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Volume of alcohol intake, heavy episodic drinking, and all-cause mortality in Spain: A longitudinal population-based study

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ABSTRACT

Introduction: The impact of alcohol consumption on health, particularly in low quantities, remains controversial. Our objective was to assess the association between alcohol volume and heavy episodic drinking (HED) with all-cause mortality, while minimizing many of the known methodological issues.

Methodology: This longitudinal study used data from the 2011–2012 National Health Survey and the 2014 European Health Survey in Spain. Data from 43,071 participants aged ≥ 15 years were linked to mortality records as of December 2021. Alcohol consumption categories were defined based on intake volume and frequency: never-drinkers, former drinkers, infrequent occasional drinkers (≤once/month), frequent occasional drinkers (<once/week to > once /month). Regular drinkers (≥once/week) were further classified by volume: >0–10 g/day, >10–20 g/day, >20–40 g/day, and > 40 g/day. Heavy Episodic Drinking (HED) was defined as ≥ 6 and ≥ 5 standard drinks (10 g) within 4–6 h for men and women, respectively. Hazard ratios (HR) were calculated using Cox regression, adjusting for sociodemographic variables, lifestyle factors, health status, and alcohol volume or HED.

Results: Compared to infrequent occasional drinkers, HRs for never-drinkers and former drinkers were 1.30 (95 % CI:1.14–1.47) and 1.32 (95 %CI:1.15–1.50), respectively. No differences in mortality risk were observed for intakes up to 20 g/day, but it increased for consumptions > 20–40 g/day and > 40 g/day (HR = 1.29; 95 % CI:1.05–1.58 and HR = 1.57; 95 %CI:1.14–2.17, respectively). The HR of weekly HED vs. never was 1.31 (95 % CI:0.98–1.75).

Conclusions: Compared to infrequent occasional drinking, consuming low amounts of alcohol had no impact on mortality risk. However, never-drinkers, former drinkers, individuals with regular consumption > 20 g/day, and those engaging in weekly HED, experienced higher mortality risk.

1. Introduction

In 2019, alcohol consumption ranked as the ninth most significant risk factor for premature mortality and disability worldwide, rising to the number one position among 25 to 49 year-olds (GBD 2019 Risk Factors Collaborators, 2020). Alcohol is associated with over 200 diseases and accidents (World Health Organization, 2018), contributing to 5.3 % of global mortality (GBD 2019 Risk Factors Collaborators, 2020). Between 2010 and 2017, the average annual number of deaths attributable to alcohol in Spain for those ≥ 15 years of age was 14,927 (3.9 % of overall mortality) (Donat et al., 2021).

The relationship between alcohol and health is complex. While alcohol consumption is widely recognized as one of the primary risk factors for the global burden of disease, some studies confer a potential protective effect for specific diseases, such as ischemic heart disease, and diabetes(Griswold et al., 2018). The dose–response association between alcohol intake and all-cause and cardiovascular mortality, tends to exhibit a J-shaped curve (Andréasson, 1998; Plunk et al., 2014). This shape conveys that consuming small amounts of alcohol (the bottom part of the curve) is associated with lower mortality risks than

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abstinence. However, the dose–response curve and the definition of "small amount" vary across studies, countries, sex, age, race, and the specific diseases of interest (Rehm et al., 2021).

Equipped with new methodological approaches, authors have challenged these hypothetical beneficial effects (Chikritzhs et al., 2015; Holmes et al., 2014). It is worth stressing that the study of the alcohol-mortality relationship has often been based on convenience samples, with sociodemographic characteristics and distributions of mortality causes not representative of the population at large (Rehm, 2019). Further, the distribution of confounding variables associated with low alcohol consumption may vary across non-representative cohorts, which tend to concentrate in higher socioeconomic status (SES) strata, potentially biasing the magnitude and pattern of the association (Naimi, 2019). Finally, the bulk of the research analyzes only middle-aged and older participants, which may introduce a survival bias (Naimi et al., 2017).

