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ORIGINAL INVESTIGATIONS

Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults

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ABSTRACT

BACKGROUND Previous studies have revealed inconsistent findings regarding the association of light to moderate alcohol consumption with cardiovascular disease (CVD) and cancer mortality.

OBJECTIVES The aim of this study was to examine the association between alcohol consumption and risk of mortality from all causes, cancer, and CVD in U.S. adults.

METHODS Data were obtained by linking 13 waves of the National Health Interview Surveys (1997 to 2009) to the National Death Index records through December 31, 2011. A total of 333,247 participants ≥18 years of age were included. Self-reported alcohol consumption patterns were categorized into 6 groups: lifetime abstainers; lifetime infrequent drinkers; former drinkers; and current light, moderate, or heavy drinkers. Secondary exposure included participants' binge-drinking status. The main outcome was all-cause, cancer, or CVD mortality.

RESULTS After a median follow-up of 8.2 years (2.7 million person-years), 34,754 participants died of all causes (including 8,947 CVD deaths and 8,427 cancer deaths). Compared with lifetime abstainers, those who were light or moderate alcohol consumers were at a reduced risk of mortality for all causes (light—hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.76 to 0.82; moderate—HR: 0.78; 95% CI: 0.74 to 0.82) and CVD (light—HR: 0.74; 95% CI: 0.69 to 0.80; moderate—HR: 0.71; 95% CI: 0.64 to 0.78), respectively. In contrast, there was a significantly increased risk of mortality for all causes (HR: 1.11; 95% CI: 1.04 to 1.19) and cancer (HR: 1.27; 95% CI: 1.13 to 1.42) in adults with heavy alcohol consumption. Binge drinking ≥1 d/week was also associated with an increased risk of mortality for all causes (HR: 1.13; 95% CI: 1.04 to 1.23) and cancer (HR: 1.22; 95% CI: 1.05 to 1.41).

CONCLUSIONS Light and moderate alcohol intake might have a protective effect on all-cause and CVD-specific mortality in U.S. adults. Heavy or binge drinking was associated with increased risk of all-cause and cancer-specific mortality.
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CVD = cardiovascular disease

HR = hazard ratio

NDI = National Death Index

NHIS = National Health Interview Survey

PA = physical activity

High alcohol consumption poses a significant health care and economic burden in the United States, and it has been linked to mortality due to injuries, violence, poisoning, liver cirrhosis, and cancer, and to morbidity due to several chronic diseases (1,2). The 2015 U.S. Dietary Guidelines for Americans (3) indicate that if alcohol is consumed, it should be consumed in moderation (≤2 drinks/day for men and ≤1 drink/day for women). The 2015 European Code against Cancer-4th Edition recommended that drinkers should limit alcohol intake, and no drinking is better for cancer prevention (4). It is well established that excessive alcohol consumption has an adverse effect on human health and mortality (1). However, evidence regarding the risk of morbidity and mortality among light to moderate drinkers is inconsistent. Previous studies have reported a lower risk of total mortality or cardiovascular disease (CVD) among light to moderate drinkers (1,5), whereas a few studies reported a higher risk of breast cancer (6).

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Many studies have investigated the association between alcohol consumption and all-cause mortality but with inconsistent findings. A majority of studies found a "J-shaped" relationship (1,5,7), and several reported a nonsignificant association (8,9). However, most previous cohort studies were subject to serious methodological issues, such as "abstainer bias" (i.e., former drinker misclassified as abstainer), insufficient adjustment for potential confounding factors ("limited confounding adjustment issue"), and the inclusion of subjects with serious illness ("sick quitter phenomenon"). Recently, Stockwell et al. (8) performed a meta-analysis of 87 publications reporting alcohol-related mortality and replicated the classic J-shaped curve. However, in a subsequent analysis of 13 of these studies with no abstainer bias that controlled for potential confounding factors, the protective effect of low-volume drinking disappeared. In addition, among the 6 higher quality bias-free studies included in that meta-analysis, only 2 studies included populations from the United States, and they provided inconsistent findings on the association between alcohol consumption and mortality risk (10,11).

To address the abstainer bias, limited confounding adjustment issue, and sick quitter phenomenon seen in earlier studies, the present study used a nationally representative sample of U.S. adults to assess the association of alcohol consumption with mortality from all causes, cancer, or CVD.

