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Alcohol Intake and Cognitively Healthy Longevity in Community-Dwelling Adults: The Rancho Bernardo Study

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Abstract. To better understand the association of alcohol intake with cognitively healthy longevity (CHL), we explored the association between amount and frequency of alcohol intake and CHL among 1,344 older community-dwelling adults. Alcohol intake was assessed by questionnaire in 1984–1987. Cognitive function was assessed in approximate four-year intervals between 1988 and 2009. Multinomial logistic regression, adjusting for multiple lifestyle and health factors, was used to examine the association between alcohol consumption and CHL (living to age 85 without cognitive impairment), survival to age 85 with cognitive impairment (MMSE score >1.5 standard deviations below expectation for age, sex, and education), or death before age 85. Most participants (88%) reported some current alcohol intake; 49% reported a moderate amount of alcohol intake, and 48% reported drinking near-daily. Relative to nondrinkers, moderate and heavy drinkers (up to 3 drinks/day for women and for men 65 years and older, up to 4 drinks/day for men under 65 years) had significantly higher adjusted odds of survival to age 85 without cognitive impairment (p's < 0.05). Near-daily drinkers had 2-3 fold higher adjusted odds of CHL versus living to at least age 85 with cognitive impairment (odds ratio (OR) = 2.06; 95% confidence interval (CI): 1.21, 3.49) or death before 85 (OR = 3.24; 95% CI: 1.92, 5.46). Although excessive drinking has negative health consequences, these results suggest that regular, moderate drinking may play a role in cognitively healthy longevity.

Keywords: Alcohol drinking, aging, cognitive impairment, cohort study, longevity

INTRODUCTION

Advances in public health and biomedical science have led to significant gains in life expectancy. By 2050, the world population over age 85 is expected to grow by 350% [1]. To decrease the societal burden of this demographic shift and to enhance quality of life among older adults, it is imperative to identify factors that promote healthy longevity. One potential factor is alcohol intake. Although excessive alcohol intake and alcohol intake among vulnerable populations (e.g., adolescents, pregnant women, those with substance use disorders) is a major public health concern, moderate intake among healthy adults may be associated with health benefits and longer lifespan [2–5]. Several studies report that the benefits of moderate alcohol intake also extend to the maintenance of cognitive health in late life [6–9]; however, the association is not consistent. The majority of studies support a protective effect of moderate alcohol intake, but some

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report a negative or null association [10–12]. A meta-analysis of 23 longitudinal studies found that low to moderate alcohol intake was protective for dementia (relative risk (RR) = 0.63, 95% confidence interval (CI): 0.53, 0.75) and Alzheimer's disease (RR = 0.57, 95% CI: 0.44, 0.74), but was not significantly associated with vascular dementia or age-related cognitive decline [8]. However, the characterization of alcohol exposure, the cognitive outcomes assessed, and the consideration of confounding variables varies widely across studies [13].

Most studies have examined the association of the amount of alcohol intake with mortality or cognitive impairment; fewer have examined associations with drinking frequency [14]. However, there is increasing evidence that drinking patterns may have greater influence over health than the amount consumed in a given time period, with the most favorable profile observed in regular, moderate drinkers and the poorest outcomes associated with chronic, heavy and binge-type drinking habits [15–17]. The importance of drinking pattern in prolonging cognitive health is not well known and merits greater attention.

The objective of this study was to examine the association of the amount and frequency of alcohol intake with cognitively healthy survival to age 85 in a cohort of older community-dwelling adults, taking into account multiple potentially confounding lifestyle and health factors.

MATERIALS AND METHODS

Study participants

The Rancho Bernardo Study (RBS) is an ongoing cohort study established in 1972–1974 when 82% ($n = 6,339$) of residents aged 30 and older, from the San Diego, CA suburb of Rancho Bernardo, were recruited for a study of heart disease risk factors [18]. Participants were predominantly white (99.4%), middle to upper-middle class adults aged 30–79. In 1984–87, 82% of the surviving RBS participants ($n = 2,479$) attended a research clinic visit that included a detailed questionnaire on alcohol intake. Participants were followed for vital status through December 2013. Cognitive function was first assessed at a research visit in 1988–92, and at subsequent visits approximately every 4 years. The last visit included in this analysis occurred in 2009. Eligibility for the current study required that participants had the potential to reach age 85 during the follow-up period (i.e., age 55–84 years at the 1984–87 visit); 538 participants were excluded based on age eligibility. Additionally, those who lived to at least age 85 must have had a cognitive function assessment within two years of their 85th birthday, or must have shown intact cognitive function at any visit subsequent to their 85th birthday; 584 participants were excluded based on this criterion. After exclusion of an additional 13 participants missing educational status, there remained 1,344 participants (728 women, 616 men) for the current analysis. This study was conducted in compliance with the Declaration of Helsinki and approved by the University of California San Diego (UC San Diego) Institutional Review Board; all participants provided written informed consent prior to participation at each visit.