Other significant methodological issues associated with the overestimation of alcohoĺs health benefits are the classification issues (e.g., grouping former, occasional, and never-drinkers) and under-adjustment of relevant confounding factors. In fact, since 27 out of 30 potential confounders (demographic, social, behavioral, health conditions, and health care access factors), in the alcohol-mortality relationship are more prevalent in never-drinkers than in moderate drinkers (Naimi et al., 2005), any benefits all but disappeared through the use of sequential models for the proper adjustment for confounders (Stockwell, Zhao, Panwar, et al., 2016).

Regarding the episodic consumption of high quantities of alcohol or heavy episodic drinking (HED), there is broad consensus that this practice poses a risk to both short- and long-term health, regardless of its frequency (Molina & Nelson, 2018). However, regular alcohol consumption and HED often overlap. In fact, the majority of individuals in Spain reporting HED in the previous month fall under the category of moderate drinkers (<40 g/day in men and < 24 g/day in women) (Soler-Vila, Galán, Valencia-Martín, et al., 2014). Thus, whenever possible, studies modeling alcohol consumption and mortality should adjust for HED.

The objective of this study was to estimate the associations between volume of alcohol consumed and HED, both independently and jointly, with all-cause mortality in a large, representative cohort of the Spanish adult population.

2. Methodology

2.1. Study design and population

We used data from 43,847 individuals aged ≥ 15 years who participated in the 2011–2012 National Health Survey and the 2014 European Health Survey in Spain, which were linked to mortality records as of December 31, 2021 (MESES study − Mortality linkage to Spanish Health Surveys). Both surveys employed similar multistage sampling designs and harmonized questionnaires. First, all Spanish provinces were selected then, within each province, a sample of municipalities was chosen, stratifying according to their size. At a second stage, a sample of census sections is chosen within the selected municipalities. Finally, households are sampled, with one person aged ≥ 15 years selected within each home to be interviewed face-to-face with Computer-Assisted Personal Interviewing (CAPI) software (Ministerio de Sanidad e Instituto Nacional de Estadística, 2012, 2014). The response rate from the selected households was 71 %. Finally, the Spanish National Institute of Statistics linked these data to mortality records using the participant́s national identity document number.

2.2. Variables

2.2.1. Alcohol consumption

We classified participants based on both frequency of consumption and volume consumed into 8 categories. According to their usual frequency, individuals were classified: 1) never-drinkers (defined as those who have never consumed alcohol or just a few sips throughout their life just to taste it), 2) former drinkers (individuals who stopped drinking alcohol and report not consumption in the last 12 months), 3) infrequent occasional drinkers (consumption ≤ once/month), 4) and frequent occasional drinkers (<once/week and > once/month). Regular consumers (≥once/week) were further classified into 4 categories (below) based on their frequency and quantity of consumption of each of six types of alcoholic beverages from Monday to Sunday: wine, beer, cider (10 g of alcohol per unit of beverage), vermouth and aperitifs, spirits, cocktails (20 g of alcohol per unit of beverage). Subsequently, we calculated the grams of alcohol consumed based on the volume of alcohol in the beverages reported. Regular drinkeŕs categories: 5) > 0–10 g/day, 6) > 10–20 g/day, 7) > 20–40 g/day, 8) and > 40 g/day.

Heavy Episodic Drinking (HED) was defined as the consumption of ≥ 6 or ≥ 5 standard drinks (10 g of alcohol) within a 4–6 h period for men and women, respectively. HED frequency was recorded and classified as: never, <once/month, monthly, or weekly.

2.2.2. Covariates

Sociodemographic variables included sex, age, educational level (no formal education/primary education, secondary education-first stage, secondary education-second stage, and university), marital status (single, married, widowed, separated/divorced), and size of the municipality of residence (<10,000 residents, 10,000–50,000, >50,000–500,000, and > 500,000).

Participants provided self-reported information on four main lifestyle behaviors. Leisure-time physical activity was divided into four categories based on frequency (no exercise/almost entirely sedentary, occasional, moderate, and high physical activity). Diet quality, i.e., adherence to the Mediterranean diet, was assessed using an adapted version of the Mediterranean Diet Adherence Screener (MEDAS) (Schröder et al., 2011), with scores ranging from 0 (lowest adherence) to 10 (highest adherence). Body Mass Index (BMI) was calculated from self-reported weight and height (kg/m2). Finally, participants were classified based on tobacco consumption as: non-smokers, former smokers, >0–14 cigarettes/day, and > 14 cigarettes/day.

