Trends in alcohol consumption in relation to cause-specific and all-cause mortality in the United States: a report from the NHANES linked to the US mortality registry

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ABSTRACT

Background: Excessive alcohol use is the third leading cause of mortality in the United States, where alcohol use consistently increased over the last decades. This trend is currently maintained, despite regulatory policies aimed to counteract it. While the increased health risks resulting from alcohol use are evident, some open questions regarding alcohol use and its consequences in the US population remain.

Objectives: The current work aims to evaluate the relation between alcohol consumption trends over a period of 15 y with all-cause and cause-specific mortality. In addition, we evaluate the adequacy of the current alcohol recommended limits according to the 2015–2020 US Dietary Guidelines for Americans (USDGA).

Methods: This was a prospective population-based study defined by the NHANES conducted over the period 1999–2014 linked to US mortality registry in 2015.

Results: The sample, composed of 34,672 participants, was observed for a median period of 7.8 y, totaling 282,855 person-years. In the present sample, 4,303 deaths were observed. Alcohol use increased during the period 1999–2014. Alcohol use above the current US recommendations was associated with increased all-cause and cause-specific mortality risk, ranging from 39% to 126%. A proportion of these deaths, ranging from 19% to 26%, could be theoretically prevented if US citizens followed current guidelines, and 13% of all-cause deaths in men could be avoided if the current US guidelines for women (1 standard drink/d) were applied to them.

Conclusions: The present study provides evidence in support of limiting alcohol intake in adherence to the USDGA recommendations. *Am J Clin Nutr* 2020;111:580–589.

Keywords: alcohol use, US guidelines, mortality, alcohol use trend, NHANES

Introduction

Excessive alcohol use is the third leading cause of mortality in the United States, after smoking and a sedentary lifestyle (1). It was estimated that during the period 2006–2010 a mean of 88,129 excessive alcohol use–related deaths occurred annually in the United States. Among those deaths, 71% (62,323) occurred in men and 44% (38,548) were attributable to chronic diseases related to alcohol (2). Whereas a light alcohol intake appears to be neutral, it has been widely reported that an alcohol intake >15 g/d increases the risk of cardiovascular diseases, stroke, type 2 diabetes, and certain types of cancers (3–5). A higher alcohol use was also associated with increased risk of all-cause mortality as well as mortality attributable to chronic diseases (6–8).

Alcohol use increased in the United States after the 1970s. This amount of intake has been consistent, despite regulatory policies aimed to counteract it (9). According to forecasts to 2022, no substantial change for beer intake and an increase in the consumption of higher-alcohol-content beverages, such as wine and spirits are predicted in the United States (10). Excessive alcohol use also has a relevant cost for the community. In 2006, the economic burden of alcohol use in the United States was assessed at US $223.5 billion (11), with a predicted $249 billion in 2010.

Based on the robust evidence regarding the health-related risks resulting from alcohol use, the 2015–2020 US Dietary Guidelines for Americans (USDGA) recommends that people not start consuming alcohol, or if alcohol is already consumed it should be used in moderation: 1 drink/d (14 g/d) for women and 2 drinks/d (28 g/d) for men during any day (12). Notably, 2 out of 3 regular drinkers in the United States reported an intake higher than the recommended alcohol limits at least once a month (13).

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Abbreviations used: PAR, population-attributable risk; UCOD, underlying cause of death; USDGA, US Dietary Guidelines for Americans.

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While the increased health risks resulting from alcohol use are evident, some open questions regarding alcohol use and its consequences in the US population remain. First, it is still not clear what the alcohol consumption trend over time in the United States is in terms of adherence to the USDGA. As a consequence, it is not clear how many Americans are at higher mortality risk because of an alcohol intake greater than what is recommended. Second, it is questionable whether the current recommended alcohol limit by the USDGA is adequate, since it is higher than what is adopted by other countries (14). Moreover, it was recently suggested that alcohol guidelines should be revised and downward adjustments were proposed (5, 8). Finally, given the mortality risk due to high alcohol intake and the prevalence of the population at higher mortality risk as a result of excessive alcohol intake, it would be informative to know the extent to which mortality could be avoided if the mean daily alcohol use was reduced according to the maximum amount consumed during any day according to the USDGA, or according to alternative, more cautious recommendations.

To address these aims, the data from the NHANES linked to the US mortality registry were investigated. The specific multistage probability sampling technique applied in the NHANES gave us the opportunity to estimate alcohol use in the United States and its trend over the last 15 y. Additionally, a nonlinear dose–response analysis investigating the relation between all-cause and cause-specific mortality was applied to determine the amount of alcohol intake associated with the lowest mortality risk. Finally, we estimated the population-attributable risks to show the total reduction in mortality across the entire population if all individuals reduced their mean daily alcohol use to the maximum amount consumed during any day according to the recommendations from the USDGA. The study's primary outcome variable was all-cause mortality.

Methods

Ethics statement

The National Center for Health Statistics Research Ethics Review Board approved the survey protocols, and written informed consent was obtained for all participants.

Study sample and study design

The NHANES is an ongoing program of studies aimed to assess the health and nutritional status of adults and children in the United States. The NHANES is based on a multistage probability sampling aimed to design a representative US sample (15). Since 1999, every year, ~5000 US citizens are involved in standardized health interviews and physical examinations to collect, among other data, sociodemographic characteristics, health status and history, smoking habits, alcohol use, physical activity, body-size measures, nutritional status, and dietary intakes. On a regular basis, the NHANES is linked to the US mortality registry (16).