METHODS

The National Health Interview Survey (NHIS) is an ongoing national cross-sectional survey, administered by the National Center for Health Statistics of the Centers for Disease Control and Prevention since 1957, to monitor the health of a civilian, noninstitutionalized U.S. population. NHIS uses a stratified, multistage sampling design to collect information from sample participants, representative of the U.S. population, using personal household interviews. One adult is randomly selected from each household for a detailed interview on health and lifestyle behaviors. The NHIS sample is redesigned every 10 years; major revisions to the survey questionnaires were made in 1982 and 1997. Thus, we used the NHIS data starting from 1997 for consistencies in self-reported responses of the survey participants. NHIS data are de-identified and do not include any protected health information. The data are publicly available and considered as exempt under the ethical board review of the corresponding author's institution.

A total of 366,376 NHIS participants ≥18 years of age from 13 cross-sectional waves conducted during 1997 to 2009 (linked to mortality data in 2011) were included in the study. Of these participants, 33,129 were excluded because of missing data on alcohol consumption (n = 5,910), missing data on covariates (i.e., demographic variables, behavior factors, history of chronic diseases; n = 23,303), or pregnancy (n = 3,916), resulting in a final analytical sample of 333,247 participants.

STUDY OUTCOME: MORTALITY. The NHIS data from 1997 to 2009 were linked to the National Death Index (NDI) records through December 31, 2011, using a probabilistic matching algorithm to determine mortality status (12). All NHIS participants ≥18 years of age were eligible for mortality follow-up. Participants not matched with a death record were considered alive during the follow-up period. The validation studies (13,14) showed that all-cause and cause-specific death information in the NDI records was accurate and that the matching algorithm yielded perfect agreement (98.5%). Using the International Classification of Diseases-10th Revision codes, study outcomes were defined as follows: 1) all-cause mortality; 2) CVD-specific mortality (codes I00 to I09, I11, I13, and I20 to I51, I60 to I69); 3) heart

disease-specific mortality (codes I00 to I09, I11, I13, and I20 to I51); 4) cerebrovascular disease-specific mortality (codes I60 to I69); and 5) cancer-specific mortality (codes C00 to C97).

STUDY EXPOSURE: ALCOHOL CONSUMPTION. NHIS study participants were administered questionnaires relating to their alcohol consumption status and patterns of use. These questions obtained information about the following: 1) consumption of ≥12 drinks in one's lifetime, in any previous year, or in the past year; 2) drinking frequency (days per week or month or year) and drinking quantity (drinks per day) in the past year; and 3) binge drinking in the past year. One alcoholic drink-equivalent is described as containing 14 g (0.6 fluid ounce) of pure alcohol. The following are reference beverages that are 1 alcoholic drink-equivalent: 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12% alcohol), or 1.5 fluid ounces of 80 proof distilled spirits (40% alcohol) (3).

Using self-reported responses for these questionnaires, survey participants were categorized into 6 alcohol consumption groups, as described in the previous studies (3,15). These include: 1) lifetime abstainers: <12 drinks in one's lifetime; 2) lifetime infrequent drinkers: ≥12 drinks in one's lifetime but <12 drinks in any previous year; 3) former drinkers: ≥12 drinks in a previous year; 4) current light drinker: current use of <3 drinks/week; 5) current moderate drinkers: >3 drinks/week to ≤14 drinks/week for men or >3 drinks/week to ≤7 drinks/week for women; and 6) current heavy drinkers: >14 drinks/week for men or >7 drinks/week for women. Binge drinking was defined by using the question: "In the past year, on how many days did you have 5 or more drinks of any alcoholic beverage?" (16). We then transferred the original answers using unit as days per year into the data using unit as days per week (or month).

COVARIATES. Several covariates were included as confounders in the study. Demographic variables included sex, age, race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and others), education level (did not complete high school, completed high school, and education beyond high school), marital status (married; divorced, separated, or widowed; and never married). Lifestyle variables included body mass index, physical activity (PA), and smoking status. Body mass index was calculated as weight in kilograms divided by height squared. A participant's PA was defined by using self-reported responses to the frequency (times per week) and duration (minutes per activity period) of PA. Two sets of questions assessing the frequency and duration of leisure time PA were used to define vigorous PA (e.g., running) that causes heavy sweating or large increases in breathing or heart rate, and light or moderate PA (e.g., brisk walking) that causes only light sweating or a light to moderate increase in breathing or heart rate. The 2008 Physical Activity Guidelines for Americans recommend at least 75 min of vigorous PA or 150 min of moderate PA in 1 week (17). We then categorized the participants into 2 groups based on whether they met the PA guidelines. In addition, we defined smoking status of a participant using self-reported yes or no responses to the following 2 questions: 1) Have you smoked at least 100 cigarettes in your ENTIRE LIFE? and 2) Do you NOW still smoke cigarettes? Using the responses to these questions, we categorized the participant into never (who responded "No" to both questions), former (who responded "Yes" to the first question and "No" the second), and current (who responded "Yes" to the second question) smoking. Clinical variables included participants' self-reported responses to physician diagnoses of hypertension, heart disease, stroke, cancer, or diabetes.