Alcohol consumption

Alcohol consumption was assessed using a self-administered standardized questionnaire collected during the 1984–87 visit. Participants were asked if they had ever drunk an alcoholic beverage and, if so, whether they had done so within the past 12 months. Those answering yes to these questions were queried about how often they consumed alcohol in an average week with response choices of daily/almost daily; 3-4 times/week, 1-2 times/week, 1-2 times/month, or once/month. They were also asked how many bottles or cans of beer, glasses of wine, mixed drinks, and liqueurs or other drinks they consume during an average week. The following formula was used to estimate average weekly alcohol intake: grams of ethanol = [(number of bottles or cans of beer)(12oz.)(0.045oz. ethanol/oz. beer) + (number of glasses of wine)(3.5oz.)(0.122oz. ethanol/oz. wine)+ (number of mixed drinks)(1.5oz.)(0.41oz. ethanol/oz. spirits) + (number of liqueurs)(1oz.)(0.362oz. ethanol/oz. liqueurs) × (29.6 ml/oz.)] × 0.7893 g/ml where 12 grams of ethanol is equal to one drink [19].

Individuals denying past alcohol use (lifetime abstainers) and those who did not drink within the last year (former drinkers) were categorized as non-drinkers. Using sex-specific guidelines from the National Institute on Alcohol Abuse and Alcoholism, current drinking was categorized as moderate (≤1 drink/day for men age 65 and older and women; ≤2 drinks/day for men under 65), heavy (>1–3 drinks/day for men age 65 and older and women; >2–4 for men under 65), or excessive (>3 drinks/day for men age 65 and older and women; >4 drinks/day for men under 65) [20]. To describe frequency of alcohol intake, participants were categorized as nondrinkers,

infrequent (<2 times/month), weekly (1–4 times/week), or near-daily drinkers (5–7 times/week).

Mortality assessment

Vital status was determined annually by mailed questionnaires. Date and cause of death for decedents was obtained from death certificates.

Cognitive status

Cognitive function was assessed beginning in 1988–1992 at 6 visits at approximate four-year intervals. The Mini-Mental State Examination (MMSE) [21] was administered by a trained interviewer [22]. Raw MMSE scores were converted to sex, age, and education adjusted Z-scores using normative data from the National Institute on Aging–Alzheimer's Disease Research Center Uniform Data Set [23]. Individuals with Z-scores below –1.5 were classified as having cognitive impairment [24]. Individuals surviving to age 85 with cognitive impairment were classified as having Cognitively Impaired Longevity (CIL). Those surviving to at least age 85 without cognitive impairment were classified as attaining Cognitively Healthy Longevity (CHL). To be classified as having CHL, individuals must have completed the MMSE within 2 years of age 85, or older, with a Z-score of –1.5 or higher.

Covariate assessment

Baseline data collected at the 1984–87 visit included detailed information on lifestyle, medical history, anthropometrics, and laboratory measures. Lifestyle information, including smoking, exercise (≥3 times/week), and marital status was acquired through standard questionnaires. As described previously [25], depressed mood was assessed using 18 of the 21 items on the Beck Depression Inventory [26]; scores were proportionally adjusted. Individuals with a score below 13 were considered not categorically depressed. Participants were also asked about current medication use (number of medications) and whether they had ever been diagnosed with any of the following: thyroid, liver, kidney, or cardiovascular disease, diabetes, cancer (non-skin), emphysema, arthritis, hip fracture, hypertension, stroke, or transient ischemic attack. Height, weight, and waist and hip circumference were measured with participants in light clothing and no shoes, and waist-hip ratio was calculated as a measure of central adiposity. Blood pressure was recorded as the average of two readings obtained while the participant was in the rested, seated position by a nurse trained in the Hypertension Detection and Follow-up Program protocol [27]. Metabolic syndrome was defined using 2001 NCEP-ATPIII criteria [28]. Blood samples were collected after a requested overnight fast. Total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides were measured in a Center for Disease Control certified laboratory [29]. High-sensitivity C-reactive protein (CRP) measured by immunonephelometry (N-Latex CRP mono, Dade Behring, Deerfield, Illinois) was available for 1,040 subjects. Serum aspartate aminotransferase and alanine aminotransferase were measured by spectrophotometry. Gamma-glutamyl transferase was measured using the colorimetric method by a UCSD clinical laboratory. Apolipoprotein E (APOE) genotyping was carried out for a subsample of 892 participants by Sequana Therapeutics (La Jolla, CA) [30].

Statistical analysis

Descriptive statistics were calculated for independent variables including the mean and standard deviation (SD) for continuous variables and frequencies and percent for categorical variables. Non-normally distributed variables were log-transformed prior to analysis. Differences in covariates by levels of alcohol intake were assessed by chi-square or Fisher's exact tests and ANOVAs. Tests for trend were performed using linear or logistic regression.

Multinomial logistic regression models were constructed to examine the association between alcohol consumption and the three level outcome of interest: death before 85, CIL, and CHL. Odds ratios and 95% confidence intervals were estimated unadjusted and in sequential models adding adjustment for 1 age (years), sex and education (some college; yes/no), 2 smoking (never/current/former), exercise (≥3 times/week; yes/no) and waist-hip ratio, 3 number of comorbidities and number of medications, 4 marital status (married/not-married), and 5 depression (Beck Depression Inventory score >13, yes/no). Beck Depression Inventory scores were missing for 70 participants. Missing values for depression (yes/no) were imputed using SAS PROC MI. Non-drinkers (current non-drinkers and lifetime abstainers) were used as the reference category for all models.