In this analysis, participants from the NHANESs conducted between 1999 and 2014 were merged with the 2015 US mortality registry, resulting in a dataset of 82,091 records. After exclusion of participants aged <18 y and those without information regarding mortality status, a sample size of 47,279 participants was obtained. After further exclusion of participants with missing data regarding alcohol use and covariates used in the models, a final sample size of 34,672 defined our analytical dataset. Among those participants, 10,096 (29%) were alcohol users. **Figure 1** presents a flowchart of participant selection.

Alcohol assessment

Two different tools were used for alcohol consumption assessment. First, a dietary interview was undertaken to determine the mean amount of alcohol consumed. The dietary interview was composed of 3 sections—that is, a 24-h dietary recall, an evaluation of nutritional supplement use, and a dietary post-recall. The dietary post-recall was conducted by a telephonic interview ~3–10 d after the first dietary evaluation (17). Two days of dietary data were collected for the surveys performed after 2002. Alcohol intake was categorized as follows: nondrinkers, <0.1 g/d; 0.1 to <14 g/d (reference category); 14 to <28 g/d; 28 to <42 g/d; and ≥42 g/d. This categorization was adopted considering a standard alcohol drink as defined by the current USDGA (18). Based on the guidelines, we derived that the suggested alcohol intake would correspond to 14 g/d for women (1 standard alcoholic drink/d) and 28 g/d for men (2 standard alcoholic drinks/d).

A second alcohol consumption assessment was performed by a personal computer-assisted interview conducted at the mobile examination center by trained interviewers. In particular, our analyses were focused on the item evaluating the mean volume of alcohol consumed during drinking days.

Outcome ascertainment

We estimated cause-specific mortality risks considering mortality due to cardiovascular outcomes [underlying cause of death (UCOD) = I00–I09, I11, I13, I20–I51], mortality due to cardiovascular outcomes and stroke (UCOD = I60–I69), and mortality due to cancer (UCOD = C00–C97).

Statistical methods

Sample characteristics were described according to alcohol intake. Medians and IQRs were used to describe continuous variables, whereas counts and percentages were used for categorical variables. Alcohol-use trend analysis was performed using linear or logistic regression analysis applied to alcohol use as a continuous variable and to participants categorized according to their alcohol intake (nondrinkers, alcohol users who are not compliant with the USDGA). The ordinary Wald statistical test was applied to the slope of the regressions and was interpreted as a trend over the observational time.

A multivariate Cox regression was used to estimate all-cause and cause-specific mortality risks. Cox models were adjusted for ethnicity (Hispanic, black, white, others, or mixed), education (less or more than a high school degree), BMI (kg/m^2; continuous), systolic and diastolic blood pressure (mm Hg; continuous), smoking status (smoked ≥100 cigarettes in life), energy intake (kcal/d), dietary fiber (g/d), and indicator variables for prevalent cardiovascular diseases (≥1 of the following: coronary artery disease, congestive heart failure, myocardial

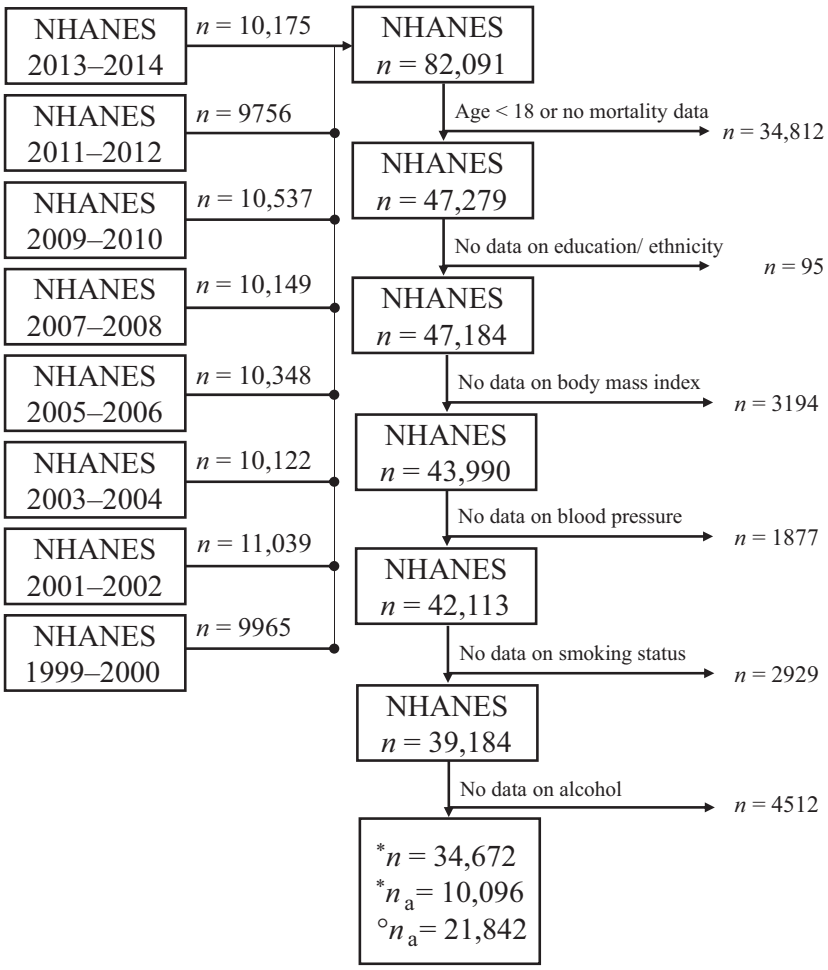

FIGURE 1 Flowchart of participant selection according to NHANES surveys conducted during the period 1999–2014 merged with 2015 US mortality registry. *Data used for analyses based on mean alcohol intake from dietary interview. °Data used for analyses based on number of drinks consumed during drinking days. n_a, alcohol users.

