (yes/no derived from blood pressure assessment in medical exam), diabetes (yes/no derived from self-reported medical history) and stroke/TIA (yes/no derived from self-reported medical history). Because of missing data on baseline predictors for the fully adjusted models, 27 individuals were excluded from these analyses ($n = 503$).

2.6 | Statistical analysis

Primary analyses were conducted within the R environment (v4.2.3), using packages gamm4, lme4 and mgcv.[26–28] Alcohol trends over the four waves were first examined using linear mixed models, which included a fixed effect for time and random intercept and slope terms for each participant.

For longitudinal analyses focusing on each brain outcome, preliminary model testing focused on whether average alcohol use and baseline age should be included as linear or non-linear terms (see Supporting Information for more details). There was no evidence of non-linear relationships between average grams of alcohol consumed per day and each of the brain outcomes of interest. Similarly, there was no evidence of non-linear relationships between baseline age and each of the outcomes of interest. As such, linear mixed models were implemented for longitudinal brain outcomes, which included linear terms for average alcohol use per day and baseline age. Models included a random intercept for each participant as well as a time by average alcohol use interaction term to examine the extent to which alcohol use explained change over time in brain outcomes. Given the structured assessment schedule implemented in Sydney MAS, time was parsimoniously modelled using a three-level variable representing assessment occasions when MRI data were collected (baseline, W2, W4). Covariates were included in separate models sequentially as

detailed above. The false discovery rate [p (FDR) < .05] was applied to correct for multiple comparisons for tests of each of the 10 brain outcomes. As dMRI data from Wave 2 only were analysed, these outcomes were modelled using linear regression, with linear terms for average alcohol use and baseline age, and covariates entered sequentially as above. The false discovery rate [p (FDR) < .05] was used to correct for multiple comparisons for tests of the two dMRI outcomes.

To further probe the directionality of effects, bivariate latent change score models were implemented for any brain outcome longitudinally associated with the continuous average alcohol use outcome. Figure S1 depicts an example of a bivariate model that captures the dynamic unfolding of alcohol use and brain structure over time (Supporting Information). The bivariate dual change score model includes aspects of autoregressive cross-lag models in that it captures associations between the variables across measurement occasions and extends this by including aspects of latent growth models that capture within-person change and between-person differences in change. Importantly, these models can test coupling effects that determine whether alcohol use leads to change in brain structure (i.e., alcohol use is the leading indicator of change), or brain structure leads to change in alcohol use (i.e., brain structure is the leading indicator of change). Latent change score models were conducted according to methodological precedents[29] using Mplus (v7.3). Missing data were handled using FIML estimation. Further details of this approach are included in the Supporting Information.

Separate analyses also investigated the relationships between each of the brain outcomes and (1) binge drinking and (2) heavier consumption of alcohol in the past. As with the continuous average alcohol use predictor, linear mixed models were implemented for longitudinal brain outcomes, which similarly included a random intercept for each participant as well as a time by alcohol use interaction to examine the extent to which each alcohol use exposure explained change over time in brain outcomes. Covariates were included in separate models sequentially as detailed above. The false discovery rate [p (FDR) < .05] was used to correct for multiple comparisons as above.

2.7 | Sensitivity analyses

Data were re-analysed with former drinkers excluded to examine the possibility of reverse causation (i.e., 'sick quitters' potentially driving relationships between alcohol use and brain health). Former drinkers were defined as those who indicated they were not current drinkers at baseline but had consumed alcohol in the past, as well as those who ceased drinking over the study period. Data were also re-analysed with those with incident dementia excluded to address the possibility of reverse causality for those in the prodromal phases of dementia who may reduce their alcohol use due to cognitive symptoms.

2.8 | Post hoc analyses

For any statistically significant relationships between alcohol use and volumetric ROIs, analyses were conducted to determine whether these relationships were specific to the right or left hemisphere (FDR corrected for tests of two outcomes). For the corpus callosum, analyses were conducted to determine whether relationships were specific to the posterior, mid-posterior, central, mid-anterior or anterior regions (FDR corrected for tests of five outcomes). To investigate cognitive outcomes, the relationships between alcohol use and cognitive domains (attention processing speed, executive functioning, language, visuospatial, verbal memory and memory domains) were investigated, as were the relationships between brain outcomes associated with alcohol use and cognitive function domains (FDR corrected for tests of six outcomes). Details on the assessment of cognitive function are included in the Supporting Information.

