Trends in alcohol consumption in relation to cause-specific and all-cause mortality in the US: A report from the National Health and Nutrition Examination Survey linked to the U.S. mortality registry

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**Abstract**

Background. Excessive alcohol use is the third leading cause of mortality in the USA 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 is evident, some open questions regarding alcohol use and its consequences in the US population remain.

Objective. The current work aims to evaluate the relationship between alcohol consumption trends over a period of 15 years with all-cause and cause-specific mortality. In addition, we evaluate the adequacy of the current alcohol use recommendation according to the 2015-2020 US Dietary Guidelines for Americans (USDGA).

Design. Prospective population based study defined by the NHANES surveys 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 years totalling 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 be 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 (one standard drink for day) were applied to them.

Conclusions. The present study provides evidence in support of limiting alcohol intake in adherence with the USDGA recommendations. .

**Introduction**

Excessive alcohol use is the third leading cause of mortality in the USA, after smoking and 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 USA. 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 as neutral, it has been widely reported that an alcohol intake higher than 15 g/day 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 USA after the 1970s. This level 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, is predicted in the USA (10). Excessive alcohol use also has a relevant cost for the community. In 2006, the economic burden of alcohol use in the US was assessed at 223.5 billion USD (11), with a predicted 249 billion USD 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 to not start consuming alcohol, or if alcohol is already consumed, it should be used in moderation in as much as one drink per day (14 g/day) for women and two drinks per day (28 g/day) for men consumed during any day (12). Notably, two out of three regular drinkers in the US reported an intake higher than the recommended alcohol use at least once a month (13).

While the increased health risks resulting from alcohol use is evident, some open questions regarding alcohol use and its consequences in the US population remain. Firstly, it is still not clear what the alcohol consumption trend over time in the US is in terms of adherence to 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. Secondly, it is questionable whether the current maximum recommended alcohol use by 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 in 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 to alternative more cautious recommendations.

To address these aims, the data from the National Health and Nutrition Examination Survey (NHANES) linked to the US mortality registry was investigated. The specific multi-stage probability sampling technique applied in the NHANES gave us the opportunity to estimate alcohol use in the US and its trend over the last 15 years. Additionally, a non-linear dose response analysis investigating the relation between all-cause and cause-specific mortality was applied to determine the level 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 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 National Health and Nutrition Examination Survey (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 study is based on a multistage probability sampling aimed to design a representative US sample (15). Since 1999, every year about 5,000 US citizens are involved in standardized health interviews and physical examinations aimed to collect, among others, socio-demographic characteristics, health status and history, smoking habit, alcohol use, physical activity, body size measures, nutritional status and dietary intakes. On a regular basis, the NHANES study is linked to the US mortality registry (16).

In this analysis, participants from the NHANES surveys conducted between 1999 and 2014 were merged to the 2015 US mortality registry resulting in a dataset of 82,091 records. After exclusion of participants aged younger than 18 years 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 the flow chart of participant selection.

**Alcohol assessment**

Two different tools were used for alcohol consumption assessment. Firstly, a dietary interview was undertaken to determine the mean amount of alcohol consumed. The dietary interview was composed of three sections, i.e., 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 approximately 3 to 10 days after the first dietary evaluation (17). Two days of dietary data were collected for the surveys performed after 2002. Alcohol intake was categorized as non-drinkers < 0.1 grams per day, 0.1 to < 14 grams per day (reference category), 14 to < 28 grams per day, 28 to < 42 grams per day and ≥ 42 grams per day. 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 grams per day for women (one standard alcoholic drink per day) and 28 grams per day for men (two standard alcoholic drinks per day).

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 (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. Median and interquartile ranges were used to describe continuous variables, while 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 continuous variable and to participants categorized according to their alcohol intake (non-drinkers, 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 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 high school degree), body mass index (continuous, kg/m2), systolic and diastolic blood pressure (continuous, mmHg), smoking status (smoked at least 100 cigarettes in life), energy intake (kcal/day), dietary fiber (grams/day) and indicator variables for prevalent cardiovascular diseases (at least one of the following - coronary heart disease, congestive heart failure, myocardial infarction or stroke) and any primary cancer at baseline. Age was used as underlying time variable and models were stratified by sex, 10-year 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’ residuals plot. A restricted cubic spline model with knots at 0.1, 7, 14, 28 grams per day in women and 0.1, 7, 14, 28, 42 grams per day 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. Test for non-linearity was undertaken by means of Wald test applied to the quadratic and cubic spline coefficients.