STATISTICAL ANALYSIS. Baseline characteristics of study participants were reported by using percentages for categorical variables and mean ± SE for continuous variables. In addition, we tested for differences between the 6 categories of alcohol consumption among participant characteristics by using an analysis of variance model for continuous variables and the chi-square test for categorical variables. To address the issue of "abstainer bias" raised by earlier studies (8), alcohol consumption was modeled for by using lifetime abstainers as the reference group.

For the primary analysis, we used multivariate Cox proportional hazards regression model with the proportionality assumption to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of alcohol consumption with mortality, adjusted for potential confounding factors. To address the "limited confounding adjustment issue" (8), models were developed that sequentially adjusted for confounding factors. Model 1 adjusted for some demographic factors (sex, age, and race or ethnicity). Model 2 additionally adjusted for lifestyle and clinical variables. To address the "sick quitter phenomenon," in which sick individuals were more likely to quit alcohol consumption, a sensitivity analysis was performed by excluding participants with a history of physician-diagnosed diseases. We also performed a sensitivity analysis after exclusion of individuals who died within the first 2 years (i.e., a 2-year lag).

TABLE 1 Baseline Characteristics

	Alcohol Consumption Status							
	Overall (N = 333,247)	Lifetime Abstainer (n = 76,869)	Lifetime Infrequent Drinker (n = 29,314)	Former Drinker (n = 24,904)	Light Drinker (n = 139,269)	Moderate Drinker (n = 46,195)	Heavy Drinker (n = 16,696)	p Value
Age, yrs								<0.001
18–39	41.4	42.8	23.6	24.6	46.0	43.1	44.7	
40–59	36.6	29.3	40.2	39.2	38.2	38.7	39.3	
≥60	22.0	27.9	36.2	36.2	15.8	18.2	16.0	
Sex								<0.001
Female	50.6	65.5	57.5	39.3	52.9	25.7	42.9	
Race or ethnicity								<0.001
Non-Hispanic white	72.2	57.1	72.2	76.4	75.2	80.5	81.6	
Non-Hispanic black	11.4	17.1	14.4	11.4	9.6	7.7	8.1	
Hispanic	11.8	17.4	9.7	9.4	11.1	9.0	7.8	
Other	4.6	8.4	3.8	2.8	4.1	2.7	2.4	
Education								<0.001
Did not complete high school	16.8	26.9	23.6	23.6	11.5	10.5	15.2	
Completed high school	29.2	31.8	34.2	33.2	27.2	25.5	30.6	
Beyond high school	54.0	41.3	42.2	43.3	61.3	64.0	54.3	
Marital status								<0.001
Married	57.2	52.4	61.8	59.2	59.8	57.2	45.8	
Divorced/separated/widowed	17.0	19.1	23.7	23.6	14.7	13.5	17.4	
Never married	25.8	28.5	14.6	17.2	25.5	29.3	36.8	
Body mass index, kg/m^2	26.97 ± 0.02	26.87 ± 0.03	27.99 ± 0.05	27.76 ± 0.05	26.98 ± 0.02	26.46 ± 0.03	26.04 ± 0.05	<0.001
Physical activity (meeting recommendation)								<0.001
Yes	40.3	28.0	32.0	30.4	44.8	52.6	47.3	
Smoking								<0.001
Never	55.4	81.2	49.4	34.3	54.9	41.8	27.1	
Former	22.2	8.9	28.0	41.0	22.3	28.6	23.9	
Current	22.4	9.9	22.6	24.7	22.8	29.6	49.0	
Physician-diagnosed disease								
Hypertension	25.2	27.3	37.2	36.9	21.1	22.1	24.4	<0.001
Heart disease	11.4	11.7	18.7	20.6	9.3	9.1	9.0	<0.001
Stroke	2.4	3.1	4.8	5.7	1.4	1.3	1.5	<0.001
Cancer	7.1	6.5	10.6	11.8	6.2	6.6	7.0	<0.001
Diabetes	7.0	9.1	14.1	14.3	5.1	3.3	2.8	<0.001

Values are % or mean ± SE.

As described earlier in this section, the missing data accounted for 8.0% (29,213 of 366,376) of the total population. Thus, a sensitivity analysis was performed after multiple imputations for variables with missing values (18). We used the Markov chain Monte Carlo imputation, which assumes that all variables in the imputation model exhibit joint multivariate normal distribution. This method is the best and most common imputation technique, which has been found to result in reliable estimates even when the distribution of variables is not normal. Multiple imputations were conducted in 3 steps: 1) the imputation phase, in which the imputed datasets were created for the variables with missing data; 2) the analysis phase, in which the imputed datasets were analyzed with outcome of interest; and 3) pooling phase, in which all coefficients and error terms from all imputed datasets were pooled to obtain 1 set of parameter estimates (19).