3 | RESULTS

Sample descriptives are included in Table 1. Average alcohol use across the study was 11.7 g per day (range: 0–75.6; SD = 14.3; Table 1), the equivalent of approximately one standard drink per day. Grams of alcohol consumed per day decreased over the study period at an average rate of 1.1 g over each wave of follow-up (95% CI: −1.5, −0.8; p < .001). Trends over time correlated negatively with baseline alcohol use (correlation between random intercept and slope = −0.7; 95% CI: −0.8, −0.6), such that those drinking more at baseline decreased their consumption at a faster rate.

TABLE 1 Alcohol use, demographic and clinical characteristics of participants in the Sydney Memory and Ageing Study (n = 530).

Alcohol exposure	
Mean (SD) Baseline alcohol use (g/day)	12.99 (16.86)
Mean (SD) Average alcohol use (g/day)	11.65 (14.32)
No. (%) Past year binge drinking (baseline)	109 (20.6)
No. (%) Reduction in drinking from pre-baseline (baseline)	273 (51.5)
Covariates	
Mean (SD) Baseline age (years)	78.4 (4.7)
No. (%) Men	244 (46.0)
No. (%) Non-English speaking background	77 (14.5)
No. (%) Never smoked	254 (48.0)
No. (%) Former smoker	258 (48.8)
No. (%) Current smoker	17 (3.2)
Mean (SD) Education (years)	11.6 (3.5)
No. (%) APOEe4 carrier	120 (23.0)
No. (%) Hypertension	429 (80.9)
No. (%) Diabetes	54 (10.2)
No. (%) Stroke	11 (2.1)

3.1 | Relationships between alcohol exposures and brain outcomes

The continuous alcohol exposure variable was associated with volume in the thalamus, such that higher average grams of alcohol consumed per day was associated with a smaller decrease in thalamus volume over time (Table 2 and Figure 2). This relationship was evident in both the left ($B = 7.50$, pFDR = .010) and the right ($B = 5.98$, pFDR = .004) thalamus. In the latent change score model, coupling effects across the four waves of alcohol use data and the three waves of thalamus data indicated that alcohol use was a leading (i.e., preceding) indicator of subsequent changes in thalamus volume ($B = 0.008$; $p = .034$). The opposite was not true; thalamus volume was not a leading indicator of subsequent changes in alcohol use ($B = 0.023$; $p = .990$). Given prior research indicating that the impact of alcohol use on thalamus volume is sex dependent,[10] a post hoc three-way interaction between alcohol use, time and sex was investigated. This interaction was not statistically significant ($B = -14.89$, $p = .170$). No other relationships between the continuous alcohol use exposure were statistically significant (Table 2).

Consuming alcohol more heavily in the past was associated with greater atrophy in the corpus callosum over the follow-up period (Table 2 and Figure 3). Exploratory analyses indicated that this relationship was only evident in anterior ($B = -12.73$, pFDR = .048) and

TABLE 2 Longitudinal relationships between alcohol use and change in brain outcomes in the Sydney Memory and Ageing Study ($n = 530$).

	Time * Average drinking (g/day)[a]	Time * Binge drinking	Time * Past drinking[a]
Total grey matter volume	$B = 48.58$ (51.12), $p = .570$	$B = 2590.88$ (1744.23), $p = .428$	$B = -1726.06$ (1429.15), $p = .760$
Total white matter volume	$B = 16.17$ (46.17), $p = .908$	$B = 1431.22$ (1574.37), $p = .607$	$B = 1226.87$ (1291.17), $p = .814$
Orbitofrontal cortex	$B = 0.62$ (3.24), $p = .942$	$B = -8.05$ (110.75), $p = .978$	$B = -33.37$ (90.84), $p = .939$
Insula	$B = -0.62$ (1.61), $p = .908$	$B = 34.82$ (55.15), $p = .728$	$B = -3.45$ (45.24), $p = .939$
Corpus callosum	$B = 1.04$ (0.49), $p = .400$	$B = 0.46$ (16.65), $p = .978$	$B = \mathbf{-41.21\ (13.54)}$, $p = \mathbf{.020}$
Hippocampus	$B = 0.06$ (1.37), $p = .964$	$B = 25.81$ (46.87), $p = .728$	$B = 3.08$ (38.36), $p = .939$
Thalamus	$B = \mathbf{13.36\ (4.24)}$, $p = \mathbf{.020}$	$B = 273.81$ (145.85), $p = .428$	$B = 239.64$ (119.64), $p = .230$
Amygdala	$B = 1.56$ (1.00), $p = .397$	$B = 53.25$ (34.27), $p = .428$	$B = -10.54$ (28.13), $p = .939$
Deep white matter lesions	$B = 0.0005$ (0.0005), $p = .570$	$B = 0.02$ (0.02), $p = .607$	$B = 0.004$ (0.01), $p = .939$
Periventricular white matter lesions	$B = 0.002$ (0.001), $p = .168$	$B = -0.01$ (0.01), $p = .428$	$B = 0.01$ (0.01), $p = .814$