Linear trends were assessed by including amount and frequency of alcohol intake as ordinal variables,

and nonlinear trends were assessed by inclusion of quadratic terms. Multiplicative interactions were evaluated by testing the significance of alcohol intake by sex and alcohol intake by *APOE* genotype interaction terms.

Potential confounding effects of diet were explored in a subset of 495 individuals who completed the 153-item Willett Food Frequency Questionnaire [31] at baseline. We calculated a modified Mediterranean diet score based on the scale by Trichopoulou et al. [32] as previously described [33]. We used the following components: vegetables, legumes, fruits, nuts, whole grains, fish, red meat, and monounsaturated-to-saturated fat ratio. Alcohol was not included as a component of the score. Individuals with red meat intake below the sex-specific median received one point and zero points otherwise. For each of the other components, those consuming above the sex-specific median received one point and zero points otherwise. The sum of these scores and the microgram amount of vitamin B12 intake from food were used as covariates in the multinomial regression model.

To address bias that may result from including individuals with poor health, we repeated these analyses excluding those who reported being in "worse" health compared to others the same age; thus, restricting the sample to those individuals reporting "better" or "the same" perceived health as their peers at baseline (N = 1,284). Measures of cognitive function were not available prior to the 1988–1992 visit; therefore we were unable to identify existing cases of cognitive impairment at baseline. As a sensitivity analysis, we repeated our analysis excluding participants above the median age of 74 years at baseline assuming they were at higher risk of cognitive impairment than younger participants. We also performed a sensitivity analysis limited to non-smokers only.

A p value below 0.05 (2-sided test) was considered statistically significant. All analyses were carried out using SAS (version 9.4, SAS Institute, Inc., Cary, NC).

RESULTS

Population characteristics

Baseline demographic and health characteristics of participants at the 1984–1987 visit according to amount of alcohol consumption are shown in Table 1. Most participants consumed some alcohol; only 157 (12%) were non-drinkers. Of these, only 28 (2.1%) were lifetime abstainers. Overall, 653 participants (49%) were moderate drinkers, 486 (36%) were heavy drinkers, and 61 (5%) reported excessive levels of drinking. Men reported more alcohol consumption than women (54.5% heavy drinkers versus 45.5% for women; $p < 0.001$). Excessive drinkers were younger than other groups (mean ± SD = 67.4 ± 6.5 versus 71.8 ± 6.7 years for non-drinkers; $p < 0.001$). Heavy and excessive drinkers were more likely to have attended college (74.6% and 80.3% versus 68.2% for non-drinkers; $p = 0.004$) and to be current smokers (17.3% and 32.8% versus 8.9% for non-drinkers; $p < 0.001$). Individuals who reported heavy drinking also exercised more frequently (87.3% exercised ≥3 times/week versus 79% for non-drinkers; $p = 0.006$). Moderate drinkers were the least likely to be married (76.2% versus 80.9% for non-drinkers; $p = 0.007$). Mean triglyceride levels were lowest in the heavy drinking group (mean ± SD = 110.5 ± 64.9 versus 128.4 ± 80.7 for non-drinkers; $p = 0.007$). Aspartate aminotransferase and alanine aminotransferase levels were highest among excessive drinkers (mean ± SD = 33.0 ± 25.5 and 24.2 ± 18.1 versus 28.8 ± 22.2 and 20.3 ± 14.7 in non-drinkers; all p's < 0.05). Number of comorbidities and frequency of cardiovascular disease and stroke decreased with increasing levels of alcohol intake (all p's $_{\text{for trend}}$ <0.05). Non-drinkers were more likely to report being in poorer health than drinkers (14% versus 2.3% in heavy drinkers; $p < 0.001$). Waist-hip ratio, diastolic blood pressure, HDL-C, and gamma-glutamyl transferase increased with increasing levels of alcohol consumption (all p's $_{\text{for trend}} < 0.05$). There were no significant differences in history of diabetes, hypertension, liver disease, transient ischemic attack, cancer, depression, *APOE* ε4 allele frequency, body mass index, or CRP by amount of alcohol consumed.

Table 2 shows baseline characteristics of the study sample by frequency of alcohol intake. Near-daily drinking was reported by almost half (48%) of study participants. Compared to men, women were more likely to be nondrinkers and to drink less frequently (59.2% non-drinkers for women versus 40.8% non-drinkers for men; $p < 0.001$). Drinking frequency did not differ by age. Current smoking was more frequent in near-daily drinkers (17.4% versus 8.2% for non-drinkers; $p < 0.001$). Infrequent drinkers were the least likely to be married or to have some college education (74.4% and 61.2% versus 80.9% and 68.2% for non-drinkers; all p's ≤ 0.01). Non-drinkers had the highest number of medications at baseline (mean ± SD = 1.2 ± 1.3 versus 1.0 ± 1.1 for near-daily drinkers; $p = 0.02$). Triglyceride and CRP

Table 1
Baseline (1984–1987) characteristics of participants according to amount of alcohol intake ($n = 1,344$); The Rancho Bernardo Study

