

Alcohol Consumption and Domain-Specific Cognitive Function in Older Adults: Longitudinal Data From the Johns Hopkins Precursors Study

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Objectives. The association of alcohol consumption with performance in different cognitive domains has not been well studied.

Methods. The Johns Hopkins Precursors Study was used to examine associations between prospectively collected information about alcohol consumption ascertained on multiple occasions starting at age 55 years on average with domain-specific cognition at age 72 years. Cognitive variables measured phonemic and semantic fluency, attention, verbal memory, and global cognition.

Results. Controlling for age, hypertension, smoking status, sex, and other cognitive variables, higher average weekly quantity and frequency of alcohol consumed in midlife were associated with lower phonemic fluency. There were no associations with four other measures of cognitive function. With respect to frequency of alcohol intake, phonemic fluency was significantly better among those who drank three to four alcoholic beverages per week as compared with daily or almost daily drinkers. A measure of global cognition was not associated with alcohol intake at any point over the follow-up.

Discussion. Results suggest that higher alcohol consumption in midlife may impair some components of executive function in late life.

Key Words: Alcohol—Cognition—Epidemiology—Older adults.

THE physical health implications of alcohol consumption have been characterized extensively among older adults, but less is known about effects of alcohol on cognitive abilities. Moderate levels of alcohol consumption are generally associated with better physical health, whereas excessive use is associated with worse outcomes (McCaul et al., 2010; Mukamal et al., 2003; Peters et al., 2008; Simons et al., 2000; Stuck et al., 1999). Characterizing the physical as well as cognitive effects of alcohol intake informs clinicians' care for older persons. Current dietary guidelines recommend alcohol use in moderation unless contraindicated by preexisting conditions (Mann & Folts, 2004; Willet & Stampfer, 2003).

Evidence for an association of alcohol intake with cognition among older adults is mixed. Studies comparing drinkers and nondrinkers report lower cognitive functioning among nondrinkers (Britton, Singh-Manoux, & Marmot, 2004; McDougall, Becker, & Areheart, 2006; McDougall et al., 2007). Many cross-sectional studies in older populations show that those consuming approximately 7–14 drinks per week have higher cognitive function than abstainers or

heavier drinkers, that is, a “j-shaped” or “u-shaped” relationship (den Heijer et al., 2004; Lang et al., 2007; Launer et al., 1996; Reid et al., 2006; Rodgers et al., 2005). Similar associations, though usually not statistically significant, have been reported in longitudinal studies (Anttila et al., 2004; Bond et al., 2005; Britton et al.; Cervilla et al., 2000; Elias et al., 1999; Flicker et al., 2005; Galanis et al., 2000; Kalmijn et al., 2002; Leroi, Sheppard, & Lyketsos, 2002; McGuire, Ajani, & Ford, 2007). Proposed biologic mediators for the association involve beneficial impacts of alcohol on lipid and lipoprotein levels, lowered risk for heart disease, and increased cerebral blood flow, all of which are good for cognitive health (Britton et al.; Fontana et al., 1999; Gaziano et al., 1993; Kalmijn et al.; Kiechl et al., 1998; Rabbia et al., 1995; Sano et al., 1993). Other cross-sectional (Anstey et al., 2005; Elwood et al., 1999; McDougall et al., 2006) and longitudinal (Espeland et al., 2005; Galanis et al.; Ganguli et al., 2005; Stampfer et al., 2005; Wright et al., 2006) studies show no significant relationship between alcohol intake and cognitive function, although there is evidence that the association may differ as a function

of cognitive domain (Anstey et al.; Britton et al.; Elias et al.; Ganguli et al.; Hebert et al., 1993; Kalmijn et al.; McDougall et al., 2006, 2007; Reid et al.; Rodgers et al.). A recent meta-analysis of 23 longitudinal studies reported no evidence of protective effects of low levels of alcohol consumption on cognitive function in adults older than 65 years of age (Peters et al.). Even among longitudinal studies that have reported statistically significant associations between better cognition and moderate alcohol consumption, magnitudes of the associations are small (e.g., Cervilla et al.).

The inconsistencies in findings outlined earlier with respect to the association between alcohol and cognition may be partly attributable to how alcohol use is quantified. Measures of alcohol use should capture both how much an individual drinks and how often he or she drinks. Quantity and frequency of alcohol intake may influence cognitive ability in qualitatively different ways. For example, the quantity of alcohol consumption is likely a more accurate measure of alcohol dose than frequency of drinking. It is also conceivable that the amount an individual drinks at any single time may be less associated with cognitive ability than one's trajectory or change in alcohol intake over time. Finally, "problem" drinkers may show particular cognitive deficits (Moselhy, Georgiou, & Kahn, 2001; Tapert et al., 2001).