Note: Binge drinking defined as drinking six or more drinks per occasion in the past 12 months. Past drinking compares those who reported drinking more heavily in the past to those who did not. Models corrected for baseline age, sex, age by sex interactions, scanner type and *z*-transformed intracranial volume.

[a]FDR adjusted *p*-value reported.

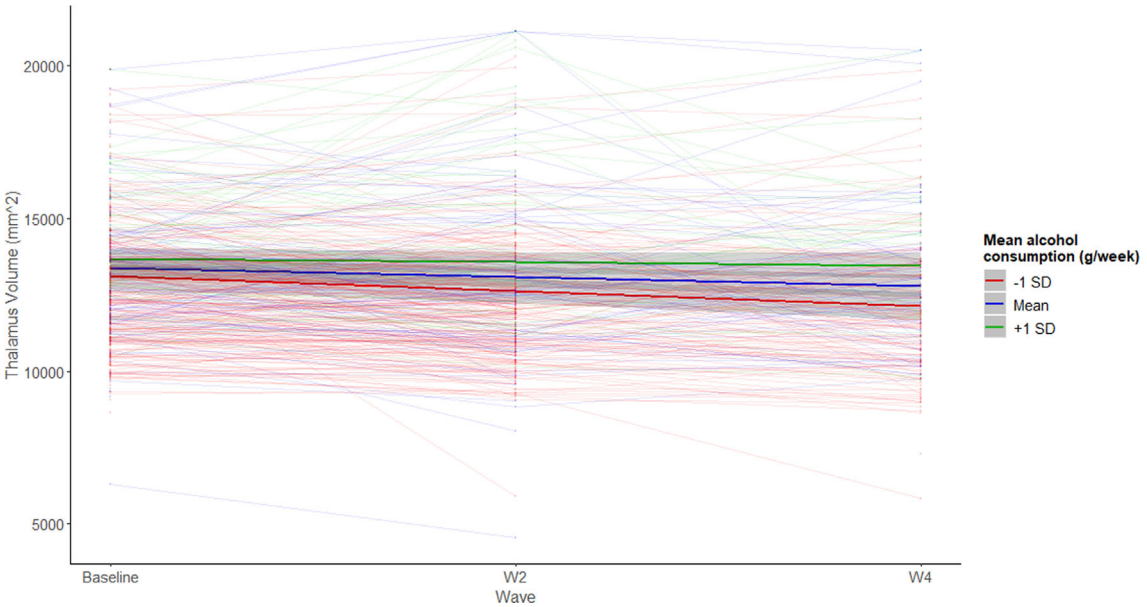


FIGURE 2 Longitudinal relationship between average grams/day and change in the thalamus volume over time. Note: Model predicted values plotted. Models corrected for baseline age, sex, scanner type and *z*-transformed intracranial volume.