	Non-drinkers ($n = 157$)		Moderate ($n = 645$)		Heavy ($n = 481$)		Excessive ($n = 61$)		p value[a]	p value[b]
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)		
Sex									<0.001	<0.001
Women $n = 728$	59.2		60.2		45.5		45.9			
Men $n = 616$	40.8		39.8		54.5		54.1			
Age in years		71.8 (6.7)		71.7 (7.0)		72.1 (6.1)		67.4 (6.5)	<0.001	0.09
Smoking Status									<0.001	<0.001
Never	61.1		42.9		27.7		23			
Past	29.9		48.5		55.1		44.3			
Current	8.9		8.5		17.3		32.8			
Exercise (≥3 times/week)	79.0		83.1		87.3		72.1		0.006	0.33
Some College	68.2		67		74.6		80.3		0.01	0.004
Married	80.9		76.2		84.2		83.6		0.007	0.03
History of CVD	22.3		18.4		15.2		13.1		0.15	0.02
History of Diabetes	19.1		14.9		12.5		21.3		0.08	0.28
History of Liver disease	7.6		8.7		6.4		9.8		0.59	0.66
History of Stroke	6.4		4.2		2.9		0		0.08	0.01
History of TIA	2.5		1.4		1.7		1.6		0.78	0.71
History of Cancer	26.8		27.3		29.9		21.3		0.41	0.70
History of Hypertension	40.8		38.1		40.1		39.3		0.90	0.91
Metabolic Syndrome $n = 1,322$	21.1		15.6		11.8		16.7		0.04	0.02
Depression[c] $n = 1,274$	10.4		6.9		6.3		11.7		0.18	0.54
Self-perceived health[d]									<0.001	0.01
Better	66.2		76.2		78.2		73.8			
Same	19.7		19.9		19.5		23			
Worse	14.0		3.9		2.3		3.3			
APOE ε4 carrier $n = 892$	25.6		25.9		26.0		29.8		0.94	0.66
Body Mass Index (kg/m^2)		24.8 (3.9)		24.7 (3.6)		24.6 (3.4)		24.9 (3.7)	0.90	0.85
Waist-Hip Ratio		0.84 (0.08)		0.84 (0.08)		0.86 (0.08)		0.89 (0.08)	<0.001	<0.001
SBP (mg/dl)		143.2 (23.1)		139.1 (20.3)		141.4 (20.7)		139.5 (20.1)	0.07	0.91
DBP (mg/dl)		75.6 (10.1)		75.6 (9.5)		77.3 (9.1)		79.4 (9.7)	0.001	<0.001
HDL-C (mg/dl)		56.6 (16.4)		60.4 (18.6)		65.6 (19.2)		68.3 (21.7)	<0.001	<0.001
LDL-C (mg/dl)		128.7 (36)		137.4 (36.1)		135.6 (37.3)		139.2 (37.8)	0.048	0.17
Triglycerides (mg/dl)		128.4 (80.7)		123.7 (75.1)		110.5 (64.9)		127 (66.9)	0.007	0.01
No. of Comorbidities		1.9 (1.3)		1.6 (1.2)		1.6 (1.2)		1.5 (1.1)	0.02	0.03
No. of Medications		1.2 (1.3)		1.0 (1.1)		1.0 (1.1)		0.9 (0.9)	0.14	0.06
GGT(IU/L)[e]		12 (11.5)		14.5 (27.1)		14.7 (17.3)		19.7 (20.8)	<0.001	<0.001
AST (IU/L)		28.8 (22.2)		27.1 (14.3)		26.2 (12.4)		33 (25.5)	0.008	0.99
ALT (IU/L)		20.3 (14.7)		19.8 (12.3)		19.1 (11.6)		24.2 (18.1)	0.03	0.69
CRP (mg/L)[e] $n = 1040$		3.1 (3.4)		2.9 (2.7)		2.7 (2.8)		2.8 (2.7)	0.29	0.11

ALT, alanine aminotransferase; APOE, Apolipoprotein E; AST, aspartate aminotransferase; CRP, C-Reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; TIA, transient ischemic attack. [a]p for differences based on ANOVA for continuous data and χ^2 or Fisher's exact test for categorical data. [b]p for trend based on linear regression for continuous data and logistic and multinomial regression for categorical data. [c]Beck Depression Inventory scale ≥13. [d]Self-perceived health compared to peers. [e]Log transformed for significance tests.

levels (mean ± SD = 113.0 ± 64.5 and 2.7 ± 2.7 for near-daily drinkers versus 128.4 ± 36.0 and 3.1 ± 3.4 for non-drinkers) and the proportion of individuals with diabetes (12.7% in near-daily drinkers versus 19.1% in non-drinkers) were significantly lower with increased drinking frequency (all p's < 0.05). Waist-hip ratio, HDL-C, and gamma-glutamyl transferase increased linearly with drinking frequency (all p's $_{\text{for trend}}$ <0.001). Exercise frequency, history of cardiovascular disease, liver disease, stroke, transient ischemic attack, and cancer, Beck Depression Inventory score, *APOE* ε4 carrier status, body mass index, aspartate aminotransferase, and alanine aminotransferase levels did not significantly differ by frequency of alcohol consumption.