Few prospective studies have addressed effects of alcohol consumption during midlife on cognition in later life. Prospective studies are important because cognitive decline may impair accurate recall of past intake. In addition, alcohol intake declines with age (Dufour & Fuller, 1995; Karlamangla et al., 2006), meaning that exposure assessment in midlife may be a more accurate measure of lifetime exposure. Furthermore, null or weak associations seen in many studies may be due to insufficient follow-up time between measurement of alcohol use and cognitive testing. Thus, exposures occurring years before measurement of cognition may be more predictive of future cognitive function than cross-sectional or recent measures of exposure.

Another limitation in many studies of the association of alcohol use with cognition is that domain-specific measures of cognition are not often employed. Cognitive ability is a multidimensional construct embracing multiple domains. Although each domain can be characterized as a conceptually distinct unit, their functions are highly interrelated (Moscovitch, 1992). Many studies use global or aggregated composite measures of cognition (Bond et al., 2005; Cervilla et al., 2000; den Heijer et al., 2004; Elwood et al., 1999; Espeland et al., 2005; Flicker et al., 2005; Galanis et al., 2000; Lang et al., 2007; Launer et al., 1996; Leroi et al., 2002; McGuire et al., 2007; Wright et al., 2006). Such measures of global mental status or tests of general intelligence show good reliability and encompass a variety of cognitive constructs but are not as sensitive to domain-specific measures of cognition (Leroi, Sheppard, & Lyketsos, 2002; Lyketsos, Chen, & Anthony, 1999). Additionally, global measures are subject to ceiling effects among cogni-

tively intact older adults (Leroi et al.). If alcohol use is associated with different mental abilities to varying degrees, such an approach might mask associations. Finally, alcohol consumption, depending on the level, can be both a risk and a protective factor for cardiovascular conditions such as stroke and hypertension, which in turn are associated with declines in specific cognitive functions (e.g., Rafnsson et al., 2007). Alcohol use affects certain brain regions, such as frontal lobe structures, more than others (Moselhy et al., 2001; Tapert et al., 2001), which may lead to differential neuropsychological test performance in domains associated with the affected brain regions (Weissenborn & Duka, 2003). Indeed, different effect sizes comparing drinkers and non-drinkers have been reported depending on the cognitive measure used; one study has shown that memory measures that rely on executive abilities like the Rivermead Behaviour Memory Test (effect size: 0.85) and the Hopkins Verbal Learning Test (HVLT; effect size: 0.62) show larger effect sizes than for visuospatial ability (effect size: 0.27; McDougall et al., 2006). Other studies have also reported deleterious effects of alcohol on executive functions or on the brain's frontal lobe region (Tapert et al.; Weissenborn & Duka).

The Johns Hopkins Precursors Study addresses these limitations in several ways. Alcohol intake was assessed prospectively on multiple occasions over 17 years from middle to old age. Alcohol intake was examined separately as an average weekly quantity, frequency of alcohol intake, annual rate of change in weekly consumption levels over 17 years, and problem drinking. Alcohol intake was characterized using these separate metrics to allow for different associations with cognitive measures. We are not aware of any other studies among older adults that have quantified alcohol use in all these ways. Additionally, a battery of neuropsychological tests was administered that assessed several domains of cognitive function, including global cognition, aspects of executive function including semantic and phonemic fluency, memory, and attention. Our objective was to examine associations between prospectively collected information about alcohol intake at various ages throughout midlife and domain-specific cognitive function measures later in life. We hypothesized that alcohol quantity and frequency are associated with cognitive measures that rely most on executive functions, namely semantic and phonemic verbal fluency.

METHODS

The Johns Hopkins Precursors Study was started in 1947 by the late Caroline Bedell Thomas as a prospective longitudinal study of medical students who graduated from The Johns Hopkins Medical School between 1948 and 1964. The cohort consisted of 1,216 men and 121 women, most of whom are White, have a medical education, and have been followed since their graduation (Klag et al., 2002). Questionnaires are mailed annually to update morbidity and

exposure information. Follow-up rates are high with annual response rates all above 72% for the years used in this article; vital status of nonrespondents is known for more than 99% of the cohort (Klag et al., 2002). This analysis consists of 588 participants, which represents 60% of those who were alive and consented to cognitive testing over the telephone in 2005. Cognitive measures were obtained from the 2005 telephone survey, and other variables including alcohol use were collected from annual mailed questionnaires.

