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The Relationship Between Midlife and Late Life Alcohol Consumption, *APOE* e4 and the Decline in Learning and Memory Among Older Adults

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Abstract — Aims: The aim of the study was to determine whether the trajectory of learning and memory is modified according to an interaction between midlife or late life alcohol consumption status and the presence of one or more *APOE* e4 alleles. **Methods:** This was a secondary analysis of cognitive, genetic and alcohol consumption data collected from members of the Framingham Heart Study Offspring Cohort. **Results:** Light and moderate alcohol consumption during late life was associated with greater decline in learning and memory among *APOE* e4 carriers, whereas light and moderate alcohol consumption was associated with an increase in learning and memory among non-*APOE* e4 carriers. There was not a significant interaction between midlife alcohol consumption status and *APOE* e4 on the trajectory of learning and memory. **Conclusion:** Light to moderate alcohol consumption during late life may protect against a decline in learning and memory for non-*APOE* e4 allele carriers, but not for older adults who carry one or more *APOE* e4 alleles.

INTRODUCTION

The relationship between alcohol consumption and cognitive functioning during old age has been examined extensively. Several studies report findings that indicate that moderate alcohol consumption during late life is associated with higher cognitive functioning (Stampfer *et al*., 2005; Lang *et al*., 2007) and a decreased risk of dementia (Anstey *et al*., 2009; Weyerer *et al*., 2011). These findings are consistent with studies that have examined the relationship between alcohol consumption during midlife and late life cognitive functioning (Virtaa *et al*., 2010; Kesse-Guyot *et al*., 2012). There are several mechanisms that may explain the observed relationship between moderate alcohol consumption and cognition, including the anti-inflammatory properties of alcohol (Wright *et al*., 2006) and moderate alcohol consumption being protective against risk factors for dementia, such as stroke (Beulens *et al*., 2010), coronary heart disease (Hvidtfeldt *et al*., 2010) and type II diabetes (Wannamethe *et al*., 2002). This is likely due to the benefits of moderate alcohol consumption on cardiovascular health (di Giuseppe *et al*., 2009; Marques-Vidal *et al*., 2010).

While current evidence suggests that moderate alcohol consumption is beneficial for cognitive functioning among older adults, the effects of moderate alcohol consumption among older adults who carry one or more apolipoprotein (*APOE*) e4 alleles are less certain. *APOE* e4 is a widely accepted genetic risk factor for Alzheimer's disease (AD) and the risk of AD has been shown to increase with each *APOE* e4 allele (Corder *et al*., 1993). The *APOE* e4 allele is also associated with lower cognition among nondemented older adults (Reinvang *et al*., 2010). *APOE* encodes the protein apoE, which is a lipid transport protein (Hauser *et al*., 2011). The *APOE* e4 allele is associated with elevated serum total cholesterol (Bennet *et al*., 2007) and adults who carry one or more *APOE* e4 alleles are at an increased risk of coronary heart disease (Yang *et al*., 2006).

There is increasing evidence that cholesterol plays an important role in the pathogenesis of AD (Morgan, 2011). The benefits of moderate alcohol consumption for cardiovascular health and the role of apoE in cholesterol transport suggest that alcohol consumption may be able to limit the cognitive decline that has been repeatedly observed among older adults who carry one or more *APOE* e4 alleles. Accordingly, the purpose of the current study is to examine the relationship between the decline in learning and memory during late life, alcohol consumption during midlife and late life, and *APOE* e4 to determine whether moderate alcohol consumption during midlife or late life limits the severity of cognitive decline among *APOE* e4 carriers.

MATERIALS AND METHODS

Sample population

The Framingham Heart Study (FHS) is an ongoing longitudinal study that began in 1948 and was designed to identify traits associated with cardiovascular disease (Dawber *et al*., 1951). The FHS Offspring cohort was initiated in 1971 and includes the children of the Original cohort and their spouses. Details regarding the design and methods of data collection of the FHS Offspring cohort have been described previously (Feinleib *et al*., 1975). Investigators not affiliated with the FHS can be approved access to FHS data by submitting a research proposal to the database of genotypes and phenotypes.