Mortality risks for alcohol intake in alcohol users (alcohol intake > 0.1 grams per day for data regarding mean alcohol use and for non-missing values for data on mean alcohol use during drinking days) were performed by thresholds defined according to the recommendation of the USDGA.

Finally, population attributable risks (PAR) were performed considering the mean prevalence of alcohol users over the observational period (Pr) and the hazard ratios (HR) 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 cluster were included in the survey statistical procedures to take into account the complex multi-stage probability sampling, to avoid differential probabilities of selection among sub-groups 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 over adjustment a further sensitivity analysis was undertaken using models not adjusted for BMI and blood pressure. The STATA software vers.15 was used for all statistical analysis. All statistical tests were two-tailed and type-I error rate was set to 5% (α = 0.05).

**Results**

The sample, composed of 34,672 participants, was observed for a median period of 7.8 years (interquartile range = 4.3, 11.9) totalling 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 (UCOD = I00-I09, I11, I13, I20-I51) and 165 to stroke (UCOD = I60-I69). The median age of the participants was 48 years (interquartile range = 34 to 64) 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 grams by survey (two years) 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 grams by two years, respectively.

When looking at number of drinks consumed during a typical drinking day we also observed a reduction in the number of men consuming more than two drinks per day (P = 0.024). On the other hand, there was no change in the number of women consuming more than one 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 recommendation were 11.1 and 71.3% in men and 12.3 and 60.1% in women (Figure 2). All-cause and cause-specific mortality risk 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 hazard ratios, we observed that non-consumers (<0.1 g/day alcohol) had higher mortality risk with respect to the reference category (>0.1 to <14g/day) in both sexes (HR = 1.40, 95% CI = 1.20, 1.63 and HR = 1.21, 95% CI = 1.01, 1.44 in men and women respectively). We also observed an increased risk for all-cause mortality in men and women when merging all categories with alcohol intake higher than one drink during a drinking day (HR = 1.17, 95% CI = 1.04, 1.33 and HR = 1.49, 95% CI = 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 CVD mortality risk in men but not in women. This was confirmed by analyses conducted on 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 = 1.55, 95% CI = 1.23, 1.96 and HR = 1.38, 95% CI = 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 = 1.39, 95% CI = 1.24, 1.55 and HR = 1.49, 95% CI = 1.30, 1.71 for all-cause mortality in men and women, respectively). We observed a clear J-shape relation between all-cause mortality risk and mean alcohol use (figure 3). The Wald test for non-linearity was statistically significant for the quadratic (PQ < 0.001, PQ = 0.030 in men and women, respectively) and the cubic component of the spline (PC < 0.001, PC = 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 non-consumers was included in the model (PQ = 0.37 in men and PQ = 0.12 in women, PC = 0.29 in men and PC = 0.12 in women). When considering number of drinks during drinking days in relation to all-cause mortality, a monotone non-linear relation was observed in men (PQ < 0.001 and PC < 0.001) while a monotone linear relation was observed in women (PC = 0.45 and PQ = 0.56).

Population attributable risks 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 (one standard drink per day, 14 grams per day) was applied to men, 9.7% of all-cause deaths would be avoided.

Finally, if number of drinks consumed in a typical drink day was reduced to align with the USDGA, an expected reduction of 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 on if number of drinks consumed in a typical drink day was reduced to align with the USDGA. Furthermore, if the limit of one 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% to 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 body mass index and blood pressure did not affect the results.