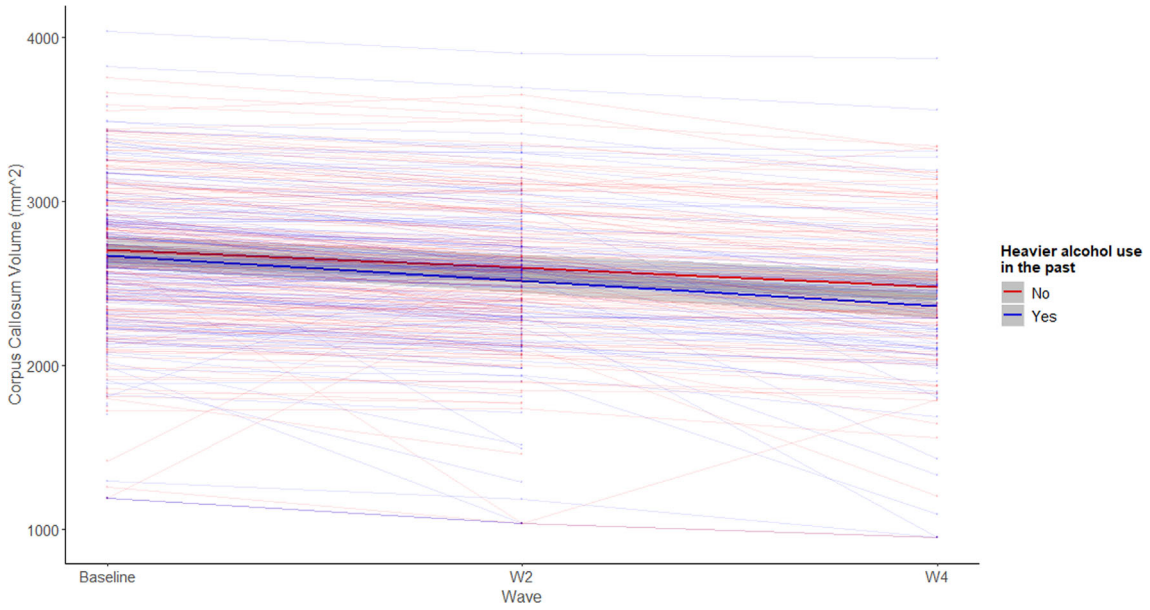


FIGURE 3 Longitudinal relationship between heavier alcohol use in the past and change in corpus callosum volume over time. Note: Model predicted values plotted. Models corrected for baseline age, sex, scanner type and *z*-transformed intracranial volume.

posterior ($B = -17.88$, pFDR = .004) callosal volumes. There were no statistically significant relationships between past-year binge drinking and change in each of the ROIs over time. Longitudinal relationships were robust to the inclusion of additional demographic covariates ($n = 503$; Table S2).

Wave 2 PSMD was not related to baseline grams of alcohol per day ($B = 0.0002$, $p = .416$), binge drinking ($B = 0.01$, $p = 0.271$) nor heavier drinking prior to baseline assessment ($B = 0.01$, $p = .176$). Wave 2 DDF was not related to baseline grams of alcohol per day ($B = -0.00002$, $p = .086$) nor heavier drinking prior to baseline assessment ($B = -0.004$, $p = .330$). Wave 2 DDF was related to binge drinking ($B = -0.013$, pFDR = .024) such that the presence of past-year binge drinking was related to poorer white matter integrity, although this relationship was no longer statistically significant when average grams of alcohol per day were additionally controlled for ($B = -0.01$, $p = .062$). The inclusion of additional demographic and clinical confounders did not alter these findings with respect to dMRI outcomes.

3.2 | Sensitivity analyses

When excluding former drinkers ($n = 461$) from the analysis, the longitudinal relationship between average alcohol consumed per day and the thalamus ($B = 12.56$, pFDR = 0.050) was no longer statistically significant, although the magnitude of change in the regression estimates was minimal. When those who were diagnosed with dementia over follow-up were excluded from the analysis ($n = 481$), the longitudinal relationship between heavier drinking prior to baseline assessment and the corpus callosum was no longer statistically significant in the reduced sample ($B = -36.19$, pFDR = .060), although the magnitude of change in the regression coefficients was minimal.

3.3 | Relationships with cognitive function

There were no statistically significant relationships between any of the alcohol use exposure variables at baseline and change in cognition over time. Thalamus volume at baseline was not associated with change over time in any area of cognitive function. Meanwhile, volume of the corpus callosum at baseline was associated with declines over time in both attention processing speed ($B = 0.0001$, pFDR < .001) and executive functioning ($B = 0.0001$, pFDR = .006).

4 | DISCUSSION

Within the context of this community sample of older adults, largely representative of low-to-moderate drinkers (averaging approximately one standard drink per day), the current study found that alcohol use does not appear to have consistent or robust impacts on brain outcomes over time. Higher average alcohol use was related to a slower decrease in bilateral thalamus volume over time in later life. Meanwhile, those who reported consuming alcohol more heavily in the past demonstrated a faster decrease in white matter volume in the anterior and posterior corpus callosum in later life. However, these relationships were not robust to the exclusion of former drinkers and those who developed dementia over the follow-up, respectively. When investigating a marker of problematic drinking, those who reported past-year binge drinking at baseline demonstrated poorer white matter integrity at Wave 2.