Self-perceived health status was recorded using five categories: very good, good, fair, poor, and very poor. Functional limitation was assessed through the Global Activity Limitation Indicator (GALI) with the question: "Thinking about the last 6 months, to what extent have you been limited due to a health problem in performing activities that people usually do?" Respondents could report: a) severely limited, b) limited but not severely, or c) not limited at all (Van Oyen et al., 2018). Finally, we included information on the following chronic diseases, diagnosed by a physician: myocardial infarction, other heart diseases, stroke, chronic obstructive pulmonary disease (COPD), diabetes, stomach ulcer, cirrhosis/hepatomegaly, and malignant tumors. Participants were classified according to the number of diseases reported into three categories: none, 1, ≥2.

2.3. Statistical analysis

Of the 43,847 individuals in the original sample, 776 were excluded due to missing data for any of the variables included in our analyses; thus, the final sample was composed of 43,071 individuals.

Cox regression models calculated Hazard Ratios (HR) for mortality with their corresponding 95 % confidence intervals (CI). Schoenfeld residuals tests confirmed that the condition of proportionality of hazards was met. Models included sociodemographic variables (sex, age −with quadratic transformation-, marital status, size of the municipality of residence, and level of education), lifestyle variables (smoking, physical activity, adherence to the Mediterranean diet, and body mass index), and health status (perception of health, functional limitation, and history of chronic diseases). Using infrequent occasional drinkers (<once/

month) as the reference category for alcohol volume consumption, two sequential models were developed: Model 1: adjusting for sociodemographic variables, lifestyles, and health status; and Model 2: Model 1 + HED.

To analyze the dose–response relationship of alcohol volume with mortality risk, restricted cubic splines with nodes at different percentiles of the distribution were used adjusting for sociodemographic variables, lifestyles, health status, and HED. Four dose–response models were developed: 1) excluding former drinkers and keeping never-drinkers and occasional drinkers with 0 g/day consumption, using nodes at the 60th, 75th, and 90th percentiles of the distribution; 2) excluding former drinkers and occasional drinkers, and keeping never-drinkers with 0 g/day consumption, using nodes at the 50th, 75th, and 90th percentiles; 3) excluding former drinkers and never-drinkers, and keeping occasional drinkers with 0 g/day alcohol consumption, using nodes at the 50th, 75th and 90th percentiles; 4) excluding former drinkers, never-drinkers, and occasional drinkers, using nodes at the 5th, 50th and 95th percentiles. In the first three models the reference was set at 0 g/day, and in the last model at 1 g/day.

Average alcohol volume analyses were stratified by sex, age (<65 years vs. ≥ 65 years) and educational level (≥secondary school-second stage vs. ≤ secondary school-first stage), combining the two highest volume categories as > 20 g/day, to reduce the variability of the estimates.

To analyze the association with HED, two analyses were developed, one excluding former drinkers, and the other considering only drinkers

Table 1
Sample characteristics according to categories of average alcohol consumption. Population of Spain aged ≥ 15 years.