**Discussion**

In the present work we showed an apparently contradictory alcohol use trend in the USA during the period 1999-2014. The amount of alcohol consumed, among users, is decreasing while, on the other hand, the proportion of individuals consuming more than the recommended USDGA intake 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 however, decreasing irrespective of sex. A trend towards higher alcohol intakes was consistently reported in recent surveys conducted in the USA (9, 10, 19). The most comprehensive evidence regarding alcohol use in the USA comes from a recent meta-analysis including six national surveys (9). According to this study, alcohol use is increasing in the USA, confirming our trend analyses. This study also pointed out that specific risky behaviours 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 in the USA(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 production of wine and its internal market has been increasing in the USA 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 one standard drink would be a much more prudent recommendation for men also. Notably, when the non-linear analysis on mean alcohol use in relation to all-cause mortality is applied to men only, the recommended alcohol intake according to USDGA (28 grams per day) is confirmed to be significantly related to an increased risk for all-cause mortality (Figure 3). According to the present study, a stricter guideline in the USA, limiting alcohol use to one standard alcohol drink during a drinking day also for men would result in a 13% (95% CI = 3.4, 22.3) all-cause mortality reduction.

If such a guideline had been applied in the past, more than 1,000 deaths per year could possibly have been avoided in men during the period 2006-2010.Guidelines for alcohol use in different countries are sparse, and define a wide range of alcohol use recommendations (14). In this wide spectrum of alcohol use recommendations, the current US guidelines have the highest threshold for men while some of other countries have guidelines suggesting a much more moderate alcohol use below 20 grams per day. 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 grams of alcohol per week, which is less than 15 grams per day (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-C, 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 behaviours resulting in injuries and violence upon acute drinking.

We additionally observed increased all-cause and cause-specific mortality for non-drinkers compared to light alcohol users. This evidence is consistent with previous studies and is likely due to the fact that non-drinkers differ systematically from alcohol drinkers in a way that may influence mortality risk (24-26). More specifically, it should be considered that non-drinkers might abstain from alcohol because of poor health which, in turn, may result in increased mortality risk regardless of the alcohol intake (27-28). Our result of an increased mortality risk for non-drinkers 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 non-drinkers to perform population attributable risks. 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. Firstly, it is based on a rigorous sampling technique aimed to provide population-based estimates. Secondly, novel results were reported regarding alcohol use trend and alcohol use in relation to all-cause and cause-specific mortality risk in the USA 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 non-drinkers is a possibility. However, we based our PAR estimates on risk performed excluding non-drinkers. After exclusion of individuals without information on mortality status our sample 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 non-response 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.