infarction, or stroke) and any primary cancer at baseline. Age was used as an underlying time variable, and models were stratified by sex, 10-y age classes, and survey. The Cox assumption of hazards proportionality was investigated, including in the model an interaction term between exposure and age at the event and by visual inspection of Schoenfeld's residuals plot. A restricted cubic spline model with knots at 0.1, 7, 14, and 28 g/d in women and 0.1, 7, 14, 28, and 42 g/d in men was used to determine the shape of the association between mortality risk and mean alcohol use. The same analysis with knots at 1, 2, 3, and ≥4 drinks was conducted on mean alcohol use during drinking days. A test for nonlinearity was undertaken by means of the Wald test applied to the quadratic and cubic spline coefficients.

Mortality risks for alcohol intake in alcohol users (alcohol intake >0.1 g/d for data regarding mean alcohol use and for nonmissing values for data on mean alcohol use during drinking days) were performed by thresholds defined according to the recommended limits of the USDGA.

Finally, population-attributable risks (PARs) were performed considering the mean prevalence of alcohol users over the observational period (Pr) and the HRs from the multivariate-adjusted Cox model. The following formula was used: PAR = Pr (HR − 1)/Pr (HR − 1) + 1. Survey weights, sample strata, and sample clusters were included in the survey statistical procedures to take into account the complex multistage probability sampling, to avoid differential probabilities of selection among subgroups and to compensate for exclusion of sampling areas from the sampling frame. Sensitivity analyses were undertaken excluding participants who died during the first year of observation, excluding those with baseline prevalent cardiovascular disease or cancer, and adjusting for sedentary time. Finally, to investigate for possible model overadjustment, a further sensitivity analysis was undertaken using models not adjusted for BMI and blood pressure. The STATA software version 15 (StataCorp) was used for all statistical analysis. All statistical tests were 2-tailed, and type I error rate was set to 5% ($\alpha = 0.05$).

Results

The sample, composed of 34,672 participants, was observed for a median period of 7.8 y (IQR = 4.3–11.9 y), totaling 282,855 person–years. In the present sample, 4,303 deaths were observed. Among those, 988 deaths were attributable to cancer (UCOD = C00–C97), 721 to cardiovascular disease

TABLE 1 Baseline characteristics of study participants according to USDGA-defined alcohol consumption categories[1]

	Mean alcohol consumption			Number of drinks consumed on drinking days		
	<14 g/d	14–28 g/d	≥28 g/d	1 drink/d	2 drinks/d	≥3 drinks/d
Men						
Age, y	50 (35–66)	49 (35–64)	44 (32–57)	57 (41–71)	49 (35–62)	47 (32–63)
Race/ethnicity, *n* (%)						
Hispanic	3333 (82)	338 (8)	412 (10)	515 (13)	549 (13)	3019 (74)
White	6430 (79)	880 (11)	841 (10)	1836 (23)	1597 (20)	4718 (58)
Black	2678 (81)	303 (9)	306 (9)	555 (17)	625 (19)	2107 (64)
Other or mixed ethnicity	871 (83)	87 (8)	91 (9)	271 (26)	185 (18)	593 (57)
Less than high school, *n* (%)	7079 (82)	705 (8)	870 (10)	1214 (14)	1196 (14)	6244 (72)
BMI, kg/m^2	28 (25–31)	27 (24–31)	27 (24–31)	27 (25–31)	28 (25–31)	28 (24–31)
SBP, mm Hg	123 (114–134)	123 (115–135)	125 (116–134)	123 (114–135)	122 (113–133)	123 (114–134)
DBP, mm Hg	72 (64–79)	72 (64–80)	74 (66–81)	72 (64–79)	72 (65–79)	72 (64–80)
Energy, kcal/d	2115 (1551–2833)	2542 (1939–3364)	2990 (2269–4103)	2256 (1695–3000)	2303 (1720–3031)	2192 (1586–3014)
Dietary fiber, g/d	16 (11–23)	17 (12–25)	17 (11–26)	18 (12–26)	16 (11–24)	16 (10–23)
Smokers, *n* (%)	7178 (77)	991 (11)	1102 (12)	1571 (17)	1604 (17)	6096 (66)
Primary cancer, *n* (%)	1235 (82)	167 (11)	108 (7)	445 (29)	268 (18)	797 (53)
At least 1 CVD, *n* (%)	1693 (86)	177 (9)	109 (6)	488 (25)	273 (14)	1218 (62)
Women						
Age, y	47 (33–64)	49 (36–63)	45 (33–58)	52 (37–66)	43 (31–55)	47 (31–64)
Race/ethnicity, *n* (%)						
Hispanic	4348 (92)	211 (4)	155 (3)	911 (19)	637 (14)	3166 (67)
White	7497 (88)	618 (7)	438 (5)	2595 (30)	1583 (19)	4375 (51)
Black	3295 (90)	208 (6)	162 (4)	839 (23)	604 (16)	2222 (61)
Other or mixed ethnicity	1045 (90)	68 (6)	42 (4)	302 (26)	151 (13)	702 (61)
Less than high school, *n* (%)	8257 (91)	436 (5)	332 (4)	1756 (19)	1116 (12)	6153 (68)
BMI, kg/m^2	28 (24–33)	27 (23–31)	27 (23–32)	27 (24–32)	27 (23–33)	28 (24–34)
SBP, mm Hg	118 (108–134)	119 (107–135)	118 (108–131)	120 (108–135)	115 (106–127)	119 (108–135)
DBP, mm Hg	69 (61–76)	70 (62–77)	71 (63–78)	70 (62–77)	70 (62–77)	68 (61–76)
Energy, kcal/d	1805 (1333–2421)	2269 (1722–2929)	2621 (1984–3455)	1931 (1448–2540)	1956 (1444–2575)	1808 (1313–2475)
Dietary fiber, g/d	14 (10–21)	16 (11–24)	16 (10–24)	15 (11–22)	15 (10–21)	14 (9–20)
Smokers, *n* (%)	5882 (87)	506 (7)	387 (6)	1604 (24)	1355 (20)	3816 (56)
Primary cancer, *n* (%)	1480 (87)	129 (8)	85 (5)	526 (31)	228 (13)	940 (55)
At least 1 CVD, *n* (%)	1300 (93)	67 (5)	37 (3)	319 (23)	106 (8)	979 (70)