	Total	Never Drinkers	Former Drinkers	Infrequent Occasional	Frequent Occasional	>0–10 g/day	>10–20 g/day	>20–40 g/day	>40 g/day	P value
n [a]	43,071	9472	5726	8044	3699	9094	4492	2038	506	
Prevalence [b]	100	21.7	11.9	19.7	9.3	21.3	10.6	4.6	1.0	
Age, mean (SD) [b]	47.4 (18.7)	49.4 (21.8)	54.6 (20.5)	42.9 (16.9)	39.9 (15.4)	48.1 (16.6)	48.0 (16.8)	49.7 (16.5)	51.0 (16.8)	<0.001
Sex,% [b]										<0.001
Women	51.2	72.3	58.2	59.3	48.8	42.3	26.8	12.4	7.0	
Educational level,% [b]										<0.001
University	17.2	10.2	11.6	17.8	22.7	23.8	20.3	16.1	9.8	
Secondary 2nd Stage	28.1	20.2	21.0	32.1	35.0	31.2	31.5	40.0	21.6	
Secondary 1st Stage	28.2	29.1	27.9	30.2	28.1	25.3	27.5	30.1	34.8	
≤Primary	26.5	40.5	39.6	20.0	14.1	19.7	20.7	22.9	33.7	
Marital status,% [b]										<0.001
Single	30.9	30.0	20.2	35.9	44.7	27.5	30.4	29.2	35.1	
Married	56.9	52.5	62.3	53.6	47.6	62.8	61.0	61.6	52.9	
Widowed	7.4	13.8	12.4	5.2	3.1	4.8	3.9	3.3	3.6	
Separated/Divorced	4.8	3.7	5.1	5.3	4.6	4.9	4.7	5.9	8.3	
Municipality size,% [b]										<0.001
>500,000 inhab	32.5	30.1	30.6	33.8	32.8	34.8	34.0	29.2	27.7	
>50,000–500,000 inhab	20.2	21.5	21.1	21.3	21.9	18.7	17.2	17.7	15.2	
10,000–50,000 inhab	26.5	26.3	26.2	26.4	27.5	26.3	26.7	26.3	30.2	
<10,000 inhab	20.8	22.2	22.0	18.5	17.7	20.2	22.1	26.8	26.8	
Tobacco consumption,% [b]										
Non-smokers	51.1	75.0	51.1	54.1	48.9	42.6	32.7	21.1	15.2	
Former smokers	22.7	10.6	26.9	20.7	21.6	27.8	31.6	33.2	27.5	
Smokers 1–14 cig/day	16.0	8.7	12.3	16.4	19.8	19.1	21.3	23.2	22.6	
Smokers > 14 cig/day	10.1	5.7	9.7	8.8	9.7	10.5	14.3	22.5	34.7	
Leisure time physical activity,% [b]										<0.001
High	11.0	7.1	5.6	12.6	14.9	13.6	13.0	11.8	10.0	
Moderate	12.7	9.2	7.1	13.1	18.0	14.7	16.4	13.7	10.0	
Occasional	35.8	33.4	37.1	36.5	33.9	37.3	37.1	34.3	36.5	
Sedentary	40.5	50.3	50.2	37.8	33.2	34.4	33.5	40.2	43.5	
Mediterranean Diet, mean (SD) [b]	4.9 (2.0)	5.1 (1.9)	5.2 (2.0)	4.7 (2.0)	4.6 (1.9)	4.9 (1.9)	4.8 (2.0)	4.6 (2.0)	4.4 (2.0)	<0.001
Body mass index,% [b]										<0.001
Underweight	2.3	2.8	2.3	2.7	3.2	1.4	1.8	1.2	1.8	
Normal weight	43.1	41.8	36.9	46.9	51.3	45.0	40.0	34.0	33.7	
Overweight	33.6	29.3	33.8	30.4	30.4	36.5	40.4	43.5	39.9	
Obesity	15.6	17.6	18.7	15.2	11.3	13.7	14.7	18.4	19.7	
Not available	5.4	8.6	8.2	4.8	3.8	3.4	3.1	2.9	4.8	
Perceived health,% [b]										
Very good	21.3	19.9	14.8	22.9	28.3	21.9	22.2	19.6	17.2	
Good	50.2	43.0	39.5	51.6	53.8	55.8	55.4	59.4	55.4	
Fair	20.4	24.8	28.6	19.4	13.9	17.4	17.6	15.9	21.0	
Poor	6.2	9.0	12.8	4.8	3.2	3.9	4.2	4.4	5.8	
Very poor	1.9	3.3	4.3	1.4	0.8	1.0	0.6	0.6	0.6	
Functional limitations,% [b]										<0.001
None	79.0	75.4	67.0	82.4	87.2	81.7	81.5	78.6	74.6	
Moderate	15.3	15.5	21.1	13.7	10.3	13.8	14.3	16.3	18.7	
Severe	5.7	7.1	11.9	3.9	2.5	4.6	4.1	5.1	6.6	
Chronic diseases,% [b]										<0.001
None	79.0	75.4	67.0	82.4	87.2	81.7	81.5	78.6	74.6	
1	15.3	17.5	21.1	13.7	10.3	13.8	14.3	16.3	18.7	
≥2	5.7	7.1	11.9	3.9	2.5	4.6	4.1	5.1	6.6	

[a] Unweighted; [b] %/Weighted means.