 **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 USA 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. .

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| --- | --- | --- | --- | --- |
|  |  | **Mean alcohol consumption** |  | **Number of drinks consumed on drinking days** |
| **Men** |  | < 14 g/day |  | 14 to 28 g/day |  | ≥ 28 g/day |  | 1 drink/day |  | 2 drinks/day |  | ≥ 3 drink/day |
| Age (years) |  | 50 (35, 66) |  | 49 (35, 64) |  | 44 (32, 57) |  | 57 (41, 71) |  | 49 (35, 62) |  | 47 (32, 63) |
| 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%) |
| < High school  |  | 7079 (82%) |  | 705 (8%) |  | 870 (10%) |  | 1214 (14%) |  | 1196 (14%) |  | 6244 (72%) |
| BMI (kg/m2) |  | 28 (25, 31) |  | 27 (24, 31) |  | 27 (24, 31) |  | 27 (25, 31) |  | 28 (25, 31) |  | 28 (24, 31) |
| SBP (mmHg) |  | 123 (114, 134) |  | 123 (115, 135) |  | 125 (116, 134) |  | 123 (114, 135) |  | 122 (113, 133) |  | 123 (114, 134) |
| DBP (mmHg) |  | 72 (64, 79) |  | 72 (64, 80) |  | 74 (66, 81) |  | 72 (64, 79) |  | 72 (65, 79) |  | 72 (64, 80) |
| Energy (kcal/day) |  | 2115 (1551, 2833) |  | 2542 (1939, 3364) |  | 2990 (2269, 4103) |  | 2256 (1695, 3000) |  | 2303 (1720, 3031) |  | 2192 (1586, 3014) |
| Dietary fiber (grams/day) |  | 16 (11, 23) |  | 17 (12, 25) |  | 17 (11, 26) |  | 18 (12, 26) |  | 16 (11, 24) |  | 16 (10, 23) |
| Smokers |  | 7178 (77%) |  | 991 (11%) |  | 1102 (12%) |  | 1571 (17%) |  | 1604 (17%) |  | 6096 (66%) |
| Primary Cancer |  | 1235 (82%) |  | 167 (11%) |  | 108 (7%) |  | 445 (29%) |  | 268 (18%) |  | 797 (53%) |
| At least one CVD  |  | 1693 (86%) |  | 177 (9%) |  | 109 (6%) |  | 488 (25%) |  | 273 (14%) |  | 1218 (62%) |
| **Women** |  |  |  |  |  |  |  |  |  |  |  |  |
| Age (years) |  | 47 (33, 64) |  | 49 (36, 63) |  | 45 (33, 58) |  | 52 (37, 66) |  | 43 (31, 55) |  | 47 (31, 64) |
| 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%) |
| < High school  |  | 8257 (91%) |  | 436 (5%) |  | 332 (4%) |  | 1756 (19%) |  | 1116 (12%) |  | 6153 (68%) |
| BMI (kg/m2) |  | 28 (24, 33) |  | 27 (23, 31) |  | 27 (23, 32) |  | 27 (24, 32) |  | 27 (23, 33) |  | 28 (24, 34) |
| SBP (mmHg) |  | 118 (108, 134) |  | 119 (107, 135) |  | 118 (108, 131) |  | 120 (108, 135) |  | 115 (106, 127) |  | 119 (108, 135) |
| DBP (mmHg) |  | 69 (61, 76) |  | 70 (62, 77) |  | 71 (63, 78) |  | 70 (62, 77) |  | 70 (62, 77) |  | 68 (61, 76) |
| Energy (kcal/day) |  | 1805 (1333, 2421) |  | 2269 (1722, 2929) |  | 2621 (1984, 3455) |  | 1931 (1448, 2540) |  | 1956 (1444, 2575) |  | 1808 (1313, 2475) |
| Dietary fiber (grams/day) |  | 14 (10, 21) |  | 16 (11, 24) |  | 16 (10, 24) |  | 15 (11, 22) |  | 15 (10, 21) |  | 14 (9, 20) |
| Smokers |  | 5882 (87%) |  | 506 (7%) |  | 387 (6%) |  | 1604 (24%) |  | 1355 (20%) |  | 3816 (56%) |
| Primary Cancer |  | 1480 (87%) |  | 129 (8%) |  | 85 (5%) |  | 526 (31%) |  | 228 (13%) |  | 940 (55%) |
| At least one CVD  |  | 1300 (93%) |  | 67 (5%) |  | 37 (3%) |  | 319 (23%) |  | 106 (8%) |  | 979 (70%) |
| Notes: **BMI**: Body Mass Index, **SBP**: Systolic Blood Pressure, **DBP**: Diastolic Blood pressure, **Cer/Ov/Ut**: Cervix, Ovarian and Uterus cancers, **CVD**: Cardiovascular Disease, **CHF**: Congestive Heart Failure, **CHD**: Coronary Heart Disease, **HA**: Heart Attack. |