To quantitatively assess the dose-response association of current alcohol consumption (as a continuous variable) with all-cause and cause-specific mortality, Cox models with penalized splines (20) were performed by using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). The output includes a graphic representation of the fitted splines and SE bars, with log HR for mortality on the y-axis and current alcohol consumption on the x-axis. In addition, stratified analyses were conducted a priori to assess whether the association of alcohol consumption with mortality varied among different sexes, age groups, race or ethnic groups, and participant smoking status. For binge-drinking status, the participants were categorized into 5 subgroups

TABLE 2 All-Cause and Cause-Specific Mortality According to Alcohol Consumption Status

	Alcohol Consumption Status					
	Lifetime Abstainer*	Lifetime Infrequent Drinker	Former Drinker	Light Drinker	Moderate Drinker	Heavy Drinker
All-cause						
Deaths	10,109	5,212	5,281	9,049	3,466	1,637
Person-years	621,157	230,997	192,215	1,180,790	385,185	136,965
Model 1†	1	1.19 (1.14–1.23)	1.35 (1.30–1.41)	0.76 (0.74–0.79)	0.74 (0.71–0.78)	1.29 (1.21–1.38)
Model 2‡	1	1.03 (0.99–1.07)	1.07 (1.02–1.11)	0.79 (0.76–0.82)	0.78 (0.74–0.82)	1.11 (1.04–1.19)
2-yr lag model§	1	1.02 (0.98–1.06)	1.04 (0.99–1.09)	0.80 (0.77–0.93)	0.81 (0.77–0.85)	1.13 (1.05–1.21)
Cancer						
Deaths	1,974	1,155	1,251	2,456	1,052	539
Person-years	576,333	208,541	171,748	1,140,959	370,861	130,714
Model 1†	1	1.30 (1.19–1.41)	1.61 (1.48–1.76)	0.95 (0.88–1.02)	1.00 (0.91–1.10)	1.86 (1.66–2.08)
Model 2‡	1	1.03 (0.95–1.12)	1.14 (1.04–1.24)	0.86 (0.80–0.93)	0.87 (0.80–0.96)	1.27 (1.13–1.42)
2-yr lag model§	1	1.05 (0.96–1.16)	1.12 (1.01–1.25)	0.89 (0.82–0.97)	0.95 (0.85–1.05)	1.40 (1.23–1.58)
CVD						
Deaths	2,846	1,456	1,360	2,195	780	310
Person-years	580,988	210,423	172,182	1,140,015	369,298	129,539
Model 1†	1	1.23 (1.14–1.32)	1.27 (1.17–1.37)	0.68 (0.64–0.73)	0.62 (0.56–0.68)	0.97 (0.84–1.11)
Model 2‡	1	1.05 (0.97–1.14)	0.99 (0.91–1.08)	0.74 (0.69–0.80)	0.71 (0.64–0.78)	0.92 (0.80–1.06)
2-yr lag model§	1	1.06 (0.97–1.16)	0.93 (0.84–1.02)	0.73 (0.68–0.79)	0.72 (0.65–0.81)	0.96 (0.82–1.11)
Heart disease						
Deaths	2,120	1,134	1,090	1,727	622	251
Person-years	577,075	208,654	170,831	1,137,264	368,413	129,174
Model 1†	1	1.24 (1.14–1.36)	1.29 (1.18–1.42)	0.69 (0.64–0.74)	0.62 (0.55–0.69)	1.02 (0.87–1.19)
Model 2‡	1	1.05 (0.95–1.15)	0.99 (0.90–1.10)	0.75 (0.69–0.81)	0.71 (0.63–0.80)	0.96 (0.82–1.14)
2-yr lag model§	1	1.06 (0.95–1.17)	0.93 (0.83–1.03)	0.74 (0.68–0.81)	0.73 (0.64–0.83)	0.99 (0.84–1.18)
Cerebrovascular disease						
Deaths	726	322	270	468	158	59
Person-years	570,200	204,458	166,994	1,129,976	365,767	128,048
Model 1†	1	1.20 (1.03–1.40)	1.21 (1.01–1.45)	0.65 (0.57–0.74)	0.59 (0.49–0.71)	0.77 (0.56–1.05)
Model 2‡	1	1.08 (0.93–1.26)	1.00 (0.82–1.20)	0.72 (0.62–0.83)	0.68 (0.56–0.82)	0.77 (0.56–1.06)
2-yr lag model§	1	1.10 (0.93–1.29)	0.95 (0.78–1.15)	0.71 (0.61–0.83)	0.69 (0.56–0.86)	0.82 (0.58–1.16)

Values are n or hazard ratio (95% confidence interval). *Value of 1 is the hazard ratio. †Model 1: Adjusted for sex, age, and race or ethnicity. ‡Model 2: Model 1 plus additional adjustments for education, marital status, body mass index, physical activity, smoking, and physician-diagnosed diseases (hypertension, heart disease, stroke, cancer, and diabetes). §Two-yr lag model: Lagged analyses excluded individuals who died within the first 2 yrs after administration of the respective National Health Interview Survey (1997 to 2009) and adjusted for potential covariates listed in Model 2.