Cognitively healthy longevity by amount of alcohol intake

Over an average of 14.2 ± 7.8 years of follow-up (median = 13.9 years), 353 (26%) individuals were classified as CHL, 445 (33%) as CIL, and

Table 2
Baseline (1984–1987) characteristics of participants according to the frequency of alcohol intake ($n = 1,343$); The Rancho Bernardo Study

	Non-drinkers ($n = 157$)		Infrequent ($\leq$2/mo) ($n = 309$)		Weekly ($n = 239$)		Near-daily ($n = 638$)		p value[a]	p value[b]
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)		
Sex									<0.001	<0.001
Women $n = 728$	59.2		67.0		53.6		47.0			
Men $n = 616$	40.8		33.0		46.4		53.0			
Age in years		71.8 (6.7)		72.0 (7.1)		71.2 (6.6)		71.6 (6.6)	0.57	0.54
Smoking Status									<0.001	<0.001
Never	61.1		50.2		35.6		28.7			
Past	29.9		40.5		56.9		53.9			
Current	8.9		9.4		7.5		17.4			
Exercise ($\geq$3 times/week)	79.0		81.2		86.2		85.0		0.14	0.05
Some College	68.2		61.2		74.9		73.8		<0.001	0.002
Married	80.9		74.4		76.2		83.9		0.002	0.01
History of CVD	22.3		17.2		18		16.3		0.35	0.16
History of Diabetes	19.1		17.8		13.8		12.7		0.08	0.01
History of Liver disease	7.6		10.0		7.1		7.1		0.47	0.33
History of Stroke	6.4		4.2		3.8		3.0		0.23	0.05
History of TIA	2.5		1.3		1.3		1.7		0.72	0.79
History of Cancer	26.8		26.2		25.1		30.1		0.32	0.15
History of Hypertension	40.8		40.8		30.1		41.5		0.01	0.84
Metabolic Syndrome $n = 1,322$	21.1		19.3		12.0		12.4		0.002	<0.001
Depression[c] $n = 1,274$	10.4		8.4		5.7		6.7		0.28	0.11
Self-perceived health[d]									<0.001	0.01
Better	66.2		77		76.9		76.8			
Same	19.7		18.1		20.6		20.5			
Worse	14.0		4.9		2.5		2.7			
APOE ε4 carrier $n = 892$	25.6		24.6		20.8		28.9		0.21	0.22
Body Mass Index (kg/m^2)		24.8 (3.9)		24.8 (3.8)		24.8 (3.6)		24.5 (3.4)	0.44	0.16
Waist-Hip Ratio		0.84 (0.08)		0.84 (0.08)		0.85 (0.09)		0.86 (0.08)	<0.001	<0.001
SBP (mg/dl)		143.2 (23.1)		140.3 (20.9)		137.6 (19.1)		140.9 (20.7)	0.046	0.51
DBP (mg/dl)		75.6 (10.1)		75.9 (9.3)		75.6 (8.7)		77.1 (9.6)	0.04	0.01
HDL-C (mg/dl)		56.6 (16.4)		58.4 (17.4)		61.6 (19.7)		65.6 (19.4)	<0.001	<0.001
LDL-C (mg/dl)		128.7 (36)		139.6 (37.9)		137.2 (35.2)		135.2 (36.6)	0.02	0.001
Triglycerides (mg/dl)		128.4 (80.7)		127.8 (78.4)		121.3 (76.2)		113 (64.5)	0.009	0.001
No. of Comorbidities		1.9 (1.3)		1.7 (1.3)		1.4 (1.1)		1.6 (1.2)	0.001	0.01
No. of Medications		1.2 (1.3)		1.1 (1.2)		0.9 (1.0)		1.0 (1.1)	0.02	0.02
GGT(IU/L)[e]		12.0 (11.5)		13.3 (22.1)		15.0 (29.8)		15.6 (21)	<0.001	<0.001
AST (IU/L)		28.8 (22.2)		27.5 (14.4)		26.1 (10.5)		27.3 (15.7)	0.40	0.37
ALT (IU/L)		20.3 (14.7)		19.7 (13.2)		19.8 (10.9)		19.8 (12.6)	0.97	0.75
CRP (mg/L)[e] $n = 1040$		3.1 (3.4)		3.0 (2.8)		2.7 (2.6)		2.7 (2.7)	0.04	0.03

ALT, alanine aminotransferase; APOE, Apolipoprotein E; AST, aspartate aminotransferase; CRP, C-Reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; TIA, transient ischemic attack. [a]p for differences based on ANOVA for continuous data and χ^2 or Fisher's exact test for categorical data. [b]p for trend based on linear regression for continuous data and logistic and multinomial regression for categorical data. [c]Beck Depression Inventory scale $\geq$13. [d]Self-perceived health compared to peers. [e]Log transformed for significance tests.

546 (41%) died before reaching age 85. Amount of alcohol intake was associated with greater odds of CHL compared to CIL or death before age 85 (Table 3). We found a curvilinear association between the amount of alcohol intake and CHL ($p < 0.03$ for quadratic terms). The multivariate adjusted odds of CHL compared to CIL was approximately twice as high in moderate and heavy drinkers compared to non-drinkers (odds ratio (OR) = 1.90, 95%CI: 1.13, 3.20 and OR = 2.05, 95%CI: 1.19, 3.93). Though not significant, the adjusted odds of CHL compared to CIL was also higher (OR = 1.54, 95%CI: 0.62, 3.78) in excessive drinkers compared to non-drinkers. The likelihood of CHL compared to death before age 85 increased with the level of alcohol intake from moderate (OR = 2.41, 95%CI: 1.44, 4.03) to heavy drinkers (OR = 2.88, 95%CI: 1.69, 4.91) and was also higher in excessive drinkers (OR = 2.61, 95%CI: 1.08, 6.28) compared to non-drinkers. There were no significant interactions between sex or *APOE* ε4 carrier status and amount of alcohol intake on the odds of CHL ($p_{\text{interaction}} \geq 0.05$).