Beginning in 1999, subjects still remaining in the FHS Offspring cohort were recruited to participate in a secondary study in which they received a neuropsychological battery (Massaro *et al*., 2004). A total of 2611 subjects were actively participating in the FHS in 1999 and 2045 (78.3%) of these subjects received a baseline neuropsychological battery. Participants received up to two neuropsychological batteries (baseline and follow-up) between 1999 and 2007. Because the purpose of the current study was to examine the relationship between alcohol consumption, *APOE* e4 and cognition during late life, the final sample was restricted to subjects who were 65 years of age or older upon receiving a baseline neuropsychological battery. Of the 2045 participants who received a baseline neuropsychological battery, 610 (29.8%) were 65

years of age or older. For the 610 participants included in the final sample, the average age during the first clinical examination was 44.2 years (range 35.0–59.0 years) and the average age during the eighth clinical examination was 77.1 years (range 69.0–92.0 years). These ages were used to define midlife and late life alcohol consumption and are consistent with the definitions of midlife and late life provided by previous studies (Kivipelto *et al.*, 2001; Whitmer *et al.*, 2005; Solomon *et al.*, 2009).

Subjects who received a baseline neuropsychological battery consumed more alcohol during midlife (6.8 drinks per week vs. 5.4 drinks per week, $P < 0.0001$) and late life (4.6 drinks per week vs. 3.4 drinks per week, $P < 0.0001$) compared with subjects who did not receive a neuropsychological battery. These differences likely reflect the overall worse health of participants who did not receive a baseline neuropsychological battery (Massaro *et al.*, 2004). Additional health and demographic characteristics of participants who received a neuropsychological battery have been reported by Massaro *et al.* (2004). Subjects who were younger than 65 years upon receiving a baseline neuropsychological battery ($n = 1435$) reported consuming more alcohol per week (5.2 vs. 3.5; $P < 0.0001$) and were more likely to be current smokers (11.6 vs. 4.2%; $P < 0.0001$) during the eighth clinical examination compared with subjects who were included in the final sample. These differences are to be expected given the declines in the prevalence of alcohol consumption and smoking with increasing age (Mendez *et al.*, 1998; Moore *et al.*, 2005). There were no differences in smoking status or the amount of alcohol consumed per week during the first clinical examination. There were also no differences in educational attainment or in the proportion of males and females between subjects who were younger than 65 and those included in the final sample.

Assessment of alcohol consumption

Alcohol consumption was assessed during each clinical examination using three open-ended questions administered as part of a medical history interview (MHI): (a) During the past year, how many bottles, cans or glasses of beer did you consume per week? (b) During the past year, how many glasses of wine did you consume per week? and (c) During the past year, how many cocktails (i.e. drinks containing liquor) did you consume per week? This assessment was compared with a validated food frequency questionnaire (FFQ; Rimm *et al.*, 1992) administered during the eighth clinical examination. The correlations between the FFQ and MHI for weekly beer ($r = 0.84$), wine ($r = 0.78$) and liquor ($r = 0.80$) consumption were all highly significant ($P < 0.001$). Paired *t*-tests were used to compare the average weekly consumption of beer, wine and liquor. There were no significant differences between the FFQ and MHI for the amounts of beer, wine or liquor consumed per week.

Midlife and late life alcohol consumption was determined by summing the amounts of beer, wine and liquor consumed per week as reported by participants during the first and eighth clinical examinations, respectively. Alcohol consumption data collected during clinical examinations two through seven were not included in any analyses. Participants were grouped into the following categories to define midlife and late life alcohol consumption status: (a) abstinent; (b) light, 1–6 drinks per week; (c) moderate, 7–14 drinks per week and (d) heavy, >14 drinks per week. These alcohol consumption categories are consistent with the guidelines established by the National Institute on Alcohol Abuse and Alcoholism (Dufour, 1999). Abstainers were treated as the reference category in all analyses.

Assessment of learning and memory

The FHS neuropsychological battery included six subtests of the Wechsler Memory Scale (Wechsler, 1945; immediate and delayed recall of logical memory, paired-associate learning, and visual reproductions). These subtests are commonly used measures of verbal memory, new learning and visual memory (Au *et al.*, 2004). The raw scores from each assessment were standardized according to the sample mean and standard deviation; the standardized scores were then averaged to create a summary score of learning and memory. This method has been used previously (Wilson *et al.*, 2011).