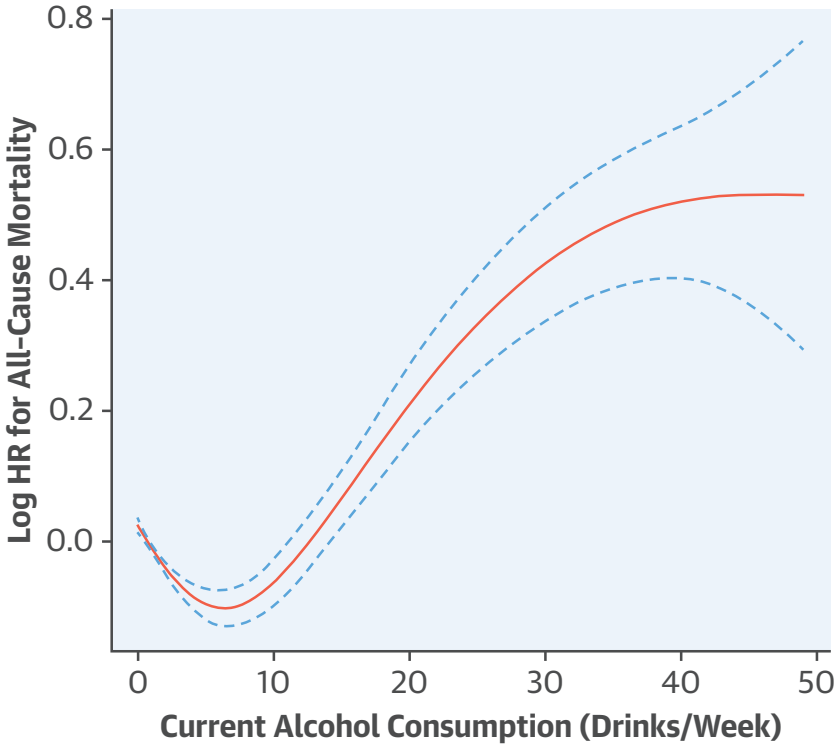
(lifetime abstainer, drinker without binge drinking, drinker with binge drinking <1 drink/month, drinker with binge drinking <1 drink/week, and drinker with binge drinking ≥1 drink/week). NHIS includes data from different years (13 waves) and different samples using a multistage area probability sampling design. Thus, all analyses were conducted by using the final weights, which represent a product of weights for corresponding units computing in each of the sampling stage. As recommended by the Centers for Disease Control and Prevention, we accounted for weights, strata, and cluster in the NHIS design during the analysis. All data analyses were performed by using SAS version 9.3 and SAS-Callable SUDAAN version 11.0 (SAS Institute, Inc., Cary, North Carolina). Two-sided p values <0.05 were considered significant for statistical inferences.

RESULTS

Table 1 shows the baseline characteristics of study participants according to their alcohol consumption status. There were statistically significant differences in each baseline characteristic across the 6 categories of alcohol consumption (all $p < 0.001$).

After a median follow-up of 8.2 years (2.7 million person-years), 34,754 participants died of all causes, of which 8,947 were CVD-specific deaths (6,944 heart disease-related and 2,003 cerebrovascular disease-related deaths), and 8,427 were cancer-specific deaths. Table 2 presents HRs for all-cause and cause-specific mortality according to alcohol consumption status. Compared with lifetime abstainers, former drinkers had a higher risk of all-cause, cancer, and CVD mortality in the initial analyses, adjusted for

CENTRAL ILLUSTRATION Alcohol Consumption and All-Cause Mortality Risk in U.S. Adults



Xi, B. et al. J Am Coll Cardiol. 2017;70(8):913–22.