Table 3
Association between the amount of alcohol intake and Cognitively Healthy Exceptional Longevity (CHL); results of multinomial logistic regression

	Odds of CHL versus Death before age 85								Odds of CHL versus Cognitively Impaired Longevity (CIL)							
	Non-drinkers		Moderate		Heavy		Excessive		*p* value[b]	Non-drinkers		Moderate		Heavy		Excessive		*p* value[b]
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	
Unadjusted	1	Referent	2.13	1.31, 3.45	2.21	1.35, 3.64	1.10	0.48, 2.50	<0.001	1	Referent	1.69	1.01, 2.81	1.80	1.07, 3.04	1.12	0.47, 2.68	0.03
Model 1	1	Referent	2.19	1.34, 3.58	2.42	1.46, 4.03	1.56	0.67, 3.61	0.004	1	Referent	1.70	1.02, 2.84	1.81	1.07, 3.06	1.28	0.53, 3.11	0.049
Model 2	1	Referent	2.35	1.41, 3.91	2.88	1.70, 4.90	2.48	1.03, 5.92	0.02	1	Referent	1.79	1.07, 2.99	1.95	1.14, 3.34	1.45	0.59, 3.57	0.048
Model 3	1	Referent	2.31	1.39, 3.88	2.80	1.64, 4.78	2.45	1.02, 5.88	0.02	1	Referent	1.87	1.11, 3.14	2.03	1.18, 3.48	1.52	0.62, 3.73	0.04
Model 4	1	Referent	2.35	1.40, 3.94	2.82	1.65, 4.83	2.46	1.02, 5.92	0.02	1	Referent	1.91	1.14, 3.22	2.04	1.19, 3.51	1.53	0.62, 3.76	0.03
Model 5[a]	1	Referent	2.41	1.44, 4.03	2.88	1.69, 4.91	2.61	1.08, 6.28	0.02	1	Referent	1.90	1.13, 3.20	2.05	1.19, 3.53	1.54	0.62, 3.78	0.03

CHL, cognitively healthy longevity; CIL, cognitively impaired longevity; CI, confidence interval; OR, odds ratio. Model 1: Age at baseline + Sex + Some College. Model 2: Model 1 + Smoking + Exercise + Waist-Hip Ratio. Model 3: Model 2 + Number of comorbidities + Number of Medications. Model 4: Model 3 + Marital Status. Model 5: Model 4 + Depression. [a]Generated using multiple imputation for missing values. [b]*p* value for non-linear trend.

Adjustment for Mediterranean diet and vitamin B12 did not change the results (not shown). The odds of CHL also remained significantly higher among moderate and heavy drinkers compared to nondrinkers when limited to those reporting "better" or "the same" health compared to others their age (not shown). The positive associations between amount of alcohol intake and cognitively healthy longevity were not diminished when we restricted analysis to non-smokers only (not shown). When analysis was limited to those participants below the median age, the odds ratios were slightly attenuated; however, the odds of CHEL remained highest among heavy drinkers relative to non-drinkers (not shown).

Cognitively healthy longevity and frequency of alcohol intake

The adjusted odds of CHL compared to death before age 85 and CIL increased linearly with frequency of alcohol consumption ($p = 0.03$ and <0.001, respectively; Table 4). After adjusting for covariates, near-daily alcohol intake was associated with a more than 3-fold increase in the odds of CHL compared to death (OR = 3.24, 95%CI: 1.92, 5.46). Compared to nondrinkers, those with near-daily intake of alcohol had the highest odds of CHL compared to CIL (OR = 2.06, 95%CI: 1.21, 3.49). The quadratic term for frequency of alcohol intake did not significantly add to the model. No significant interactions were detected between sex or *APOE* genotype and frequency of alcohol intake on odds of CHL ($p_{\text{interaction}} \geq 0.05$). Results were similar after adjustment for diet and vitamin B12 (not shown). Near-daily drinking retained its significant protective association with CHL when analysis was restricted to those reporting "better" or "the same" health compared to others their age (not shown). Sensitivity analysis limited to non-smokers revealed a similar trend (not shown). The odds of CHEL remained significantly higher in near-daily drinkers compared to non-drinkers but associations were slightly attenuated in the subset of participants below the median age only (not shown).