Covariates

Covariates were chosen according to those that have been included in previous studies that have examined alcohol consumption (Anttila *et al.*, 2004; Britton *et al.*, 2004; Deng *et al.*, 2006). Education status was determined during the first neuropsychological battery and was defined as no high school degree, high school degree, some college and college degree. During the first clinical examination participants were asked whether they had smoked regularly for at least 1 year (no, yes and former). During the eighth clinical examination participants were asked whether they had smoked regularly in the last year (yes or no). *APOE* e4 status was defined as e4+ or e4 − due to the low prevalence of *APOE* e4 homozygotes in the final sample. *APOE* e4− was the reference group in all analyses. Sex and age were also included as covariates.

Statistical analysis

The current study utilized a retrospective design. Differences in demographic characteristics according to midlife and late life alcohol consumption status were examined using analysis of variance (ANOVA) and Fisher's exact tests. Multiple linear regression was used to test for associations between midlife alcohol consumption and baseline learning and memory and late life alcohol consumption and baseline learning and memory. All models controlled for age, sex, education, smoking status and APOE e4.

Linear mixed modeling (Laird and Ware, 1982) was used to examine the relationship between alcohol consumption during midlife and late life, *APOE* e4, and trajectories in learning and memory. This approach was used because it provides valid estimates when data are highly unbalanced due to differences in the number and timing at which subjects are observed (Cnaan *et al.*, 1997). Random effects for age and intercept were also included in all models to allow for the trajectory of learning and memory, as well as baseline learning and memory, to vary for each subject. Two-way interaction terms between age and alcohol consumption status and age and *APOE* e4 were included to determine whether the trajectory of learning and memory differed according to alcohol consumption or *APOE* e4 status. A three-way interaction term between age, *APOE* and alcohol consumption status was included to determine whether the relationship between alcohol consumption and the trajectory of learning and memory differed according to the presence of one or more

APOE e4 alleles. All analyses were performed using the statistical package R (R Core Team, 2013).

RESULTS

Sample characteristics

A total of 610 participants received the baseline neuropsychological battery and 494 (81.0%) received a second neuropsychological battery. Participants who did not receive a second neuropsychological battery were less likely to have a high school degree ($P = 0.0002$) and had a lower summary score of learning and memory ($P < 0.0001$). There were no differences between participants who received two neuropsychological batteries and those who received only a baseline battery for age, *APOE* e4, sex or alcohol consumption during midlife and late life. The *APOE* allele frequencies of the final sample were 8.0, 81.2 and 10.8% for the e2, e3 and e4 alleles, respectively. These allele frequencies did not violate Hardy–Weinberg equilibrium. There were 126 (20.7%) subjects with one or more *APOE* e4 alleles and 484 (79.3%) subjects with no *APOE* e4 alleles. During the first clinical examination there were 59 (9.6%) abstainers, 308 (50.5%) light, 156 (25.6%) moderate and 87 (14.3%) heavy alcohol consumers. Alcohol consumption declined with increasing age ($\hat{\beta} = -0.12, \mathrm{SE} = 0.0067, P < 0.0001$). During the eighth clinical examination there were 339 (55.6%) abstainers, 115 (18.9%) light, 128 (21.0%) moderate and 28 (4.6%) heavy alcohol consumers.

Comparisons for demographic characteristics during the baseline neuropsychological battery according to midlife and late life alcohol consumption status are provided in Table 1 (approximate location: page 10). Males were more likely than females to be heavy alcohol consumers during midlife ($P < 0.0001$) and late life ($P < 0.0001$). Heavy alcohol consumption during midlife was associated with being a current smoker during midlife ($P < 0.0001$), but there was not a significant relationship between alcohol consumption during late life and smoking status during late life ($P = 0.78$). Subjects with one or more *APOE* e4 alleles were less likely to be abstainers during midlife ($P = 0.044$) and consumed more drinks per week during midlife compared with subjects with no *APOE* e4 alleles (e4+ 9.6 drinks/week; e4− 7.4 drinks/week; $P = 0.087$). Light alcohol consumption during late life was associated with higher education obtainment ($P < 0.0001$).

Relationship between alcohol consumption and baseline learning and memory

There were no significant differences in baseline learning and memory according to midlife or late life alcohol consumption status or the presence of one or more *APOE* e4 alleles after adjusting for age, sex, smoking status and education. When *APOE* and alcohol consumption status were removed from the model, higher scores on measures for learning and memory were associated with younger age, higher education and female gender (Table 2; approximate location page 11).