Measurement Strategy

Five cognitive measures are available from the telephone administered neuropsychological test battery in 2005. They include the Telephone Interview for Cognitive Status (TICS) total score, which correlates highly with the Mini-Mental State Examination and is designed for assessments of global cognitive status over the telephone (test–retest reliability: 0.96; Brandt, Spencer, & Folstein, 1988; Folstein, Folstein, & McHugh, 1975). The Verbal Fluency Test (VFT) measures the flexibility and speed of verbal thought processes, which can be interpreted as executive functions; two measures from this test were treated separately, semantic (count of animal words produced; test–retest reliability: 0.77) and phonemic (count of F, A, and S words produced; test–retest reliability: 0.82) fluency (Harrison et al., 2000). The HVLTL is a verbal word list–learning memory test of semantically related words that assesses episodic memory recall (test–retest reliability: 0.74; Brandt & Benedict, 2001), and the Brief Test of Attention (BTA) is a measure of short-term attentional monitoring (Cronbach's α : .91; Schretlen, 1989). The version of the BTA used here tested attention for both numbers and letters.

Self-reported alcohol intake was assessed with quantity–frequency measures in mailed surveys from 1986, 1989, 1993, 1997, and 2003. Questions were the same at each assessment. Separately for beer, wine, mixed drinks, and hard liquor, participants were asked for their typical weekly intake in the past year. Beverage types were combined to calculate an average total number of drinks per week consumed. Respondents also estimated the frequency with which they drank alcohol, with possible responses being “daily or almost everyday,” “3–4x/week,” “1–2x/week,” “1–2x/month,” or “rarely.” Quantity–frequency questionnaires for alcohol assessment have been shown to have good psychometric properties (Armor, Pohch, & Stambul, 1978; Midanik, 1982; Pernanen, 1974; Russell, Welte, & Barnes, 1991). In the Precursors cohort, self-reports of weight, height, blood pressure, and other variables have been shown to be valid (Klag et al., 1993), and so, self-reported alcohol consumption was also likely reported with validity. The CAGE was administered with the alcohol use questionnaire to assess problem drinking (Conigliaro, Kraemer, & McNeil, 2000; Ewing, 1984). CAGE is an acronym formed from the four items in the questionnaire, which asks if people have

felt they should “cut” down on their drinking, been “annoyed” by others’ criticisms of their drinking, felt “guilty” about their drinking, or used alcohol as an “eye-opener” in the morning. Alcohol was also assessed during medical school and periodically afterward until 1984 using different questions that do not allow calculation of counts or frequency of alcohol use. Consequently, we excluded alcohol information collected prior to 1986.

Other covariates, included in all models unless otherwise specified, were age in the year alcohol consumption was reported (coded continuously), hypertension (yes and no), sex, and smoking status (current smoker and current non-smoker). These variables were selected a priori because each is associated with cognitive abilities and alcohol intake. Incidence of hypertension and other cardiovascular diseases was assessed by a committee of internists, trained in epidemiology, who reviewed annual questionnaires and medical records. Given that hypertension might mediate the relationship between alcohol consumption and cognition, all models described subsequently were estimated with and without hypertensive status to see if any inferences changed. Each of these characteristics was time dependent and measured at the time of the alcohol intake assessment.

Analysis Plan

We first examined associations between consumption of specific beverage types and relations between alcohol and potential confounders. Next, generalized estimating equations (GEE) methods were fit to the data to describe relationships between self-reported alcohol quantity across midlife and cognition in older age because each neuropsychological measure assesses distinct but correlated domain-specific aspects of cognition within each person (Liang & Zeger, 1986). The GEE approach tests for differences in the magnitude of associations between alcohol use for each year that alcohol was measured and cognitive variables, while also accounting for nonindependence of cognitive scores. Cognitive outcomes were global cognitive status (TICS), semantic fluency (from VFT), phonemic fluency (from VFT), verbal memory (HVLTL), and attention (BTA). All five cognitive scores were regressed simultaneously on the year's consumption variable, an indicator variable for the neuropsychological test, interactions between the two, and age, hypertension, sex, and smoking status. Coefficients with Wald confidence intervals (CIs) for the linear combination between each cognitive indicator and alcohol quantity provided estimates for the association between alcohol consumption in each year for each neuropsychological test, after adjusting for correlations with other cognitive measures and potential confounders. All GEE analyses were specified with an exchangeable correlation structure and an identity link function after reviewing autocorrelation plots; inferences did not change when unstructured or autoregressive correlation matrices were specified.