(including all occasional drinkers). These analyses were adjusted for the same covariates previously described, producing two models: 1) not adjusting for average alcohol volume and 2) adjusting for average volume.

Finally, we performed additional analyses where we combined the 2 indicators of alcohol consumption to reclassify participants to reflect HED reports in the last month: never-drinkers, former drinkers, occasional drinkers (<once/week) reporting no HED, occasional (<once/week) reporting HED, >0–20 g/day reporting no HED, >0–20 g/day reporting HED, >20 g/day reporting no HED, and > 20 g/day reporting HED.

We performed 2 sensitivity analyses for average volume and HED: 1) excluding the first year of follow-up; 2) excluding individuals with poor/very poor perceived health, severe functional limitation, body mass index < 18.5, and history of at least one chronic disease.

Estimates were weighted by sampling weights to restore proportionality. Analyses were performed with Stata v.17 (StataCorp, College Station, Texas, U.S.), using the survey data module to incorporate the complex sampling design characteristics of the surveys.

This study was approved by the Carlos III Institute of Health Ethical Research Committee, Number: CEI PI 28_2019. Informed consent was obtained from all individual participants included in the study.

3. Results

Table 1 shows the distribution of the sample by the categories of alcohol consumption based on weekly average intake. On a weighted basis, 21.7 % of the individuals in the sample were never-drinkers, 11.9 % were former drinkers, 19.7 % were infrequent occasional drinkers, 9.3 % were frequent occasional drinkers, 21.3 % regularly consumed > 0–10 g/day of alcohol, 10.6 % consumed > 10–20 g/day, 4.6 % consumed > 20–40 g/day, and 1 % consumed > 40 g/day.

Never- and former drinkers are more likely women, never smokers, and lead a sedentary life. They also were more likely to have a lower education level, greater adherence to the Mediterranean diet, poorer perceived health, greater functional limitation, and a more extensive history of chronic diseases than other participants.

Table S1 shows the characteristics of the sample according to HED frequency. A total of 82.4 % reported not engaging in HED, 10.8 % did so in the past year but not in the last month, 4.6 % did sometime in the last month but not in the last week, and 2.2 % did so on a weekly basis. Those not engaging in HED present similar sociodemographic and health status characteristics as the never-drinkers and former drinkers described above.

Table 2 displays the association between average alcohol consumption and overall mortality. The results of model 2, adjusted for HED, show that never-drinkers and former drinkers have higher mortality risk (HR = 1.30; 95 %CI: 1.14–1.47 and HR = 1.32; 95 %CI: 1.15–1.50, respectively) compared to infrequent occasional drinkers. No differences are observed for frequent occasional drinkers and regular drinkers who consumed up to 20 g/day. The risk increases again among regular drinkers consuming > 20–40 g/day (HR = 1.29; 95 %CI: 1.05–1.58) and those consuming > 40 g/day (HR = 1.57; 95 %CI: 1.14–2.17). Comparing Model 1 and 2, we see that the prognostic association of consuming > 20 g/day (vs. infrequent occasional consumption) is slightly reduced by adjusting for HED.

Fig. 1 shows the dose–response relationship between alcohol consumption volume and overall mortality according to the different classification approaches. Fig. 1A (excluding former drinkers and including never-drinkers and occasional drinkers with a consumption of 0 g/day) shows that the probability of death is at its lowest at 10 g/day and it increases above 1 starting at 20 g/day. Fig. 1B (excluding former and occasional drinkers and including never-drinkers (0 g/day)) shows that the probability of death is at its lowest at 12 g/day and it increases above 1 starting at 32 g/day. Fig. 1C (excluding former and never-drinkers, and assigning occasional drinkers a consumption of 0 g/day) shows a linear mortality risk increase starting at very small amounts of consumption. Fig. 1D (excluding never-drinkers, former, and occasional drinkers) shows a fairly linear rise in mortality risk as the volume of consumption increases.

Table 2
Association between average alcohol consumption and all-cause mortality. Population of Spain aged ≥ 15 years.