Relationship between alcohol consumption and trajectory of learning and memory

Subjects with one or more *APOE* e4 alleles exhibited greater decline in learning and memory compared with subjects with no *APOE* e4 alleles ($\hat{\beta} = -0.026, \mathrm{SE} = 0.0094, P = 0.005$). The trajectory of learning and memory was not associated with midlife or late life alcohol consumption status and there were no differences in the trajectory of learning and memory according to gender or education. Furthermore, there was not a statistically significant three-way interaction between age, *APOE* and midlife alcohol consumption status. The findings from the model that included the interaction between age, *APOE* and late life alcohol consumption status indicated that the relationship between late life alcohol consumption status and learning and memory was modified according to *APOE* e4 status ($P = 0.021$; Table 3; approximate location page 11). When subjects were stratified according to *APOE* e4 status, moderate alcohol consumption was associated with greater decline in learning and memory among those who were *APOE* e4+, ($\hat{\beta} = -0.038, \mathrm{SE} = 0.021, P = 0.077$) compared with abstainers, whereas among subjects who were *APOE* e4−, moderate alcohol consumption was associated with an increase in learning and memory ($\hat{\beta} = 0.027, \mathrm{SE} = 0.011, P = 0.012$) compared with abstainers. A similar trend was observed for light alcohol consumers. Light alcohol consumption was associated with greater decline in learning and memory compared with abstainers among *APOE* e4+ older adults ($\hat{\beta} = -0.037$, SE = 0.022, P = 0.091), whereas light alcohol consumption was associated with an increase in learning and memory among those who were *APOE* e4− ($\hat{\beta} = -0.011$, SE = 0.011, P = 0.29). Heavy alcohol consumption was associated with an increase in learning and memory among subjects who were *APOE* e4+. It is possible that this finding is due to a small sample size because only five subjects were *APOE* e4+ and heavy alcohol consumers during late life. There was not a significant three-way interaction between age, *APOE* and midlife alcohol consumption status on the trajectory of learning and memory.

DISCUSSION

In the present study we did not find evidence that the trajectory of learning and memory during late life is modified according to midlife alcohol consumption status. However, our findings provide evidence that the relationship between late life alcohol consumption and the decline in learning and memory is modified according to *APOE* e4 status. Moderate alcohol consumption during late life was associated with an increase in learning and memory among subjects who were *APOE* e4−, whereas moderate alcohol consumption during late life was associated with greater decline among subjects who were *APOE* e4+. These findings are consistent with previous research on the effect of *APOE* e4 and alcohol consumption on cognitive decline and the risk of Alzheimer's disease. In one such study, Dufouil *et al*. (2000) observed that the risk for decline on the MMSE decreased with greater alcohol consumption during late life for older adults with no *APOE* e4 alleles, but the opposite trend was observed for older adults with one or more *APOE* e4 alleles. In a second study, Anttila *et al*. (2004) reported the risk of dementia increased with greater alcohol consumption for *APOE* e4 carriers, but not for non-*APOE* e4 carriers. Similarly, Harwood *et al*. (2010) observed an additive effect of *APOE* e4 and heavy alcohol consumption on the age of onset for AD.

The findings of the current study should be interpreted with some caution because of the relatively small size of the final

Table 1. Demographic characteristics of subjects who received a neuropsychological battery between 1999 and 2005 according to midlife and late life alcohol consumption status