**Table 1.** Baseline characteristics of study participants according to USDGA-defined alcohol consumption categories

|  |
| --- |
| **All-cause mortality** |
| 1Alcohol use (g/day) |  | Deaths |  | Participants |  | Person-years |  | HR (95% CI) |
| < 0.1  |  | 1,700 |  | 10,795 |  | 86,156 |  | 1.40 (1.20, 1.63) |
| ≥ 0.1 and < 14 |  | 320 |  | 2,517 |  | 18,941 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 192 |  | 1,608 |  | 12,510 |  | 1.17 (0.94, 1.46) |
| ≥ 28  |  | 211 |  | 1,650 |  | 15,036 |  | 1.55 (1.23, 1.96) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 557 |  | 3,177 |  | 25,013 |  | 1 (ref.) |
| 2 |  | 285 |  | 2,956 |  | 24,492 |  | 0.83 (0.69, 1.00) |
| 3 |  | 151 |  | 1,785 |  | 14,458 |  | 0.96 (0.76, 1.21) |
| ≥ 4 |  | 1,430 |  | 8,652 |  | 68,681 |  | 1.34 (1.18, 1.53) |
| **Cardiovascular and stroke mortality** |
| 1Alcohol use (g/day) |  |  |  |  |  |  |  |  |
| < 0.1  |  | 398 |  | 10,795 |  | 86,156 |  | 1.97 (1.44, 2.71) |
| ≥ 0.1 and < 14 |  | 67 |  | 2,517 |  | 18,941 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 40 |  | 1,608 |  | 12,510 |  | 1.36 (0.83, 2.22) |
| ≥ 28  |  | 44 |  | 1,650 |  | 15,036 |  | 1.96 (1.19, 3.22) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 125 |  | 3,177 |  | 25,013 |  | 1 (ref.) |
| 2 |  | 74 |  | 2,956 |  | 24,492 |  | 0.86 (0.60, 1.24) |
| 3 |  | 24 |  | 1,785 |  | 14,458 |  | 0.80 (0.45, 1.44) |
| ≥ 4 |  | 326 |  | 8,652 |  | 68,681 |  | 1.17 (0.89, 1.53) |
| **Cardiovascular mortality** |
| 1Alcohol use (g/day) |  |  |  |  |  |  |  |  |
| < 0.1  |  | 331 |  | 10,795 |  | 86,156 |  | 1.81 (1.29, 2.53) |
| ≥ 0.1 and < 14 |  | 61 |  | 2,517 |  | 18,941 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 31 |  | 1,608 |  | 12,510 |  | 1.30 (0.76, 2.23) |
| ≥ 28  |  | 36 |  | 1,650 |  | 15,036 |  | 1.79 (1.04, 3.09) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 107 |  | 3,177 |  | 25,013 |  | 1 (ref.) |
| 2 |  | 64 |  | 2,956 |  | 24,492 |  | 0.86 (0.58, 1.27) |
| 3 |  | 19 |  | 1,785 |  | 14,458 |  | 0.74 (0.39, 1.39) |
| ≥ 4 |  | 269 |  | 8,652 |  | 68,681 |  | 0.99 (0.74, 1.33) |
| **Cancer mortality** |
| 1Alcohol use (g/day) |  |  |  |  |  |  |  |  |
| < 0.1  |  | 414 |  | 10,795 |  | 86,156 |  | 1.29 (0.95, 1.75) |
| ≥ 0.1 and < 14 |  | 79 |  | 2,517 |  | 18,941 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 42 |  | 1,608 |  | 12,510 |  | 0.91 (0.58, 1.43) |
| ≥ 28  |  | 48 |  | 1,650 |  | 15,036 |  | 1.27 (0.77, 2.08) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 124 |  | 3,177 |  | 25,013 |  | 1 (ref.) |
| 2 |  | 64 |  | 2,956 |  | 24,492 |  | 0.68 (0.46, 1.00) |
| 3 |  | 55 |  | 1,785 |  | 14,458 |  | 1.29 (0.86, 1.94) |
| ≥ 4 |  | 340 |  | 8,652 |  | 68,681 |  | 1.29 (0.99, 1.68) |
| Notes: 1Analysis performed on mean daily intake, 2Analysis performed on number of drinks typically consumed on drinking days |

Table 2 All cause and cause-specific mortality hazard ratios (HR) in relation to alcohol use in men

Table 3 All cause and cause-specific mortality hazard ratios (HR) in relation to alcohol use in women