Table 1. Demographic, Alcohol, and Cognitive Measures From 1986 Through 2003 in 588 Men and Women Who Participated in Cognitive Function Assessments in 2005: Data From The Johns Hopkins Precursors Study

	1986	1989	1993	1997	2003	2005
Number of participants, <i>n</i> (% of 588)	487 (83)	484 (82)	489 (83)	499 (85)	508 (86)	588 (100)
Age in years, mean (<i>SD</i>)	55.5 (5.1)	58.5 (5.1)	62.5 (5.1)	66.5 (5.1)	72.5 (5.1)	
Hypertension, <i>n</i> (% yes)	116 (20)	138 (23)	170 (29)	218 (37)	299 (51)	
Male, <i>n</i> (%)	544 (92)					
Smoking status, <i>n</i> (% yes)	41 (8)	31 (6)	25 (5)	26 (5)	21 (4)	
Amount of alcohol consumption, drinks per week, mean (<i>SD</i>)						
Total	8.6 (7.9)	8.0 (7.7)	8.5 (8.5)	8.7 (8.3)	8.8 (8.1)	
Beer	1.6 (3.3)	1.5 (3.3)	1.5 (3.7)	1.4 (3.9)	1.3 (3.5)	
Hard liquor	0.5 (1.6)	0.4 (1.5)	0.4 (1.9)	0.3 (1.2)	0.2 (1.1)	
Mixed drinks	3.3 (5.4)	2.9 (5.0)	2.9 (5.2)	3.1 (4.9)	3.3 (5.1)	
Wine	3.3 (4.4)	3.2 (4.6)	3.8 (5.5)	4.0 (5.0)	4.2 (5.0)	
Frequency of alcohol consumption, <i>n</i> (%)						
Daily/almost daily	209 (44)	198 (42)	212 (44)	235 (48)	266 (53)	
3–4×/wk	80 (17)	106 (22)	98 (20)	82 (18)	87 (17)	
1–2×/wk	100 (21)	79 (17)	86 (18)	85 (17)	72 (14)	
2×/month or less	89 (19)	93 (20)	86 (18)	87 (18)	73 (15)	
CAGE, <i>n</i> positive (%)	161 (27)	66 (12)	51 (9)	54 (10)	66 (11)	
Cognitive scores, mean (<i>SD</i>)						
Semantic fluency, VFT						18.3 (4.7)
Attention, BTA						13.1 (4.1)
Phonemic fluency, VFT						42.5 (14.2)
Verbal memory, HVLTL						21.9 (5.9)
Global cognition, TICS						34.3 (3.6)

Note: BTA = Brief Test of Attention; HVLTL = Hopkins Verbal Learning Test; TICS = Telephone Interview for Cognitive Status; VFT = Verbal Fluency Test.

Presence of quadratic relationships between amount of alcohol consumed and each cognitive variable was assessed by adding quadratic terms to models. Because some evidence indicates that cognitive abilities may be lower among those with cardiovascular disease (Launer et al., 1996), interaction terms were added between cardiovascular disease and each year's alcohol intake. Next, we explored whether any association between amount of alcohol consumed and cognition differs at different ages by adding interaction terms to models and inspecting nonparametric lowess plots (Cleveland, 1979). Basic regression assumptions were assessed using variance inflation factors and assorted graphical displays, including quantile–quantile plots, residuals plots, and nonparametric lowess plots.

A second set of GEE models considered frequency of alcohol use. Drinking frequency was categorized as daily or almost daily drinkers, one to two drinks per week, three to four drinks per week, and monthly drinkers (2×/month or less). The two least frequent drinking categories (“1–2×/month” and “rarely”) were consolidated because of the small numbers of respondents in these categories. The group of daily or almost daily drinkers served as the reference category. To see if the frequency of alcohol use was associated with cognition in later age, each cognitive outcome was regressed onto indicator variables for frequency of use with adjustment for age, hypertension, sex, and smoking status.

Third, to see if the rate of change over the years in average reported weekly alcohol consumption was associated with cognitive outcomes, individual linear slopes were cal-

culated using random effects models to summarize the rate of change for each individual over the course of 17 years (Laird & Ware, 1982). Each neuropsychological test score was then regressed on these change slopes. These models adjusted for age, current smoking status, sex, hypertensive status, and baseline (i.e., 1986) alcohol quantity.