This study examined the association between alcohol consumption and mortality risk in U.S. adults, using data from the National Health Interview Surveys of 333,247 participants ≥18 years of age and categorizing participants according to self-reported alcohol consumption patterns. Median follow-up was 8.2 years. Compared with lifetime abstainers, individuals who were light or moderate consumers were at a reduced risk of all-cause mortality, but that risk increased significantly with heavy alcohol consumption, as seen in this J-shaped curve. HR = hazard ratio. **Blue lines** = 95% confidence interval.

sex, age, and race or ethnicity. However, the increased risk in former drinkers disappeared after further adjustment for lifestyle factors and clinical variables. In contrast, light or moderate drinkers had a lower risk of mortality from all causes and CVD in the initial analyses. Further adjustment for other covariates had little effect on the estimates, including the 2-year lag analysis model after exclusion of early deaths. Although there was a statistical association of light or moderate drinking with cancer risk in the multivariate adjustment model, the protective effect disappeared in the moderate drinking group but remained for light drinking in the 2-year lag analysis model.

Cox models with penalized splines showed a nonlinear relationship of current alcohol consumption (as a continuous variable) with all-cause and cause-specific mortality (all $p < 0.05$ for the nonlinear test). The dose-response association of current alcohol consumption with all-cause and cause-specific mortality is displayed in the **Central Illustration,** Online Figures 1A to 1D. These results were consistent with those when alcohol consumption was treated as a category variable (lifetime abstainers, current light drinkers, current moderate drinkers, and current heavy drinkers) in **Table 2**.

Heavy drinkers had an increased risk of mortality due to all causes (HR: 1.29; 95% CI: 1.21 to 1.38) and cancer (HR: 1.86; 95% CI: 1.66 to 2.08) in the initial model, although the estimates were attenuated after adjustment for additional confounders. There was no association between heavy drinking and CVD mortality in each model. In addition, the exclusion of participants with physician-diagnosed diseases had little effect on risk estimates (Online Table 1). We also performed a sensitivity analysis after multiple imputations for all variables with missing values, and we obtained similar results (data not shown).

TABLE 3 All-Cause and Cause-Specific Mortality According to Binge Drinking Status

	Lifetime Abstainer*	Drinker Without Binge Drinking	Drinker With Binge Drinking <1 d/month	Drinker With Binge Drinking <1 d/week	Drinker With Binge Drinking ≥1 d/week
All-cause					
Deaths	10,109	11,095	1,276	509	1,196
Person-years	621,157	1,128,132	296,774	112,864	152,322
Model 1†	1	0.77 (0.74–0.79)	0.86 (0.79–0.93)	0.98 (0.86–1.10)	1.44 (1.32–1.56)
Model 2‡	1	0.80 (0.77–0.83)	0.84 (0.78–0.91)	0.87 (0.77–0.98)	1.13 (1.04–1.23)
2-yr lag model§	1	0.81 (0.78–0.85)	0.87 (0.80–0.95)	0.94 (0.82–1.07)	1.16 (1.07–1.27)
Cancer					
Deaths	1,974	3,127	359	135	366
Person-years	576,333	1,080,413	291,177	110,547	147,578
Model 1†	1	1.00 (0.94–1.07)	0.98 (0.85–1.14)	0.99 (0.80–1.24)	1.84 (1.59–2.14)
Model 2‡	1	0.90 (0.83–0.97)	0.81 (0.70–0.94)	0.76 (0.60–0.95)	1.22 (1.05–1.41)
2-yr lag model§	1	0.95 (0.87–1.03)	0.89 (0.76–1.04)	0.82 (0.64–1.04)	1.34 (1.13–1.58)
CVD					
Deaths	2,846	2,653	290	113	226
Person-years	580,988	1,078,520	290,748	110,431	146,700
Model 1†	1	0.66 (0.62–0.70)	0.94 (0.81–1.10)	1.16 (0.91–1.47)	1.20 (1.02–1.41)
Model 2‡	1	0.73 (0.68–0.79)	0.99 (0.85–1.16)	1.10 (0.87–1.39)	1.03 (0.88–1.21)
2-yr lag model§	1	0.73 (0.67–0.79)	0.97 (0.82–1.16)	1.16 (0.89–1.50)	1.13 (0.95–1.35)
Heart disease					
Deaths	2,120	2,084	231	93	194
Person-years	577,075	1,075,202	290,395	110,308	146,538
Model 1†	1	0.66 (0.61–0.71)	0.93 (0.78–1.12)	1.20 (0.93–1.55)	1.26 (1.05–1.51)
Model 2‡	1	0.73 (0.67–0.80)	0.98 (0.82–1.18)	1.13 (0.88–1.47)	1.07 (0.89–1.28)
2-yr lag model§	1	0.73 (0.67–0.80)	0.97 (0.79–1.18)	1.20 (0.90–1.59)	1.17 (0.96–1.42)
Cerebrovascular disease					
Deaths	726	569	59	20	32
Person-years	570,200	1,066,560	289,369	109,826	145,543
Model 1†	1	0.63 (0.55–0.71)	1.00 (0.73–1.38)	0.94 (0.56–1.59)	0.92 (0.62–1.37)
Model 2‡	1	0.72 (0.62–0.83)	1.06 (0.78–1.46)	0.92 (0.54–1.56)	0.83 (0.55–1.24)
2-yr lag model§	1	0.71 (0.61–0.83)	1.03 (0.72–1.48)	0.96 (0.53–1.74)	0.91 (0.58–1.41)