Variable	Abstainer	Light	Moderate	Heavy	*P*-value
	n = 59	*n* = 308	*n* = 156	*n* = 87	
Midlife alcohol consumption status					
Age[a], midlife (SD)	43.9 (4.4)	44.1 (4.6)	44.6 (4.5)	44.1 (4.5)	0.72
Age[a], late life (SD)	76.7 (4.3)	77.1 (4.4)	77.4 (4.4)	76.7 (4.3)	0.58
Number of years between NP examinations[b]	6.3 (0.79)	6.2 (1.2)	6.1 (0.97)	6.0 (1.0)	0.46
Midlife smoking status (%)					
Current smoker	10 (16.9)	98 (31.9)	63 (40.4)	36 (41.4)	**<0.0001**
Former smoker	11 (18.6)	76 (24.8)	46 (29.5)	42 (48.3)	
Non-smoker	38 (64.4)	133 (43.3)	47 (30.1)	9 (10.3)	
Late life smoking status (%)					
Non-smoker	55 (93.2)	293 (95.4)	150 (96.2)	84 (96.6)	0.78
Current smoker	4 (6.8)	14 (4.6)	6 (3.8)	3 (3.4)	
Drinks per week (SD)	0.0 (0.0)	2.8 (1.4)	10.1 (2.4)	27.1 (12.9)	**<0.0001**
Education (%)					
Less than high school	5 (8.5)	18 (5.8)	11 (7.1)	6 (6.9)	0.48
High school	28 (47.5)	126 (40.9)	53 (34.0)	36 (41.4)	
Some college	15 (25.4)	71 (23.1)	41 (26.3)	15 (17.2)	
College	11 (18.6)	93 (30.8)	51 (32.7)	30 (34.5)	
Gender (%)					
Male	16 (27.1)	104 (33.8)	90 (57.7)	70 (80.5)	**<0.0001**
Female	43 (72.9)	204 (33.4)	66 (42.3)	17 (19.5)	
APOE e4					
e4−	53 (89.8)	250 (81.2)	116 (74.4)	65 (74.7)	**0.044**
e4+	6 (10.2)	58 (18.8)	40 (25.6)	22 (25.3)	
	n = 339	*n* = 115	*n* = 128	*n* = 28	
Late life alcohol consumption status					
Age[a], midlife (SD)	44.3 (4.6)	44.1 (4.6)	43.8 (4.1)	44.6 (4.3)	0.72
Age[a], late life (SD)	77.2 (4.4)	76.9 (4.5)	76.7 (4.0)	77.0 (4.2)	0.65
Number of years between NP examinations[b]	6.2 (1.1)	6.0 (1.2)	6.0 (1.1)	6.0 (0.92)	0.12
Smoking, midlife (%)					
Yes	105 (31.1)	40 (34.8)	48 (37.5)	14 (50.0)	**0.0005**
Former	81 (24.0)	39 (33.9)	45 (35.2)	10 (35.7)	
No	152 (45.0)	36 (31.3)	35 (27.3)	4 (14.3)	
Smoking, late life (%)					
Current smoker	17 (5.0)	4 (3.5)	6 (4.7)	0 (0)	0.78
Non-smoker	322 (95.0)	110 (96.5)	122 (95.3)	28 (100.0)	
Drinks per week (SD)	0.0 (0.0)	3.1 (1.7)	9.4 (2.8)	22.1 (4.5)	**<0.0001**
Education (%)					
Less than high school	32 (9.4)	3 (2.6)	4 (3.1)	1 (3.6)	**<0.0001**
High school	157 (46.3)	37 (32.2)	39 (30.5)	10 (35.7)	
Some college	78 (23.0)	22 (19.1)	35 (27.3)	7 (25.0)	
College	72 (21.2)	53 (46.1)	50 (39.1)	10 (35.7)	
Gender (%)					
Male	125 (36.9)	60 (52.2)	70 (54.7)	25 (89.3)	**<0.0001**
Female	214 (63.1)	55 (47.8)	58 (45.3)	3 (10.7)	
APOE e4 allele status					
e4−	269 (79.4)	90 (78.3)	102 (79.7)	23 (82.1)	0.98
e4+	79 (20.6)	25 (21.7)	26 (20.3)	5 (17.9)	

Bold values indicate statistical significance $P < 0.05$. ANOVA was used for continuous characteristics and Fisher's exact test for categorical characteristics.
[a]Midlife was defined as the age during the first examination. Late life was defined as the age during the eighth examination.
[b]Based on 494 subjects (273 abstainers, 93 light, 104 moderate and 24 heavy).

sample, in particular for participants who were *APOE* e4+ and heavy alcohol consumers during late life. However, the finding that the relationship between moderate alcohol consumption during late life and the trajectory of learning and memory is modified according to *APOE* e4 is consistent with previous research, and there are biological mechanisms that support these results. First, moderate alcohol consumption has been shown to be beneficial for cardiovascular health (Mukamal and Rimm, 2008), but moderate alcohol consumption is associated with higher LDL cholesterol among *APOE* e4 carriers when compared with non-carriers (Corella *et al.*, 2001). Elevated serum cholesterol during midlife is a risk factor for AD and vascular dementia (Solomon *et al.*, 2009) and may contribute to the observed decline in learning and memory among moderate alcohol consumers who are *APOE* e4+ in the current study. Second, the apoE protein is involved in neuronal repair and carriers of the *APOE* e4 allele have an impaired neuronal repair mechanism (Mahley and Huang, 2012). Even moderate alcohol consumption can lead to increased brain atrophy (Anstey *et al.*, 2006) and *APOE* e4 carriers may be more susceptible to the neurotoxic effects of alcohol consumption due to an impaired neuronal repair mechanism (Kim *et al.*, 2012).