A final set of models evaluated the association of problem drinking, as defined by a CAGE score greater than 1, on cognitive outcomes. The CAGE has been shown to be a reliable predictor of alcoholism (Bernadt, Mumford, Taylor, Smith, & Murray, 1982; Wallace & Haines, 1985). Each neuropsychological test score was regressed on the presence of problem drinking separately in each year, controlling for covariates, using linear regression methods.

RESULTS

Table 1 shows characteristics at baseline in 1986 and at subsequent follow-up. Most participants in the sample were White men. The sample age at the time of cognitive testing ranged from 60 to 86 years. Alcohol consumption was consistently high, with the mean weekly consumption ranging between seven and nine drinks per week (Table 1). Between 1986 and 2003, members of the cohort decreased their intake of beer and hard liquor ($p = .007$ and $p = .002$, respectively) but increased wine consumption ($p = .002$). Consumption of mixed drinks and overall consumption did not change over follow-up ($p = .45$ and $p = .29$, respectively). Consequently, overall mean quantities of alcohol

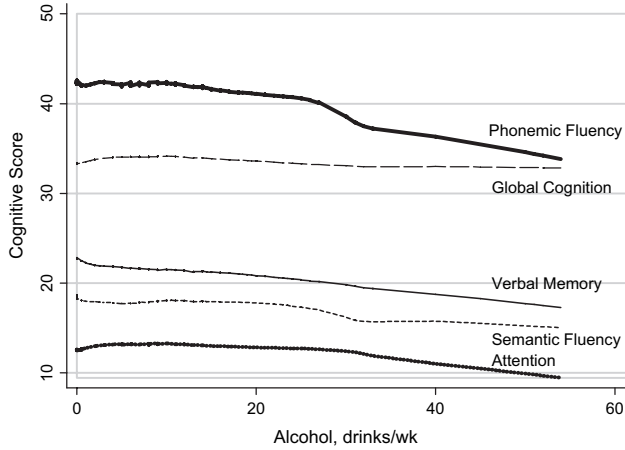


Figure 1. Nonparametric plot of cognitive scores by amount of alcohol consumption assessed in 1993 in 588 men and women: data from The Johns Hopkins Precursors Study.

consumed per week did not change over time (Table 1). The Spearman's *r* for intake assessed by frequency compared with quantity is approximately .65 in all years alcohol use was measured.

Means and standard deviations for cognitive outcomes administered over the telephone are also displayed in Table 1. Cohort members who did not undergo cognitive testing in 2005 did not differ from those who were tested in terms of alcohol consumption (data not shown; *p* = .11). Likewise, respondents to the telephone cognitive assessment who did not complete all cognitive tests did not differ by age, sex,

smoking status, or alcohol consumption at any point in time compared with those who completed the interview (all *p* > .13). Persons with incomplete data did have a higher prevalence of hypertension (odds ratio [OR] = 3.5, *p* = .01).

Quantity of Alcohol Intake and Cognition

Figure 1 shows a lowess plot of cognitive scores, assessed in 2005, by level of alcohol consumption in 1993. All cognitive measures tended to be lower at higher levels of alcohol intake. This decrease was most pronounced for phonemic fluency, and in fact, parametric analysis showed this to be the only reliable effect. Analogous graphs for alcohol assessed in other years showed similar linear patterns, but the drop in phonemic fluency was less pronounced than for alcohol intake assessed in 1993.

Parametric analysis yielded similar inferences. The results of five separate GEE analyses, one for each year of alcohol consumption, are shown in Figure 2. Greater quantity of alcohol intake was associated with lower mean adjusted phonemic fluency, but no associations were detected for other cognitive scores. In every year of assessment, a one drink per week greater alcohol intake was associated with lower phonemic fluency assessed in 2005. This inverse association was statistically significant in 1986 (*p* = .02), 1993 (*p* = .004), and 2003 (*p* = .03). The effect was strongest for alcohol intake in 1993, with a 0.12 point lower phonemic fluency score assessed 12 years later; the magnitude of this association relative to other cognitive measures is apparent from the slope of the lowess plot for phonemic