Although this study has many strengths, including longitudinal, multimodal neuroimaging and alcohol use assessment in a relatively large, well-characterised general population sample, some limitations need to be acknowledged. Given the lack of longitudinal neuroimaging

studies focusing on the alcohol–brain relationship, this study was not hypothesis driven. Future replication efforts could focus on characterising the alcohol–brain relationship using longitudinal neuroimaging data from large-scale consortia or Biobank samples when available. As a sample of older adults aged 70–90 years in the general population, survivor bias may be an issue. Alcohol use was self-reported, although this has been shown to be a pragmatic and reliable method for obtaining alcohol use data in large-scale general population samples.[30] Although we were able to include some indication of historical alcohol use, a full history of alcohol use in earlier life was not available. Finally, although we were able to investigate the impact of a wide range of demographic and clinical variables on the alcohol–brain relationship, other drug use was not assessed and therefore unable to be controlled for in the current study.

In contrast to the current study, heavy and dependent drinking (i.e., alcohol use disorder) is associated with neurological complications, including Wernicke's encephalopathy and Korsakoff's syndrome, as well as all-cause and alcohol-related dementia.[31] Reviews of the neuroimaging literature have identified accelerated ageing of selective brain structures among individuals with alcohol use disorder, most robustly in the frontal cortex and hippocampus, but also within parietal, cerebellar and thalamic structures.[32,33] However, the effect of lower levels of drinking on brain health is less clear. In the general population, prior research has identified positive relationships between alcohol use, total grey matter and various grey matter structures,[13,14,16,17,20] although the apparent protective effect of alcohol use on change in the thalamus over time has not been identified previously. There is some controversy over the potential mechanisms that may underpin the protective effect of low-level alcohol use on brain health, but possible mechanisms include indirect effects through reduced cardiometabolic disease,[34] or through modulation of amyloid beta deposition and glymphatic function.[35,36]

It has been suggested that the protective effect of alcohol use on brain health in older adults may be spurious and explained by reverse causation. That is, reductions in brain health lead to lower levels of drinking, rather than lower levels of drinking leading to poorer brain health. In the current sample, the relationship between alcohol use and the thalamus was attenuated when former drinkers were excluded from the analysis, somewhat supporting the presence of reverse causation. However, additional analyses that focused on the dynamic bivariate relationships between alcohol use and the thalamus provided evidence that alcohol use was the leading indicator of change in the thalamus, rather than the reverse.

Contrary to the current findings, general population data from the UK Biobank have indicated that the thalamus has one of the strongest *negative* associations with alcohol use when compared with other subcortical structures.[9] In another UK Biobank study, analyses stratified by sex indicated that the negative effect of alcohol use on the thalamus was restricted to females, whereas in males, there was a modest positive effect of alcohol use on thalamus volume.[10] Although a post hoc three-way interaction indicated that the relationship between alcohol use and the thalamus over time did not differ by sex in the current study, the power to detect such nuanced differences was limited. Interestingly, another UK Biobank study investigating brain iron accumulation as a potential mechanism of alcohol-related cognitive decline identified lower levels of iron in the thalamus associated with higher alcohol use.[37] This finding was contrary to expectations and inconsistent with other brain regions studied, where higher alcohol use was associated with higher brain iron accumulation. Together, these findings suggest that the thalamus may be particularly sensitive to the impacts of alcohol use and that the alcohol–thalamus relationship may differ according to age, sex and the quantity-frequency of alcohol consumed. Understanding the complex alcohol–thalamus relationship may be an interesting focus of future research using large-scale, longitudinal epidemiological data.