Values are n or hazard ratio (95% confidence interval). *Value of 1 is the hazard ratio. †Model 1: Adjusted for sex, age, and race or ethnicity. ‡Model 2: Model 1 plus additional adjustments for education, marital status, body mass index, physical activity, smoking, and physician-diagnosed diseases (hypertension, heart disease, stroke, cancer, and diabetes). §Two-yr lag model: Lagged analyses excluded individuals who died within the first 2 yrs after administration of the respective National Health Interview Survey (1997 to 2009) and adjusted for potential covariates listed in Model 2.

In the stratified analyses (Online Table 2), light or moderate drinking was associated with a lower risk of all-cause, CVD, and heart disease mortality in both men and women. Heavy drinking was associated with risk of all-cause and cancer-specific mortality in men but not in women. The protective effect of light or moderate drinking on all-cause and cause-specific mortality was more pronounced in older adults (≥60 years of age) than in middle-aged adults (40 to 59 years of age). However, there was no significant association in young adults (18 to 39 years of age). Light or moderate drinking was associated with a lower risk of mortality in non-Hispanic white subjects but not in non-Hispanic black subjects. Furthermore, the protective effect of light or moderate drinking on mortality was more pronounced in never and former smokers, but there was limited beneficial effect in current smokers.

Compared with lifetime abstainers, drinkers with binge drinking ≥1 drink/week had a higher risk of all-cause, cancer, CVD, or heart disease-related mortality in the initial analyses (Table 3). The associations were slightly attenuated for all-cause and cancer-specific mortality but disappeared for CVD and heart disease in the multivariable adjustment model.

DISCUSSION

In a pooled analysis of 13 nationally representative samples of 333,247 U.S. adults, light and moderate alcohol consumption might be associated with a decreased risk of all-cause and CVD mortality. Only light alcohol consumption was associated with a reduced risk of cancer mortality. Heavy alcohol drinking, as well as binge drinking ≥1 drink/week,

was associated with an increased risk of all-cause and cancer-specific mortality but was not associated with CVD-specific mortality. The protective effect of light to moderate alcohol consumption was more pronounced in women, middle-aged and older populations, non-Hispanic white subjects, and never or ever smokers.

Our findings were consistent with several previous studies (1,5,21,22) but at variance with 2 recent studies (8,9). A previous meta-analysis of 34 prospective studies suggested a J-shaped relationship between alcohol consumption and all-cause mortality (1). Another previous meta-analysis of 18 prospective studies found that light to moderate alcohol consumption (2.5 to 14.9 g/day) might have a protective effect on mortality due to CVD (5). These findings were similar to ours; however, the protective effect of light to moderate alcohol consumption on all-cause mortality was challenged by more recent publications (8,9). One meta-analysis of 7 higher quality cohort studies (free from abstainer biases) showed no protective effect of low levels of alcohol consumption on risk of mortality (8). In addition, 1 pooled analysis of 9 national cohorts from the Health Survey for England showed that low to moderate alcohol consumption was beneficial to women ≥65 years of age but not for other age/sex groups (9). The authors surmised that the protective association between light to moderate alcohol consumption and all-cause mortality was mainly due to inappropriate selection of a referent group and inadequate adjustment for confounders (9). Interestingly, the PURE (Prospective Urban Rural Epidemiology) study suggested that, compared with lifetime abstainers, light and moderate alcohol drinking had a beneficial effect on all-cause mortality in high- and middle-income countries but an increased mortality risk in low-income countries (2). This outcome seemed to support our finding that light and moderate drinking decreased risk of all-cause mortality in the United States, which is indeed a high-income country.

One previous meta-analysis showed that light drinking increased the risk of cancer of the oral cavity, pharynx, and esophagus (23). Based on this outcome, the World Health Organization and several cancer prevention associations insist on the health hazards of alcohol even when consumed in light amounts. However, that meta-analysis was subject to serious methodological issues because the conclusions were mainly based on results from case-control studies (24). In addition, moderate alcohol drinking was found to be associated with risk of breast cancer in women on the basis of 2 large-scale cohort studies (25,26) and 1 recent meta-analysis (6). However, 1 meta-analysis of 18 cohort studies showed the benefit of light drinking (≤12.5 g/day) and the hazard of heavy drinking (≥50 g/day) for all cancer mortality, whereas there was no significant association between moderate drinking (12.6 to 49.9 g/day) and all cancer mortality (21). These findings of the meta-analysis were consistent with our results.