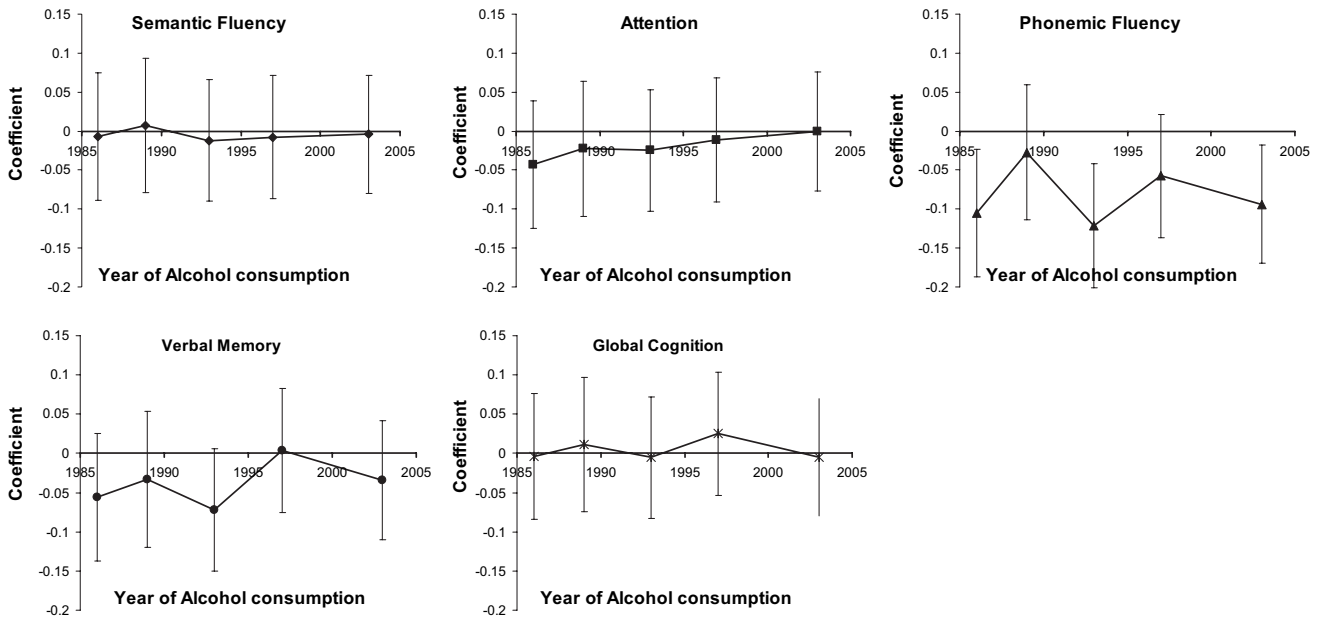


Figure 2. Adjusted (all models were adjusted for age, hypertension, sex, and smoking status. Vertical bars represent 95% pointwise confidence intervals) difference in cognitive scores for a one drink per week greater alcohol consumption by year of alcohol use assessment in 588 men and women: data from the Johns Hopkins Precursors Study.

Table 2. Adjusted^a Differences in Cognitive Scores Associated With Frequency of Alcohol Consumption in 588 Men and Women: Data From The Johns Hopkins Precursors Study

	Difference, compared with persons drinking more than four times per week (<i>n</i> = 492)
	β (95% CI)
Semantic fluency, VFT	
3–4×/week	–0.81 (–2.65 to 1.02)
1–2×/week	0.10 (–1.60 to 1.80)
2×/month or less	0.41 (–1.38 to 2.19)
Attention, BTA	
3–4×/week	0.43 (–1.34 to 2.20)
1–2×/week	–0.21 (–2.14 to 1.72)
2×/month or less	0.36 (–1.47 to 2.20)
Phonemic fluency, VFT	
3–4×/week	3.04* (1.23–4.86)
1–2×/week	1.96* (0.13–3.80)
2×/month or less	2.03* (0.15–3.91)
Verbal memory, HVLTL	
3–4×/week	–0.57 (–2.45 to 1.30)
1–2×/week	1.11 (–0.74 to 2.95)
2×/month or less	0.55 (–1.30 to 2.41)
Global cognition, TICS	
3–4×/week	0.15 (–1.63 to 1.93)
1–2×/week	–0.10 (–2.07 to 1.87)
2×/month or less	–0.09 (–1.99 to 1.81)

Note: BTA = Brief Test of Attention; HVLTL = Hopkins Verbal Learning Test; TICS = Telephone Interview for Cognitive Status; VFT = Verbal Fluency Test.

^aAll models were adjusted for age, hypertension status, sex, and current smoking status. The reference group for alcohol frequency coefficients is daily or almost daily drinkers.

**p* < .05.

fluency in Figure 1. Estimates of verbal memory were also lower for three of the five alcohol intake assessments, with the greatest difference seen in 1993 ($\beta = -.068$; *p* = .09), but none of the differences were statistically significant.