The strengths of the present study include the ability to analyze both midlife and late life alcohol consumption, the use of multiple questions to assess alcohol consumption and

Table 2. Baseline learning and memory according to age, gender, smoking status and education

Variable	Point estimate	Standard error	*P*-value
Age	–0.020	0.0063	**0.0011**
Gender			
Male (ref)	–	–	–
Female	0.25	0.055	**<0.0001**
Smoking, late life			
Non-smoker (ref)	–	–	–
Smoker	–0.13	0.13	0.31
Smoking, midlife			
Non-smoker (ref)	–	–	–
Smoker	0.041	0.066	0.54
Former smoker	0.090	0.067	0.18
Education			
< High school (ref)	–	–	–
High school	0.37	0.11	**0.00087**
Some college	0.53	0.12	**<0.0001**
College degree	0.87	0.11	**<0.0001**

Bold values indicate statistical significance $P < 0.05$. All models adjusted for age, gender, smoking status and education.

Table 3. Interaction between age, *APOE* and late life alcohol consumption status on the trajectory of learning and memory

Alcohol consumption	Point estimate	Standard error	*P*-value
APOE e4+			
Abstainer (ref), $n = 70$	–	–	–
Light, $n = 25$	–0.037	0.022	0.091
Moderate, $n = 26$	–0.038	0.021	0.077
Heavy, $n = 5$	0.055	0.036	0.13
APOE e4–			
Abstainer (ref), $n = 269$	–	–	–
Light, $n = 90$	0.012	0.011	0.29
Moderate, $n = 102$	0.027	0.011	**0.012**
Heavy, $n = 23$	0.016	0.02	0.43

Bold values indicate statistical significance $P < 0.05$. All models adjusted for age, gender, smoking status and education. The interaction between age, *APOE* and midlife alcohol consumption status on the trajectory of learning and memory was not statistically significant.

the use of multiple cognitive measures to create a summary score of learning and memory. Despite these strengths there are limitations that need to be addressed. First, the final sample may not represent the general population due to a survivor effect among participants who remained in the FHS and were healthy enough to receive a neuropsychological battery. Both heavy alcohol consumption (Roerecke *et al*., 2011) and the *APOE* e4 allele (Christensen *et al*., 2006) are associated with an increased incidence of mortality. This may have contributed to the very low number of subjects included in the final sample who were *APOE* e4+ and heavy alcohol consumers during late life. Furthermore, the small size of the final sample increases the likelihood for spurious results. There is strong biological evidence to support the findings of the current study and the findings are consistent with previous research. This decreases the likelihood that our finding that moderate alcohol consumption limits the decline in learning and memory among *APOE* e4– subjects but not *APOE* e4+ subjects is due to chance. Additional research using larger sample populations is necessary to replicate these findings. A second limitation is the use of self-reported measures of alcohol consumption. Alcohol consumption data collected during the eighth clinical examination were compared with a FFQ that has been shown to be valid in other sample populations but biases may have been introduced into the analysis. Finally, the FHS only examined cognitive functioning during two time periods. It is necessary to have more than two repeated measures of cognition in order to determine the long-term effects that late life alcohol consumption, *APOE* e4 and interactions between these factors have on cognitive decline.

The findings from the current study provide evidence that moderate alcohol consumption during late life is associated with less decline in learning and memory for older adults with no *APOE* e4 alleles, but not for those who carry one or more *APOE* e4 alleles. Additional research using larger sample populations that includes several repeated measures of cognitive functioning is necessary to replicate these findings and to determine whether an interaction between alcohol consumption and *APOE* e4 extends to other cognitive domains and the long-term trajectories of cognitive decline according to alcohol consumption status and *APOE* e4 allele status.

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