[1]CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; USDGA, US Dietary Guidelines for Americans. Values are medians (IQRs) unless otherwise indicated.

(UCOD = I00–I09, I11, I13, I20–I51), and 165 to stroke (UCOD = I60–I69). The median age of the participants was 48 y (IQR = 34–64 y) and 52.2% (n = 18,094) were women. Baseline statistics by alcohol intake categories are reported in **Table 1**. When looking at the trend of alcohol consumption during the period 1999–2014, we observed a statistically significant reduction in mean alcohol use by as much as 0.8 g by survey (2 y) in men but not in women. When considering users with intakes higher than the maximum recommended by the USDGA, this result is confirmed in both men and women with a reduction of 2.6 and 1.4 g by 2 y, respectively.

When looking at the number of drinks consumed during a typical drinking day we also observed a reduction in the number of men consuming >2 drinks/d ($P = 0.024$). On the other hand, there was no change in the number of women consuming >1 drink during a typical drink day. During the period 1999–2014, the mean proportion of participants with a mean alcohol intake and number of drinks during drinking days higher than the maximum USDGA recommended limits were 11.1% and 71.3% in men and 12.3% and 60.1% in women (**Figure 2**). All-cause and cause-specific mortality risks in relation to alcohol intake are reported in **Tables 2** and **3** for men and women, respectively.

When looking at both all-cause and cause-specific mortality HRs, we observed that nonconsumers (<0.1 g/d alcohol) had a higher mortality risk with respect to the reference category (>0.1 to <14 g/d) in both sexes [HR (95% CI): 1.40 (1.20, 1.63) and 1.21 (1.01, 1.44) in men and women, respectively]. We also observed an increased risk of all-cause mortality in men and women when merging all categories with alcohol intake >1 drink during a drinking day [HR (95% CI): 1.17 (1.04, 1.33) and 1.49 (1.30, 1.71) in men and women, respectively]. When looking at the cause-specific mortality hazards, similar results were observed for cancer mortality in both sexes. On the other hand, the highest alcohol intake category was associated with cardiovascular disease mortality risk in men but not in women. This was confirmed by analyses conducted in alcohol users only where a higher all-cause and cause-specific mortality risk was reported after merging all categories with alcohol intakes above the recommended maximum intake [HR (95% CI): 1.55 (1.23, 1.96) and 1.38 (1.05, 1.83) for all-cause mortality in men and women, respectively]. When looking at mean alcohol use during drinking days, alcohol intakes above the recommended maximum USDGA intake resulted in significant all-cause and cause-specific mortality risk [HR (95% CI): 1.39 (1.24, 1.55)