|  |
| --- |
| **All-cause mortality** |
| 1Alcohol use (g/day) |  | Deaths |  | Participants |  | Person-years |  | HR (95% CI) |
| < 0.1  |  | 1,487 |  | 13,772 |  | 116,019 |  | 1.21 (1.01, 1.44) |
| ≥ 0.1 and < 14 |  | 212 |  | 2,413 |  | 19,028 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 111 |  | 1,105 |  | 8,257 |  | 1.34 (0.95, 1.87) |
| ≥ 28  |  | 67 |  | 797 |  | 6,822 |  | 1.38 (1.05, 1.83) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 408 |  | 4,647 |  | 38,697 |  | 1 (ref.) |
| 2 |  | 158 |  | 2,975 |  | 25,001 |  | 1.16 (0.93, 1.44) |
| 3 |  | 63 |  | 1,291 |  | 10,893 |  | 1.38 (0.96, 1.98) |
| +4 |  | 1,248 |  | 9,174 |  | 75,534 |  | 1.59 (1.38, 1.83) |
| **Cardiovascular and stroke mortality** |
| 1Alcohol use (g/day) |  |  |  |  |  |  |  |  |
| < 0.1  |  | 279 |  | 13,772 |  | 116,019 |  | 1.43 (0.95, 2.15) |
| ≥ 0.1 and < 14 |  | 34 |  | 2,413 |  | 19,028 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 20 |  | 1,105 |  | 8,257 |  | 0.59 (0.18, 1.97) |
| ≥ 28  |  | 4 |  | 797 |  | 6,822 |  | 1.69 (0.86, 3.32) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 73 |  | 4,647 |  | 38,697 |  | 1 (ref.) |
| 2 |  | 8 |  | 2,975 |  | 25,001 |  | 0.73 (0.39, 1.35) |
| 3 |  | 18 |  | 1,291 |  | 10,893 |  | 1.14 (0.49, 2.63) |
| +4 |  | 238 |  | 9,174 |  | 75,534 |  | 1.52 (1.08, 2.12) |
| **Cardiovascular mortality** |
| 1Alcohol use (g/day) |  |  |  |  |  |  |  |  |
| < 0.1  |  | 214 |  | 13,772 |  | 116,019 |  | 1.42 (0.91, 2.21) |
| ≥ 0.1 and < 14 |  | 28 |  | 2,413 |  | 19,028 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 17 |  | 1,105 |  | 8,257 |  | 0.68 (0.20, 2.33) |
| ≥ 28  |  | 3 |  | 797 |  | 6,822 |  | 1.70 (0.83, 3.49) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 59 |  | 4,647 |  | 38,697 |  | 1 (ref.) |
| 2 |  | 6 |  | 2,975 |  | 25,001 |  | 0.76 (0.37, 1.55) |
| 3 |  | 13 |  | 1,291 |  | 10,893 |  | 1.18 (0.46, 2.99) |
| +4 |  | 184 |  | 9,174 |  | 75,534 |  | 1.59 (1.08, 2.32) |
| **Cancer mortality** |
| 1Alcohol use (g/day) |  |  |  |  |  |  |  |  |
| < 0.1  |  | 303 |  | 13,772 |  | 116,019 |  | 1.30 (0.90, 1.88) |
| ≥ 0.1 and < 14 |  | 48 |  | 2,413 |  | 19,028 |  | 1 (ref.) |
| ≥ 14 and < 28 |  | 31 |  | 1,105 |  | 8,257 |  | 1.64 (0.95, 2.84) |
| ≥ 28  |  | 22 |  | 797 |  | 6,822 |  | 2.25 (1.23, 4.13) |
| 2Alcohol use (drink/day) |  |  |  |  |  |  |  |  |
| 1 |  | 101 |  | 4,647 |  | 38,697 |  | 1 (ref.) |
| 2 |  | 49 |  | 2,975 |  | 25,001 |  | 1.31 (0.86, 1.99) |
| 3 |  | 15 |  | 1,291 |  | 10,893 |  | 1.10 (0.55, 2.20) |
| +4 |  | 239 |  | 9,174 |  | 75,534 |  | 1.59 (1.16, 2.18) |
| Notes: 1Analysis performed on mean daily intake, 2Analysis performed on number of drinks typically consumed on drinking days |

Table 4. Population Attributable Risks (PAR) 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 2015-2020UDSGA

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Men** |  |  |  |  |  |  |
| Mean alcohol intake > 28 grams per day (two standard drinks) |
| Mortality |  | Population at risk |  | HR (95% CI) |  | PAR (95% CI) |
| 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 two 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 one 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 grams per day (one standard drinks) |
| 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 one 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) |
| Note: Population at risk performed over the period 1999-2014, HR for mortality in participants non-compliant to the current US guidelines |

**Figure legends**

**Figure 1.** Flowchart of participant selection according to NHANES surveys conducted during the period 1999-2014 merged with 2015 US mortality registry.

**Figure 2.** Trends of individuals non-compliant to USDGA by sex. P values portray trend test. (N = 5,781 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).

**Figure 3.** Non-linear dose response analysis of alcohol use and all-cause mortality by sex. Mortality hazards for mean alcohol use were modelled having an indicator variable for alcohol non users. (N = 5,781 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)