Non-participant characteristics

Cognitive function data was unavailable for 584 subjects (30% of age-eligible subjects). Compared to participants included in the analysis, these non-participants were slightly older (71.7 versus 72.7, respectively; $p = 0.005$) and more likely to be female

Table 4
Association between the frequency of alcohol intake and Cognitively Healthy Exceptional Longevity (CHL); results of multinomial logistic regression

	Odds of CHL versus Death before age 85								Odds of CHL versus Cognitively Impaired Longevity (CIL)							
	Non-drinkers		Infrequent ≤2x/mo		Weekly		Near-daily		p value[b]	Non-drinkers		Infrequent ≤2x/mo		Weekly		Near-daily		p value[b]
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	
Unadjusted	1	Referent	1.92	1.14, 3.25	1.79	1.03, 3.10	2.30	1.42, 3.73	0.003	1	Referent	1.71	0.98, 2.97	1.49	0.83, 2.65	1.78	1.07, 2.96	0.09
Model 1	1	Referent	1.86	1.09, 3.16	1.96	1.12, 3.42	2.60	1.59, 4.27	<0.001	1	Referent	1.70	0.98, 2.96	1.53	0.86, 2.74	1.81	1.08, 3.01	0.08
Model 2	1	Referent	1.96	1.14, 3.40	2.08	1.17, 3.73	3.23	1.92, 5.43	<0.001	1	Referent	1.76	1.01, 3.08	1.63	0.90, 2.93	1.96	1.16, 3.31	0.04
Model 3	1	Referent	1.96	1.13, 3.42	2.01	1.12, 3.61	3.15	1.87, 5.32	<0.001	1	Referent	1.82	1.04, 3.18	1.73	0.96, 3.13	2.04	1.20, 3.45	0.03
Model 4	1	Referent	1.99	1.14, 3.47	2.04	1.14, 3.68	3.16	1.87, 5.35	<0.001	1	Referent	1.86	1.06, 3.26	1.78	0.98, 3.22	2.05	1.21, 3.47	0.03
Model 5[a]	1	Referent	2.05	1.18, 3.56	2.11	1.17, 3.79	3.24	1.92, 5.46	<0.001	1	Referent	1.85	1.06, 3.25	1.76	0.97, 3.18	2.06	1.21, 3.49	0.03

CHL, cognitively healthy longevity; CIL, cognitively impaired longevity; CI, confidence interval; OR, odds ratio. Model 1: Age at baseline + Sex + Some College. Model 2: Model 1 + Smoking + Exercise + Waist-Hip Ratio. Model 3: Model 2 + Number of comorbidities + Number of Medications. Model 4: Model 3 + Marital Status Model 5: Model 4 + Depression. [a]Generated using multiple imputation for missing values. [b]p value for linear trend.

(54% versus 62%, respectively; $p = 0.003$). The proportion of non-drinkers did not differ (10% versus 12%; $p = 0.38$), but among those who did drink, non-participants reported lower average weekly alcohol intake (73 versus 93 grams/week; $p < 0.001$) and were less likely to drink on a near-daily basis (45% versus 54%; $p < 0.001$).

Former drinkers versus lifetime abstainers

Compared to lifetime abstainers ($n = 28$), former drinkers ($n = 129$) were significantly more likely to be past (14% versus 33%, respectively) or current smokers (0% versus 11%, respectively; $p = 0.01$). Women made up 71% of the lifetime abstainers and 56% of the former drinkers ($p = 0.15$ for sex differences). Though not significant, lifetime abstainers had higher exercise frequency (89% versus 77% exercised 3 or more times/week; $p = 0.14$) and were more likely to have attended some college (79% versus 66%; $p = 0.19$) compared to former drinkers. Lifetime abstainers and former drinkers were similar with regards to the number of comorbidities (mean $\pm$ SD = 1.8 ± 1.2 versus 1.9 ± 1.3, respectively; $p = 0.67$) and number of medications (mean $\pm$ SD = 1.1 ± 1.3 versus 1.2 ± 1.3, respectively; $p = 0.70$).

DISCUSSION

In this study of 1,344 community-dwelling older adults, we found significant associations between amount and frequency of alcohol intake and cognitively healthy longevity. Moderate and heavy drinkers (up to 3 drinks/day for women and for men 65 years and older, up to 4 drinks/day for men under 65 years) had 2-fold higher odds of living to age 85 without cognitive impairment relative to non-drinkers. Individuals who drank on a near-daily basis were also more likely to live to age 85 without cognitive impairment than those who drank less frequently or did not drink at all. These associations remained significant after adjustment for numerous lifestyle and health characteristics.

To our knowledge, this is the first study to examine the association of the amount and frequency of alcohol consumption with cognitively healthy longevity versus being cognitively impaired in later life or dying before age 85. Our results are in accord with the existing body of literature that supports a U-shaped or J-shaped association between alcohol consumption and mortality [3–5]. Our results are also in agreement with previous reports that suggest lower risk

of cognitive impairment among moderate drinkers than non-drinkers [7, 8, 34, 35]. A meta-analyses of 74 studies [34] reported an RR of 0.77 for cognitive impairment in moderate drinkers compared to nondrinkers with an increased risk of cognitive impairment in excessive drinkers. While our study did not find a higher likelihood of cognitive impairment in advanced age in excessive drinkers, very few participants in our cohort reported drinking to excess.