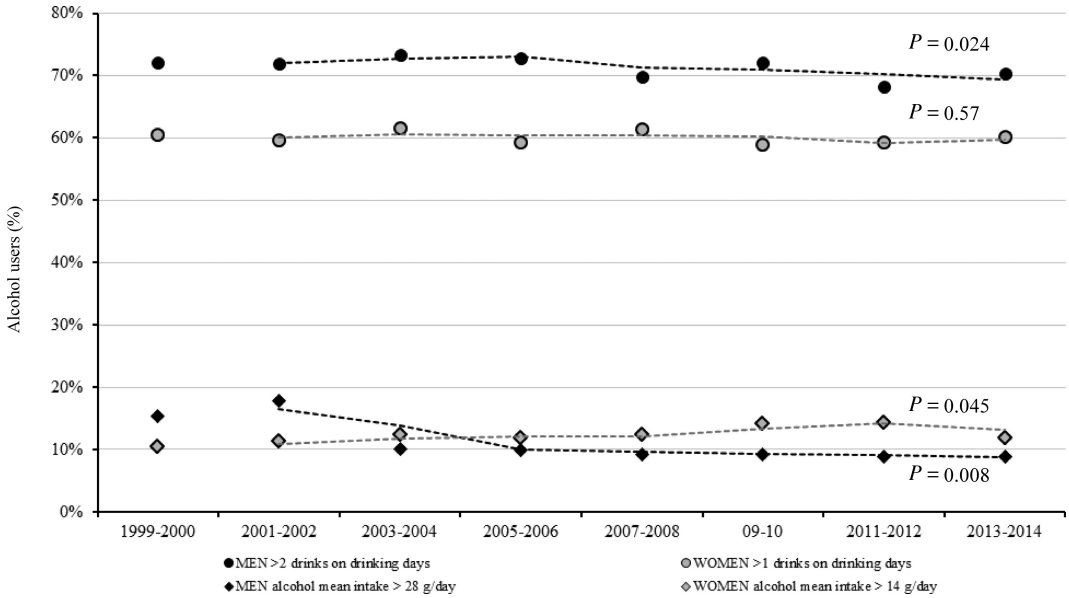

FIGURE 2 Trends of individuals noncompliant to the USDGA by sex. *P* values portray trend test ($n = 5781$ men and 4315 women for the analysis on mean alcohol intake; $n = 11{,}584$ men and 7839 women for the analysis on number of drinks during a drinking day). USDGA, US Dietary Guidelines for Americans.

and 1.49 (1.30, 1.71) for all-cause mortality in men and women, respectively]. We observed a clear J-shaped relation between all-cause mortality risk and mean alcohol use (**Figure 3**). The Wald test for nonlinearity was statistically significant for the quadratic ($P_Q < 0.001$, $P_Q = 0.030$ in men and women, respectively) and the cubic component of the spline ($P_C < 0.001$, $P_C = 0.038$ in men and women, respectively). The statistical significances of the quadratic and the cubic components of the spline were lost when an indicator variable coding for nonconsumers was included in the model ($P_Q = 0.37$ in men and $P_Q = 0.12$ in women, $P_C = 0.29$ in men and $P_C = 0.12$ in women). When considering the number of drinks during drinking days in relation to all-cause mortality, a monotone nonlinear relation was observed in men ($P_Q < 0.001$ and $P_C < 0.001$), whereas a monotone linear relation was observed in women ($P_C = 0.45$ and $P_Q = 0.56$).

PARs were performed to identify the population at risk during the period 1999–2014. According to our calculation, mean alcohol reduction to levels in agreement with the USDGA would reduce attributable all-cause mortality by 8.8% and 5.5% in men and women, respectively; cardiovascular disease and stroke and cardiovascular mortality in men by 10.3% and 8.5%, respectively; and cancer mortality by 10% in men and 13.4% in women. If the current guideline for women (1 standard drink/d, 14 g/d) was applied to men, 9.7% of all-cause deaths would be avoided.

Finally, if the number of drinks consumed in a typical drink day was reduced to align with the USDGA, an expected reduction in alcohol-related all-cause and cancer-related mortality of 19.2% and 23.4% would be observed in men. On the other hand, no consequences on cardiovascular and stroke mortality are expected if the number of drinks consumed in a typical drink day was reduced to align with the USDGA. Furthermore, if the limit of 1 drink would be applied to men, all-cause related mortality would be reduced by 13%. In women, if the limit of a single drink during a drinking day was respected, all-cause, CVD, stroke, and cancer mortality attributable to alcohol would be reduced in the range of 20.8–25.8% (**Table 4**).

All previous results were confirmed when excluding participants who died in the first year of follow-up, after exclusion of baseline-prevalent cases of cancer and cardiovascular diseases and when adjusting for sedentary time. Analysis further adjusted for energy intake and not adjusted for BMI and blood pressure did not affect the results.

Discussion

In the present work we showed an apparently contradictory alcohol-use trend in the United States during the period 1999–2014. The amount of alcohol consumed, among users, is decreasing, whereas the proportion of individuals consuming more than the recommended USDGA limit is, on average, increasing in women and declining in men. On the other hand, the proportion of individuals having more drinks during drinking days than what is recommended by the USDGA is declining in men but appears to be stable in women. In women, we also observed that light alcohol consumers either started to abstain or moved into the higher-intake categories. Despite this increase in numbers, it seems as though the mean alcohol volume consumed, within the respective categories, is decreasing irrespective of sex. A trend toward higher alcohol intakes was consistently reported in recent surveys conducted in the United States (9, 10, 19). The most comprehensive evidence regarding alcohol use in the United States comes from a recent meta-analysis including 6 national surveys (9). According to this study, alcohol use is increasing in the United States, confirming our trend analyses. This study also pointed out that specific risky behaviors, such as binge drinking, alcohol intake in women, and alcohol use in both men and women over the age of 50, are also increasing. A recent survey conducted

TABLE 2 All-cause and cause-specific mortality HRs in relation to alcohol use in men[1]