To overcome several methodological issues seen in most previous studies, we used lifetime abstainers as the referent category in the present study to address abstainer bias. We adjusted for many confounders, including demographic variables, lifestyle factors, and physician-diagnosed diseases, to address the limited confounding adjustment issue. We also performed sensitivity analyses, after exclusion of participants with physician-diagnosed diseases, to address the "sick quitter phenomenon," as drinkers might reduce or stop drinking because of illness. These robust analytical strategies presented supporting evidence for the existence of a J-shaped curve for the association between alcohol consumption and all-cause mortality in U.S. adults.

A previous Mendelian randomization meta-analysis using the rs1229984 variant of the alcohol dehydrogenase 1B gene as a proxy for alcohol intake failed to confirm the J-shaped association between alcohol consumption and coronary heart disease risk (27). Although Mendelian randomization is less susceptible to the effects of confounding and reverse causality than observational studies, this earlier study had several limitations (28), which made it unable to draw a final conclusion. Because the performance of large-scale randomized controlled trials to test the causal association between alcohol and mortality is unlikely (given ethical issues), the quasi-experimental study will be useful to further address this important question in the future (28).

We found that heavy drinking or binge drinking was associated with all-cause and cancer-specific mortality but not with CVD-specific mortality. The nonsignificant associations between heavy drinking and CVD-specific mortality in our study were consistent with previous studies (5,7,29). It also seemed that there was an L-curved relationship between alcohol consumption and risk of CVD mortality. This finding might be due to deaths from competing risks (causes other than CVD) in heavy or binge drinkers (7). Another explanation might be ingestion of large amounts of polyphenols from heavy alcohol consumption that might have a protective effect on the cardiovascular system. The more significant association in older people than in young people might be due to the insufficient

number of outcomes during follow-up in the latter group. In addition, we found racial and ethnic differences in the association between alcohol consumption and mortality risk, similar to those identified in previous studies (15,30). The racial and ethnic differences in this association might be due to different drinking patterns and genetic backgrounds within these populations (30). Studies have reported the genetic variations in alcohol dehydrogenase 1B isoforms or other alcohol-metabolizing enzymes in different racial and ethnic groups (31) that might explain the differences in the association seen in our study.

STUDY LIMITATIONS. First, alcohol consumption status was obtained by using survey responses and might be subject to recall bias. Second, alcohol consumption status was obtained with the use of self-reported responses at baseline, and it is possible that study participants changed their consumption behavior during follow-up (32). Third, although we adjusted for many confounding factors in our study, residual confounding cannot be fully ruled out. Fourth, information on type of alcoholic beverage was not available. However, a previous meta-analysis showed that all alcoholic drinks at the moderate level were associated with a lower risk of heart disease, suggesting that the major benefit is from ethanol rather than other components of each type of drink (33). Fifth, because quitting is significantly risky, to avoid selection and misclassification biases with high-risk individuals influencing the estimates, we performed sensitivity analyses by excluding participants with a history of physician-diagnosed diseases and those who died in the first 2 years, and the results were consistent. However, these methods might not sufficiently address this issue. Sixth, the NHIS is a passive follow-up study that relies on probabilistic matching to the NDI to assess the vital status of participants. Some data suggest that linkage quality is lower for Hispanic and foreign-born adults compared with non-Hispanic white and U.S.-born adults (34). Finally, specific details about the types of cancer and stroke were not available.

CONCLUSIONS

Using a large sample of U.S. adults, our study re-emphasized the existence of a J-shaped curve in the alcohol-mortality association, supporting current findings that light to moderate drinking might be protective, especially for CVD, but heavy drinking or binge drinking has serious health consequences, including death. A balance between beneficial and detrimental effects of alcohol consumption on health should be considered when making individual or population-wide recommendations, but the reduction of harmful or high consumption of alcohol remains necessary and essential.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In a large prospective cohort of adults in the United States, the relationship of alcohol consumption to mortality seems to follow a J-shaped curve, such that light to moderate intake is associated with lower rates of all-cause and cardiovascular mortality, whereas heavy drinking or binge drinking increases the risk of all-cause and cancer-related mortality.

TRANSLATIONAL OUTLOOK: Individual education and broad societal efforts are needed to individualize recommendations involving the balance between the beneficial and detrimental effects of alcohol on health and to reduce excessive consumption.

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APPENDIX For a supplemental figure and tables, please see the online version of this article.