Prior investigations used alternative approaches to study associations with healthy longevity in women. Our findings are in accord with those of a recent study from the Women's Health Initiative Memory Study [36] designed to identify predictors of preserved cognitive function in women age 80 or older. That study reported a significant association between moderate alcohol intake and preserved cognition. Similarly, results from the Nurses' Health Study, showed an association between moderate, regular alcohol consumption at midlife and successful aging defined as living to age 70 without physical or cognitive impairment [37]. Although our outcome differs from these previous studies, they are all in agreement concerning the potential benefits of alcohol consumption for healthy aging. Our study extends these findings to men and to a longer cognitive healthspan. We found no significant variation in the association between alcohol intake and cognitively healthy longevity according to sex.

Our results are in contrast to those of a population study in Norway that found that frequent drinking was associated with increased dementia risk compared to non-frequent drinking [11]. However, in that study, frequent drinkers were defined as those consuming five or more drinks in a 14-day period and comprised only 6.5% of the population, a drinking pattern very different than that observed in our cohort. Furthermore, no information was provided on whether alcohol intake was spread across the 14-day period or concentrated in a few days (e.g., weekends), and, as our results show, frequency of drinking affects the association of alcohol with cognitive function.

Potential biological mechanisms for a beneficial effect of moderate alcohol intake on cardiovascular health have been extensively investigated [38]. However, the exact mechanisms by which alcohol may provide neuroprotective effects are not fully understood. Effects may be mediated through increased HDL and antioxidant activity and decreased LDL, fibrinogen, and platelet activity, slowing the formation of amyloid plaques and preserving optimal vascular function in the brain [39]. In the RBS, moderate and heavy drinkers and those reporting near-daily drinking had a more favorable cardiovascular profile including higher HDL-C and lower triglyceride levels than non-drinkers. Alcohol also stimulates acetylcholine release in the hippocampus, positively affecting learning and memory [40]. The influence of moderate alcohol intake on psychosocial factors such as stress and depression, which may also impact cognitive function, merits further study [41].

As we have noted previously [19, 42], the prevalence of any alcohol use in this study population is higher (88%) than that in the general U.S. population (46% of older adults aged 55 years and older according to the 1990 National Health Interview Survey [43]). The demographic profile of the RBS cohort, which is predominantly white and middle-class with some college education, may contribute to this difference. U.S. population surveys have shown that the proportion of drinkers increases with income and education level, and that whites are more likely to drink than individuals from other ethnic groups [44, 45]. These differences between the RBS cohort and general U.S. population may limit generalizability, but the homogeneity of the cohort increases the internal validity of our results by reducing potential confounding by these factors. There are a number of other limitations to this study. We examined alcohol consumption at only one time point; however, drinking patterns within this cohort remain relatively stable over time [19]. As in the majority of alcohol-related studies, we used self-report to assess alcohol intake. This may underestimate actual amount consumed. However, this is unlikely to affect the rank-order of exposure categories and would introduce a conservative bias leading to underestimation of the association. Additionally, RBS self-reported alcohol intake correlated with values obtained from interviews conducted by trained dietitians [46] and corresponded to indirect markers of alcohol intake including aspartate aminotransferase, alanine aminotransferase, HDL-C, and gamma-glutamyl transferase [46–49].

The reference group was composed of lifetime abstainers and former drinkers, raising the possibility of reverse causation by including individuals who may have stopped drinking due to poor health (i.e., "sick quitters"). However, adjustment for health-related variables including the number of medications and comorbidities did not attenuate the association. Additionally, a sensitivity analysis limited to individuals reporting "better" or "the same" health as others

their age yielded similar findings. This is consistent with a meta-analysis of 19 studies that excluded "sick quitters" from the reference category and found that the significant beneficial association of alcohol consumption remained [34].

We had no assessments of cognitive function at or prior to the assessment of alcohol intake. Therefore, we cannot exclude the possibility of reverse causation that may have resulted if pre-existing cognitive impairment led to a decrease in drinking. However, we believe this was unlikely as alcohol intake was measured approximately 4 years before the first cognitive exam, and cognitively impaired individuals are less likely to attend follow-up visits. As a sensitivity analysis, we excluded individuals above the median age of 74 years at baseline, because they are at higher risk of cognitive impairment than younger participants. Although odds ratios were attenuated, the associations did not change direction.

Although the MMSE has high sensitivity for detecting dementia [50], we did not have a neurological exam to corroborate the existence of cognitive impairment. Additionally, cognitive test scores may fluctuate over time, and it is possible that some individuals who did not meet criteria for impairment at age 85 or older, may have scored below the MMSE threshold on a prior assessment. As this misclassification was likely not associated with alcohol use and therefore non-differential with regards to exposure, results may have been biased to the null.

There were several strengths to our study. The extensive data collected on this cohort allowed for control of many potential confounders such as education, diet, smoking, and physical activity. Further, we addressed the heterogeneity of alcohol metabolism between men and women by using sex-specific cutoffs when defining exposure categories for the amounts of alcohol consumed. Finally, we considered the effects of both amount and frequency of alcohol consumption in the analysis.

In conclusion, this study found a positive association between moderate alcohol intake and cognitively healthy longevity, an association that was greatest in individuals with a regular, moderate drinking pattern. In the United States, alcohol use contributes to 88,000 deaths annually and has a substantial number of additional adverse health, economic, and societal consequences [51]. For these reasons, it is not appropriate to recommend that abstainers initiate drinking. However, among those who choose to consume alcohol, regular, moderate drinking may play a role in promoting cognitively healthy longevity.

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