	Deaths, *n*	Participants, *n*	Person–years	HR (95% CI)
All-cause mortality				
Alcohol use,[2] g/d				
<0.1	1700	10,795	86,156	1.40 (1.20, 1.63)
≥0.1 and <14	320	2517	18,941	1 (ref)
≥14 and <28	192	1608	12,510	1.17 (0.94, 1.46)
≥28	211	1650	15,036	1.55 (1.23, 1.96)
Alcohol use,[3] drinks/d				
1	557	3177	25,013	1 (ref)
2	285	2956	24,492	0.83 (0.69, 1.00)
3	151	1785	14,458	0.96 (0.76, 1.21)
≥4	1430	8652	68,681	1.34 (1.18, 1.53)
Cardiovascular and stroke mortality				
Alcohol use,[2] g/d				
<0.1	398	10,795	86,156	1.97 (1.44, 2.71)
≥0.1 and <14	67	2517	18,941	1 (ref)
≥14 and <28	40	1608	12,510	1.36 (0.83, 2.22)
≥28	44	1,650	15,036	1.96 (1.19, 3.22)
Alcohol use,[3] drinks/d				
1	125	3177	25,013	1 (ref)
2	74	2956	24,492	0.86 (0.60, 1.24)
3	24	1785	14,458	0.80 (0.45, 1.44)
≥4	326	8652	68,681	1.17 (0.89, 1.53)
Cardiovascular mortality				
Alcohol use,[2] g/d				
<0.1	331	10,795	86,156	1.81 (1.29, 2.53)
≥0.1 and <14	61	2517	18,941	1 (ref)
≥14 and <28	31	1608	12,510	1.30 (0.76, 2.23)
≥28	36	1650	15,036	1.79 (1.04, 3.09)
Alcohol use,[3] drinks/d				
1	107	3177	25,013	1 (ref)
2	64	2956	24,492	0.86 (0.58, 1.27)
3	19	1785	14,458	0.74 (0.39, 1.39)
≥4	269	8652	68,681	0.99 (0.74, 1.33)
Cancer mortality				
Alcohol use,[2] g/d				
<0.1	414	10,795	86,156	1.29 (0.95, 1.75)
≥0.1 and <14	79	2517	18,941	1 (ref)
≥14 and <28	42	1608	12,510	0.91 (0.58, 1.43)
≥28	48	1650	15,036	1.27 (0.77, 2.08)
Alcohol use,[3] drinks/d				
1	124	3177	25,013	1 (ref)
2	64	2956	24,492	0.68 (0.46, 1.00)
3	55	1785	14,458	1.29 (0.86, 1.94)
≥4	340	8652	68,681	1.29 (0.99, 1.68)

[1] ref, reference.
[2] Analysis performed on mean daily intake.
[3] Analysis performed on number of drinks typically consumed on drinking days.

in the United States (10) reported that the increased alcohol use could be due to a partial substitution of beer for wine and spirits. This evidence is also corroborated by market data showing that the production of wine and its internal market has been increasing in the United States since 1999 (20, 21).

In the present work we showed that alcohol intake higher than the recommendation proposed by the USDGA resulted in increased all-cause and cause-specific mortality risk. According to our analysis, 1 standard drink would also be a much more prudent recommended limit for men. Notably, when the nonlinear analysis on mean alcohol use in relation to all-cause mortality is applied to men only, the recommended alcohol limit according to USDGA (28 g/d) is confirmed to be significantly related to an increased risk of all-cause mortality (Figure 3). According to the present study, a stricter guideline in the United States, limiting alcohol use to 1 standard alcohol drink during a drinking day also for men would result in a 13% (95% CI: 3.4, 22.3) reduction in all-cause mortality.

If such a guideline had been applied in the past, >1000 deaths/y could possibly have been avoided in men during the period 2006–2010. Guidelines for alcohol limits in different countries are sparse and define a wide range of alcohol limit recommendations (14). In this wide spectrum of alcohol limit recommendations, the current US guidelines have the highest

TABLE 3 All-cause and cause-specific mortality HRs in relation to alcohol use in women[1]

	Deaths, *n*	Participants, *n*	Person–years	HR (95% CI)
All-cause mortality				
Alcohol use,[2] g/d				
<0.1	1487	13,772	116,019	1.21 (1.01, 1.44)
≥0.1 and <14	212	2413	19,028	1 (ref)
≥14 and <28	111	1105	8257	1.34 (0.95, 1.87)
≥28	67	797	6822	1.38 (1.05, 1.83)
Alcohol use,[3] drinks/d				
1	408	4647	38,697	1 (ref)
2	158	2975	25,001	1.16 (0.93, 1.44)
3	63	1291	10,893	1.38 (0.96, 1.98)
≥4	1248	9174	75,534	1.59 (1.38, 1.83)
Cardiovascular and stroke mortality				
Alcohol use,[2] g/d				
<0.1	279	13,772	116,019	1.43 (0.95, 2.15)
≥0.1 and <14	34	2413	19,028	1 (ref)
≥14 and <28	20	1105	8257	0.59 (0.18, 1.97)
≥28	4	797	6822	1.69 (0.86, 3.32)
Alcohol use,[3] drinks/d				
1	73	4647	38,697	1 (ref)
2	8	2975	25,001	0.73 (0.39, 1.35)
3	18	1291	10,893	1.14 (0.49, 2.63)
≥4	238	9174	75,534	1.52 (1.08, 2.12)
Cardiovascular mortality				
Alcohol use,[2] g/d				
<0.1	214	13,772	116,019	1.42 (0.91, 2.21)
≥0.1 and <14	28	2413	19,028	1 (ref)
≥14 and <28	17	1105	8257	0.68 (0.20, 2.33)
≥28	3	797	6822	1.70 (0.83, 3.49)
Alcohol use,[3] drinks/d				
1	59	4647	38,697	1 (ref)
2	6	2975	25,001	0.76 (0.37, 1.55)
3	13	1291	10,893	1.18 (0.46, 2.99)
≥4	184	9174	75,534	1.59 (1.08, 2.32)
Cancer mortality				
Alcohol use,[2] g/d				
<0.1	303	13,772	116,019	1.30 (0.90, 1.88)
≥0.1 and <14	48	2413	19,028	1 (ref)
≥14 and <28	31	1105	8257	1.64 (0.95, 2.84)
≥28	22	797	6822	2.25 (1.23, 4.13)
Alcohol use,[3] drinks/d				
1	101	4647	38,697	1 (ref)
2	49	2975	25,001	1.31 (0.86, 1.99)
3	15	1291	10,893	1.10 (0.55, 2.20)
≥4	239	9174	75,534	1.59 (1.16, 2.18)