In analyses to determine the presence of quadratic relationships, attention scores in 2005 were lower both at lower and at greater quantities of alcohol intake assessed in 1986 (*p* = .05). No evidence of a quadratic relationship was seen for any other cognitive score. Age and cardiovascular disease status did not significantly modify the relationship between any cognitive outcome and alcohol consumption from any year (results not shown). No inferences changed when hypertensive status was not adjusted for in GEE models.

Frequency of Alcohol Intake and Cognition

In a second set of GEE models designed to assess relationships between frequency of alcohol use and cognition, cognitive scores were regressed on alcohol drinking frequency adjusting for potential confounders (Table 2). As in the analyses using quantity of alcohol intake, higher frequency of alcohol intake was associated with lower phonemic fluency. Participants who drank more than four times per week had statistically significantly lower scores than those in other drinking categories. Frequency of alcohol intake was not associated with other measures of cognition.

Change in Alcohol Consumption Over Time and Cognition

In random effects models, average alcohol intake increased by 0.02 drinks per week annually over the 17 years of follow-up (95% CI: –0.013 to 0.053). There was significant interindividual variability (*p* < .001). We regressed cognitive scores on individual linear trajectories of change in alcohol consumption over the 17-year period estimated from the random effects model, adjusting for age, hypertension in 2003, smoking status in 2003, sex, and 1986 alcohol consumption. The random slopes represent annual changes in alcohol consumption. In linear regressions, none of the measures of cognition was associated with change in overall alcohol consumption over the 17 years ranging between midlife and later life: semantic fluency, $\beta = -0.43$ (95% CI: –3.29 to 2.44); attention, $\beta = 1.43$ (95% CI: –1.01 to 3.88); phonemic fluency, $\beta = -2.72$ (95% CI: –11.75 to 6.30); verbal memory, $\beta = -0.7$ (95% CI: –4.61 to 3.22); and global cognition, $\beta = -0.12$ (95% CI: –2.14 to 1.91).

Problem Drinking and Cognition

In analyses testing the association between problem drinking, defined by the CAGE at each assessment of alcohol use, with cognitive ability adjusted for age, hypertension, sex, and smoking status, no associations were seen for any of the cognitive scores (all *p* > .13).

DISCUSSION

Our objective was to test the prospective association of alcohol consumption, measured repeatedly in a longitudinal study, with domain-specific cognitive abilities assessed up to 17 years after the first measure of alcohol intake. We found a prospective association between higher alcohol consumption, both quantity and frequency, and lower phonemic fluency for alcohol intake assessed 2, 12, and 17 years prior to the cognitive assessment. Our data suggest that alcohol intake three to four times per week or low levels of drinks per week through midlife and into later life confer the best cognitive outcomes in old age, as defined by word-finding ability in late life, a measure of executive function. These relationships were independent of age, smoking status, hypertension, sex, and correlations with other cognitive test scores. Change in alcohol use and problem drinking were not related to any measures of cognitive ability.

We found that the heaviest drinkers (those who drank more than four times per week) had the lowest phonemic fluency scores. This result is consistent with previous findings using the VFT (Britton et al., 2004; Elias et al., 1999) and other tests of executive function (e.g., Reid et al., 2006). Our results suggest that higher alcohol consumption in midlife may impair elements of executive function in late life but that semantic fluency is unaffected by alcohol consumption. Similar associations have been found using the HVLTL and

other tests of memory that also rely on executive abilities (McDougall et al., 2006; Reid et al.; Rodgers et al., 2005). The HVLIT is a measure of verbal episodic memory, or the acquisition of new information (Albert, 2008), but because its items are semantically related words, some degree of executive control is required to strategically organize words and perform well (Woods et al., 2005). Phonemic fluency is similar in that it taps memory functions and also requires executive information processing functions to initiate and maintain systematic search strategies for information given an ambiguous cue. Impaired phonemic and semantic fluency are both predictive of dementia. Among dementia patients, semantic fluency is more impaired than phonemic fluency, although it is relatively invariant with age and relies less on executive control because the category needed for recall is provided to the respondent (Henry, Crawford, & Phillips, 2004). Alcohol consumption was not associated with semantic fluency in our study.

The meta-analysis by Peters and colleagues (2008) reported that alcohol intake of one to six drinks per week may be protective against Alzheimer's disease. Our study included only six Alzheimer's disease cases who underwent a cognitive assessment in 2005, which is not enough to detect meaningful differences in alcohol consumption levels by dementia status. The association of drinking with lower phonemic fluency in our study is consistent with an increased risk for dementia because although episodic memory distinguishes dementia from normal age-related cognitive decline, reduced executive functioning is also apparent and may precede declines in memory (Carlson, Xue, Zhou, & Fried, 2009).