	Model 1			Model 2	
	n[a]	HR	95 %CI	HR	95 %CI
Average alcohol consumption					
Never drinkers	1576/9472	**1.29**	**1.14–1.47**	**1.30**	**1.14–1.47**
Former drinkers	1249/5726	**1.31**	**1.15–1.50**	**1.32**	**1.15–1.50**
Infrequent occasional drinkers	496/8044	1 (ref)		1 (ref)	
Frequent occasional drinkers	154/3699	0.95	0.76–1.19	0.95	0.76–1.19
>0–10 g/day	777/9094	1.03	0.90–1.18	1.03	0.90–1.18
>10–20 g/day	364/4492	1.04	0.87–1.24	1.03	0.87–1.23
>20–40 g/day	218/2038	**1.32**	**1.08–1.61**	**1.29**	**1.05–1.58**
>40 g/day	81/506	**1.68**	**1.24–2.28**	**1.57**	**1.14–2.17**

Model 1: Hazard ratios (HR) calculated using Cox regression models adjusting for age, sex, education, marital status, size of municipality, tobacco consumption, leisure time sedentarism, adherence to the Mediterranean diet, body mass index, perceived health, functional limitations, and chronic disease history.
Model 2: Model 1 plus heavy episodic drinking (HED) in the last month.
[a] Deceased individuals/exposed individuals.

Supplementary Tables S2-S4 describe the prognostic associations of average alcohol consumption by sex, age, and educational level. Men and women shared similar risks across the different categories of alcohol consumption, except for the category of regular consumption of > 20 g/day where women had a substantially higher risk than men (HR = 1.97; 95 %CI: 1.15–3.36 and 1.24; 95 %CI: 1.00–1.55, respectively). In terms of age groups, former drinkers aged 15–64 years displayed a significant increased risk, HR = 1.65 (95 %CI: 1.22–2.24), and regular drinkers > 20 g/day also showed a slight increase in risk.

Finally, those with lower educational level and consumptions of ≥ 20 g/day, presented an HR of 1.41 (95 %CI: 1.14–1.75) compared to those with higher educational level (1.15; 95 %CI: 0.77–1.70). However, when assessing whether these variations in the magnitude were statistically different, the only interaction term reaching statistical significance was for the difference in HR observed in former drinkers ≥ 65 vs. < 65 years (Suppl. Table S3).

Table 3 shows the association between HED and all-cause mortality. The top panel presents estimates after excluding former drinkers. Before adjusting for the average volume of alcohol (Model 1), individuals engaging in HED in the last month and those who reported doing it on a weekly basis experienced a higher mortality risk than those who never practiced HED (HR = 1.33; 95 %CI: 1.07–1.64 and HR = 1.50; 95 %CI: 1.14–1.96, respectively). However, when average alcohol consumption was adjusted for (Model 2), the resulting reduced estimates no longer reached statistical significance (HR = 1.19; 95 %CI: 0.95–1.50 and HR = 1.31; 95 %CI: 0.98–1.75, respectively). Similar associations were observed when only alcohol consumers were included in the analyses. Unfortunately, low statistical power did not allow to further examine these relationships across sex, age, or educational level.

Table 4 shows the results of classifying participants by both average intake and HED in the last month engagement using occasional drinkers not reporting HED as the reference category. Regular drinkers with intakes > 0–20 g/day who reported HED had a HR of 1.23 (95 %CI: 0.82–1.85) with respect to those reporting same volume of alcohol but not engaging in HED (HR = 1.04; 95 %CI: 0.92–1.17). Regular drinkers