[1] ref, reference.
[2] Analysis performed on mean daily intake.
[3] Analysis performed on number of drinks typically consumed on drinking days.

threshold for men while some of the other countries have guidelines suggesting a much more moderate alcohol use of <20 g/d. These guidelines are also in agreement with the most recent evidence (5, 8). Recently, according to a study based on almost 600,000 participants from 83 cohort studies, an even more prudent alcohol intake recommendation was defined as 100 g alcohol/wk, which is <15 g/d (5).

High-dose alcohol consumption can contribute to mortality through several mechanisms. Animal studies have reported reduced cardiomyocyte contractility and ischemia-induced angiogenesis as well as increased cardiomyocyte apoptosis (22). In humans, it has been linked to endothelial dysfunction, increased LDL cholesterol, oxidative stress, myocardial wall stress, atrial fibrillation, hypertension, cardiomyopathy, and both occlusive and hemorrhagic stroke (22, 23). High-dose alcohol consumption not only increases mortality risk depending on the pathophysiological consequences of alcohol itself; mortality risk is also related to volume and pattern of drinking as well as to behaviors resulting in injuries and violence upon acute drinking.

We additionally observed increased all-cause and cause-specific mortality for nondrinkers compared with light alcohol users. This evidence is consistent with previous studies and is likely due to the fact that nondrinkers differ systematically

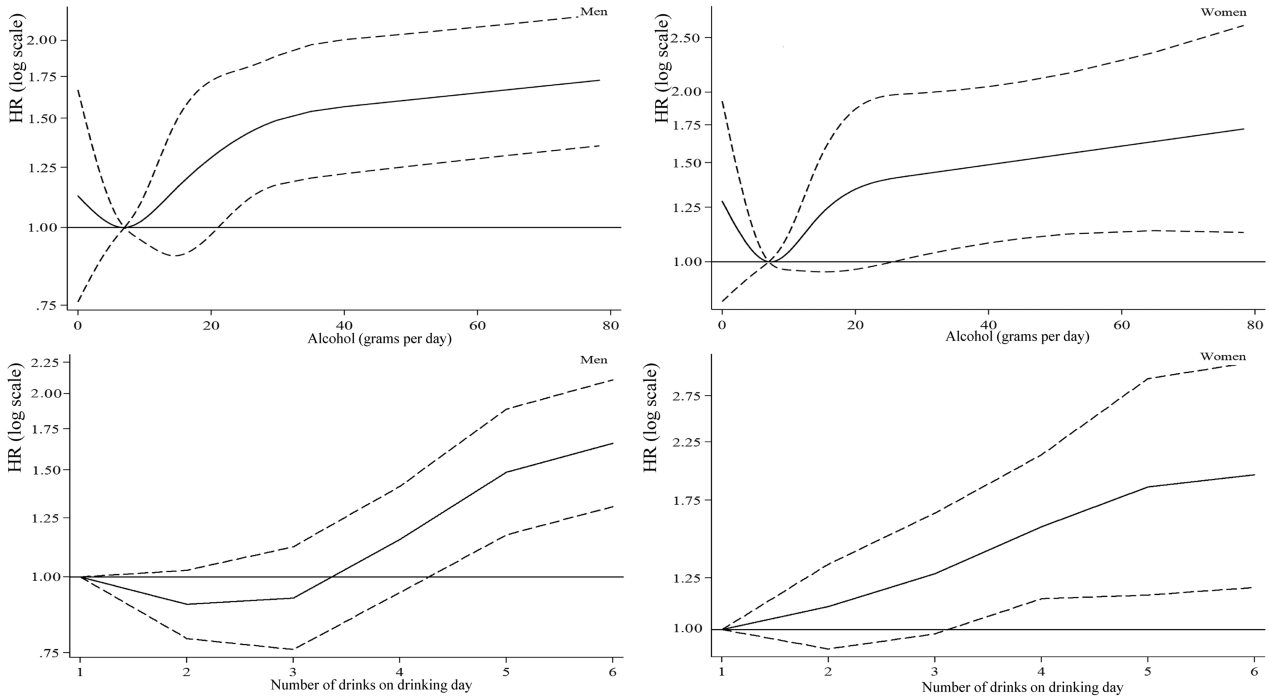

FIGURE 3 Nonlinear dose–response analysis of alcohol use and all-cause mortality by sex. Mortality hazards for mean alcohol use were modeled with an indicator variable for alcohol nonusers. $n = 5781$ men and 4315 women for the analysis on mean alcohol intake; $n = 11584$ men and 7839 women for the analysis on number of drinks during a drinking day.

from alcohol drinkers in a way that may influence mortality risk (24–26). More specifically, it should be considered that nondrinkers might abstain from alcohol because of poor health, which, in turn, may result in increased mortality risk regardless of alcohol intake (27, 28). Our result of an increased mortality risk for nondrinkers was maintained when excluding cardiovascular and cancer cases at baseline, showing that other underlying factors increasing mortality could be present. These underlying causes are difficult to model and including supplementary covariates may not sufficiently reduce residual confounding. We consequently decided to exclude nondrinkers in performing PARs. Notably, this approach resulted in a monotone linear relation between alcohol use and mortality risk, in agreement with what is reported by the Global Burden of Disease Study (8).