This study has a number of strengths. First, the Precursors cohort has been followed for several decades and is well characterized. In the present analysis, cognitive abilities were assessed at around age 72 years, 17 years after the first assessment of alcohol use, a longer duration than most other prospective studies that have addressed this question. Second, the Precursors Study is comprised of mainly White men who attended medical school. Thus, participants were selected at baseline for a high and homogenous level of cognitive ability. In contrast, most studies try to account for baseline differences in cognitive abilities by statistically adjusting for years of education, social status, reading ability, or test scores collected at the start of a study (Britton et al., 2004; Elias et al., 1999; Krahn et al., 2003), which offer incomplete metrics of one's cognitive function. A third strength of our sample is a comparatively higher level of drinking than is found in population-based samples, providing a more normally distributed and wider range of alcohol consumption. In many studies among population-dwelling older adults in the United States, less than half of samples report any drinking (Bond et al., 2005; McDougall et al., 2006; Stampfer et al., 2005). Fourth, we used a battery of cognitive measures to assess domain-specific associations between alcohol and cognition.

In view of the strengths of this study, several limitations should be highlighted. First, the Precursors Study is an observational cohort study, not a clinical trial. Therefore, participants choose how much alcohol to drink. Changes in executive function or memory ability might lead to changes in patterns of alcohol use, creating either a spurious association or a bias toward the null. Such a bias is most likely to be seen in cross-sectional analyses, when alcohol use and cognition are assessed at the same time, but less likely in a prospective study because alcohol intake is assessed long before the determination of cognitive function. A second limitation is that detected associations might be the product of differential loss to follow-up. However, this is probably not the case in this study as 69% of those who answered the alcohol information in 1986 received neuropsychological testing in 2005. Third, some evidence suggests that alcohol consumption may have a stronger effect in older women than in older men (Elias et al., 1999; Kalmijn et al., 2002; Lang et al., 2007; Mann & Folts, 2004; Rodgers et al., 2005). Our study contains too few women to test for effect modification by sex. When we limited our analyses to men, however, coefficient magnitudes and directions did not differ considerably (analyses not shown). Fourth, we were unable to compare long-term cognitive outcomes among never-drinkers versus drinkers because there were very few lifetime abstainers ($n = 5$). Fifth, we were unable to study cognitive change or decline because cognitive abilities were measured only once in this cohort. Sixth, our findings may have limited generalizability to non-White, female, or less-educated persons or to groups with different patterns and levels of alcohol intake. However, our findings are consistent with other studies, and we found no reports suggesting that effect of alcohol on cognition is modified by level of education. A seventh potential limitation is that cognitive assessments were collected over a telephone; however, studies indicate that telephone cognitive assessments are valid (Crooks, Parsons, & Buckwalter, 2007) and some cognitive instruments are designed specifically for telephone use (e.g., Brandt et al., 1988). Eighth, we did not model a cumulative dose of alcohol to test associations with cognition. In regard to the associations found over time, however, it appeared that the magnitude of the effect of alcohol with phonemic fluency did not vary too considerably by length of follow-up. Finally, the power in our sample to detect significant associations was limited due to sample size and may be a reason we found few associations between alcohol intake and different cognitive ability measures. However, we were able to find significant associations between alcohol on phonemic fluency despite the sizable variability in that cognitive variable (Table 1).

This study has several important implications. Our data suggest that alcohol use in midlife should be maintained at low to moderate levels to support cognitive health in older age. Clinicians should assess alcohol intake in persons who present with impaired phonemic fluency. From an observational study

such as ours, it is not possible to know for certain that decreasing alcohol intake will maintain or improve phonemic fluency. Given the near impossibility of carrying out long-term clinical trials of alcohol intake with cognitive outcomes, however, it is advisable for individuals with impaired phonemic fluency who drink more than three to four drinks per week to decrease their alcohol intake. Future research examining alcohol and cognition should take advantage of domain-specific measures of cognition, particularly verbal fluency, rather than of global or summary measures.

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CONFLICT OF INTEREST

None of the authors have any financial, commercial, or other conflict of interests or connections, direct or indirect, that influenced the preparation of this manuscript. Human participant protection: All study procedures were approved by the Institutional Review Board (Johns Hopkins Medical Institution, Baltimore, Maryland).

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