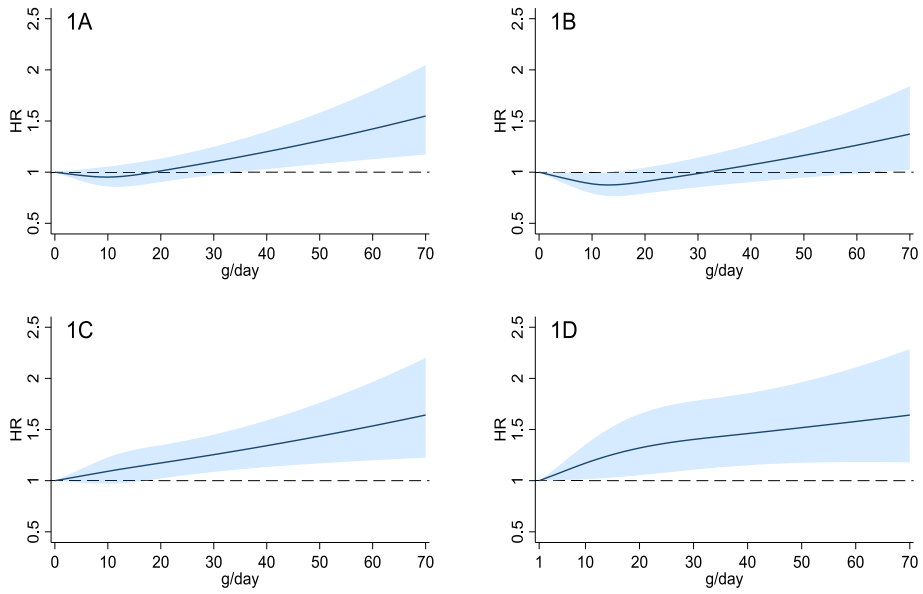

Fig. 1. Dose-response relationship of the association between alcohol volume and all-cause mortality. Population of Spain aged ≥ 15 years. Dose-response curves estimating hazard ratios (HR) with Cox regression and restricted cubic splines adjusting for sex, age, education, marital status, size of municipality, tobacco consumption, leisure time sedentarism, adherence to the Mediterranean diet, body mass index, perceived health, functional limitations, chronic disease history and heavy episodic drinking (HED). Fig. 1A: Excluding former drinkers and including never-drinkers and occasional drinkers with 0 g/day alcohol consumption, using nodes at percentiles 60, 75, and 90 of the distribution; Fig. 1B: Excluding former and occasional drinkers, and including never-drinkers with 0 g/day alcohol consumption, using nodes at the 50th, 75th, and 90th percentiles; Fig. 1C: Excluding former and never-drinkers, and including occasional drinkers with 0 g/day alcohol consumption, using nodes at the 50th, 75th, and 90th percentiles; Fig. 1D: Excluding former drinkers, never-drinkers, and occasional drinker, using nodes at the 5th, 50th, and 95th percentiles.

Table 3
Association between heavy episodic drinking (HED) and all-cause mortality. Population of Spain aged ≥ 15 years.

	Model 1			Model 2	
	n[a]	HR	95 %CI	HR	95 %CI
Overall population excluding former drinkers					
***HED* past month**					
No	3528/34504	1 (ref)		1 (ref)	
Yes	138/2841	**1.33**	**1.07–1.64**	1.19	0.95–1.50
HED Frequency					
Never	3396/30324	1 (ref)		1 (ref)	
<once a month	132/4180	1.09	0.86–1.37	1.09	0.86–1.38
Monthly but < once a week	65/1863	1.18	0.86–1.62	1.12	0.80–1.55
Weekly	73/978	**1.50**	**1.14–1.96**	1.31	0.98–1.75
Alcohol-drinking population					
***HED* past month**					
No	1319/13904	1 (ref)		1 (ref)	
Yes	121/2226	**1.39**	**1.11–1.75**	1.24	0.96–1.60
HED Frequency					
Never	1228/11286	1 (ref)		1 (ref)	
<once a month	91/2618	0.99	0.74–1.31	0.94	0.70–1.26
Monthly but < once a week	48/1248	1.28	0.88–1.86	1.15	0.78–1.70
Weekly	73/978	**1.47**	**1.12–1.94**	1.28	0.96–1.72

Model 1: Hazard ratios (HR) calculated using Cox regression models adjusting for age, sex, education, marital status, size of municipality, tobacco consumption, leisure time sedentarism, adherence to the Mediterranean diet, body mass index, perceived health, functional limitations, and chronic disease history.
Model 2: Model 1 plus average alcohol consumption
[a] Deceased individuals/exposed individuals.