The vulnerability of white matter macrostructure and microstructure to the effects of alcohol is consistent with prior research in both midlife and later-life adults.[8–10,15,38–42] The impacts of alcohol use on white matter have been attributed to both demyelination and axonal loss, possibly driven by inflammation, epigenetic processes or the direct neurotoxicity of alcohol. Microstructural tissue integrity, as measured by dMRI, underpins changes in white matter macrostructure and may be particularly vulnerable to the impacts of alcohol,[41,43] including alcohol–age interactions.[42,44] In the current study, past-year binge-drinking at baseline was associated with DDF at Wave 2, a newly developed automated neuroimaging marker of white matter integrity using dMRI data.[22] This relationship was robust to the inclusion of demographic and clinical confounders, as well as when former drinkers and those with incident dementia were excluded. Using both Sydney MAS and UK Biobank data, this measure has been shown to be more strongly correlated with both age and cognition when compared with other dMRI metrics, such as fractional anisotropy (FA), mean diffusivity (MD) and peak width of skeletonised mean diffusivity (PSMD).[22] In the current study, DDF captured a subtle negative relationship between past-year binge drinking and white matter microstructure (indicative of poorer white matter integrity), which was not apparent using other measures of white matter integrity, including PSMD and WMH burden.

In the current study, heavier consumption of alcohol in the past was also associated with an accelerated age-related decline in white matter volume in the anterior and posterior corpus callosum established using volumetric analyses of sMRI data. The association between alcohol use and callosal volume has been established in individuals with alcohol use disorder,[40] as well as in general population samples of midlife to older adults from the UK Biobank and Whitehall II studies.[8,10] Our finding that consuming alcohol more heavily in the past was related to accelerated reductions in callosal volume could be indicative of a greater susceptibility of the brain to the effects of alcohol in earlier life, with volume in the corpus callosum demonstrating sustained negative impacts despite a reported reduction in drinking in later years. However, the retrospective nature of the data collected on historical alcohol use in the current study limits the conclusions that can be drawn.

Alcohol use, however, was not associated with any of the cognitive functions assessed, indicating that any alcohol–brain relationships that were identified in the current sample of moderate drinkers are unlikely to be related to overt functional outcomes. This is consistent with a prior study using the first three waves of Sydney MAS data,

which similarly found no relationship between alcohol use and functional outcomes, including both cognition and dementia.[45] It may be that alcohol use at moderate levels leads to brain changes that are related to more subtle or circumscribed functions. In the Whitehall II Study, for example, moderate drinking was associated with lexical fluency but not semantic fluency and word recall.[8] Alcohol-related relationships with lexical fluency were partially mediated by mean diffusivity in the corpus callosum. Sydney MAS did not include a measure of lexical fluency specifically, so whether this relationship replicated in the current study could not be tested.

In conclusion, in this general population sample of low-level drinkers, there appeared to be very few detectable relationships between alcohol use and indicators of brain health measured longitudinally. Taken together, the findings from this study indicate that alcohol use may have impacts on the brain health of older adults that differ to those found in samples of midlife adults. This is consistent with the most recent report from the Global Burden of Disease (GBD) Alcohol Collaborators,[1] which indicated that population health risks associated with low-level alcohol consumption are greater for younger populations when compared with older populations. Consistent with these findings, in the current study of relatively low-level drinkers, the relationship between later-life alcohol use and the thalamus appeared to be protective and the negative association between later-life alcohol use and white matter integrity was only apparent among past-year binge drinkers, whereas the negative association between alcohol use and the corpus callosum was only apparent among those who indicated that they had consumed alcohol more heavily in the past. Because of inconsistencies in the literature on moderate alcohol use, the impact of alcohol use on brain health was not considered as part of the most recent GBD alcohol report,[1] or as part of the development of other alcohol guidelines more generally. There is a need for ongoing and rigorous research so that the impact of alcohol use on the brain is no longer neglected when alcohol guidelines are formulated.

AUTHOR CONTRIBUTIONS

Louise Mewton: Conceptualisation, methodology, formal analysis, writing—original draft, writing—review and editing; **Rachel Visontay**: Methodology, formal analysis, writing—original draft, writing—review and editing; **Gerard Hughes**: Methodology, formal analysis, writing—original draft, writing—review and editing; **Catherine Browning**: Methodology, formal analysis, writing—original draft, writing—review and editing; **Wei Wen**: Investigation, resources, data curation, writing—original draft, writing—review and editing; **Anya Topiwala**: Writing—original draft, writing—review and editing; **Brian Draper**: Writing—original draft, writing—review and editing; **John Crawford**: Methodology, writing—review and editing; **Henry Brodaty**: Writing—original draft, writing—review and editing, project management, funding acquisition; **Perminder Sachdev**: Writing—Original draft, writing—review and editing, project management, funding acquisition.

CONFLICT OF INTEREST STATEMENT

The authors have nothing to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Louise Mewton https://orcid.org/0000-0002-7812-296X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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