The present work has numerous strengths. First, it is based on a rigorous sampling technique aimed to provide population-based estimates. Second, novel results were reported regarding alcohol-use trends and alcohol use in relation to all-cause and cause-specific mortality risk in the United States based on the current USDGA for alcohol use. The present work is, however, also not free of limitations. Reverse causation and possible residual confounding resulting from the inclusion of nondrinkers is a possibility. However, we based our PAR estimates on risk performed excluding nondrinkers. After exclusion of individuals without information on mortality status, our sample was reduced from 82,091 to 47,279 subjects. Exclusion of individuals with missing values regarding self-reported smoking and alcohol use reduced our sample by a further 12%. It is possible that this could have biased our analysis, resulting in an underestimation of mortality risks due to nonresponse from smokers and participants with high alcohol intake. Missing information regarding BMI and blood pressure assessment could have biased our estimates in a similar way. Also, the absence of information on other factors, such as physical activity and type of alcohol use in the NHANES database, leaves certain open questions.

Furthermore, the main limitations of the present study are represented by lack of knowledge regarding alcohol drinking by means of objectively assessed intake, lifetime intake, and drinking patterns. Self-reported alcohol use is typically underestimated by report bias, and this could result in underestimation of mortality risk. Lifetime intake knowledge is also important since it allows for a better delineation between alcohol abstainers and those who quit alcohol use. Finally, lack of knowledge regarding drinking patterns is a main pitfall of the present work. It is acknowledged that binge drinking and regular drinking affect mortality in different ways.

In conclusion, the present study confirmed that alcohol use is increasing among US women. In addition, we reported that excessive alcohol use increases all-cause and cause-specific mortality risk in both sexes. Evidence for the use of stricter alcohol guidelines in the United States was provided. A larger impact on alcohol-attributable mortality could be achieved if the current US recommendation for women is also extended to men. Finally, the present study provides evidence in support of limiting alcohol intake in adherence with the USDGA recommendations.

TABLE 4 PARs of mean alcohol use and number of drinks during a drinking day, when consumed in amounts higher than the recommended alcohol intake according to the 2015–2020 USDGA[1]

	Population at risk, %	HR (95% CI)	PAR (95% CI), %
Men			
Mean alcohol intake >28 g/d (2 standard drinks)			
Mortality			
All causes	11.1	1.87 (1.52, 2.30)	8.8 (5.5, 12.6)
CVD and stroke	11.1	2.04 (1.25, 3.33)	10.3 (2.7, 20.5)
CVD	11.1	1.84 (1.10, 3.07)	8.5 (1.1, 18.7)
Cancer	11.1	2.00 (1.39, 2.88)	10.0 (4.1, 17.3)
More than 2 drinks during a drinking day			
All causes	60.1	1.39 (1.24, 1.55)	19.2 (12.8, 25.1)
CVD and stroke	60.1	1.19 (0.94, 1.50)	10.4 (−3.8, 23.4)
CVD	60.1	1.02 (0.79, 1.31)	1.2 (−14.7, 15.9)
Cancer	60.1	1.50 (1.20, 1.89)	23.4 (10.9, 35.2)
More than 1 drink during a drinking day			
All causes	80.7	1.17 (1.04, 1.33)	13 (3.4, 22.3)
CVD and stroke	80.7	1.06 (0.81, 1.37)	5 (−19.8, 24.4)
CVD	80.7	0.94 (0.70, 1.24)	− 6 (−35.3, 17.3)
Cancer	80.7	1.12 (0.87, 1.44)	9 (−12.8, 27.7)
Women			
Mean alcohol intake >14 g/d (1 standard drink)			
Mortality			
All causes	12.3	1.47 (1.16, 1.85)	5.5 (1.9, 9.5)
CVD and stroke	12.3	1.43 (0.82, 2.50)	5.0 (−2.3, 15.6)
CVD	12.3	1.54 (0.79, 2.99)	6.2 (−2.7, 19.7)
Cancer	12.3	2.26 (1.48, 3.45)	13.4 (5.6, 23.2)
More than 1 drink during a drinking day			
All causes	71.3	1.49 (1.30, 1.71)	25.8 (17.6, 33.5)
CVD and stroke	71.3	1.37 (1.00, 1.89)	20.8 (0.0, 38.7)
CVD	71.3	1.43 (0.99, 2.05)	23.4 (−0.7, 42.7)
Cancer	71.3	1.49 (1.11, 2.00)	25.8 (7.2, 41.5)

[1]Population at risk performed over the period 1999–2014. HRs for mortality in participants noncompliant with the current US guidelines. CVD, cardiovascular disease; PAR, population-attributable risk; USDGA, US Dietary Guidelines for Americans.

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