Table 4
Association between the combination of average alcohol consumption and heavy episodic drinking (HED) in the last month, and all-cause mortality. Population of Spain aged ≥ 15 years.

	n[a]	HR	95 %CI
Combined alcohol consumption			
Never drinkers	1605/9616	**1.30**	**1.16–1.47**
Former drinkers	1264/5800	**1.32**	**1.17–1.50**
Occasional drinker[b] no HED	641/11236	1 (ref)	
Occasional drinker + HED	19/628	0.86	0.50–1.48
>0–20 g/day no HED	1114/12358	1.04	0.92–1.17
>0–20 g/day + HED	44/1371	1.23	0.82–1.85
>20 g/day no HED	223/1701	**1.33**	**1.10–1.61**
>20 g/day + HED	78/880	**1.72**	**1.26–2.35**

Hazard ratios (HR) calculated using Cox regression models adjusting for age, sex, education, marital status, size of municipality, tobacco consumption, leisure time sedentarism, adherence to the Mediterranean diet, body mass index, perceived health, functional limitations, and chronic disease history.
[a] Deceased individuals/exposed individuals.
[b] Alcohol consumption < once a week.

consuming > 20 g/day have a significantly higher mortality risk than occasional drinkers, and the difference in risk between those engaging in HED and those who do not, is substantial (HR = 1.72; 95 %CI: 1.26–2.35 and 1.33; 95 %CI: 1.10–1.61, respectively).

Finally, supplementary analyses excluding the first year of follow-up (Tables S5 and S7), as well as those with poor/very poor perceived health, severe functional limitation, BMI < 18.5, and history of at least one chronic disease (Tables S6 and S8), showed similar results as those reported above, with the exception that the HRs were higher for regular drinkers consuming > 20 g/day of alcohol and for individuals reporting engaging in HED weekly.

4. Discussion

The main results of this study show that, taking infrequent occasional

drinkers, i.e., those who consume alcohol once a month or less frequently, as the reference category, the intake of low amounts of alcohol was not associated with a lower or higher all-cause mortality risk. However, all-cause mortality risk was higher for regular consumers of 20 g or more of alcohol per day. This risk further increases for individuals who also engaged in heavy episodic drinking (HED) in the month previous to the interview, especially for those reporting more frequent episodic drinking.

Several systematic reviews have attempted to synthesize the association between alcohol consumption and mortality (Di Castelnuovo et al., 2006; Jayasekara et al., 2014; Mayer-Davis et al., 2020; Stockwell, Zhao, Panwar, et al., 2016; Wood et al., 2018). However, results remain highly controversial. The most recent review underscores that 86 out of 107 cohort studies included former drinkers or occasional drinkers in the reference group with never-drinkers, and that only 21 papers avoided this key misclassification bias (Zhao et al., 2023).

Fortunately, discarding never-drinkers as the reference category is increasingly common (Mayer-Davis et al., 2020) in favor of using occasional drinkers as the alternative. As shown in Table 1, the population of never-drinkers display very different sociodemographic and lifestyle characteristics from the general population. More importantly, never-drinkers report a worse health status, as previously reported (John et al., 2021; Ng Fat et al., 2014), which could be related to avoiding initiating consumption due to disease history (Ng Fat et al., 2014).

It is hard to avoid certain misclassification as a majority of the population who define themselves as lifetime never-drinkers have actually previously consumed alcohol (John et al., 2021). In fact, according to sociodemographic, lifestyle, and health status characteristics, our findings show never-drinkers being quite similar to former drinkers, whereas both frequent and infrequent occasional current drinkers more closely resemble the general population. Further, one would be hard-pressed to find evidence of any biological health effect (either beneficial or harmful) of the sporadic consumption of this group, especially the infrequent occasional drinkers.

Another important limitation of the existing literature is that the study of alcohol consumption as a prognostic factor has used non-representative cohorts, where participant selection aims at minimizing losses in follow-up, resulting in convenience samples with sociodemographic characteristics and causes of mortality distribution that differ from the general population (Rehm, 2019). A recent UK Biobank-based study, with a response rate of 5.4 % out of 500,000+ individuals, exemplifies how a severe lack of representativeness can distort the association between alcohol consumption and cardiovascular mortality (Stamatakis et al., 2021).

Another issue is that many of these longitudinal cohort studies are mostly made up of middle-aged and older participants. Given that alcohol consumption usually starts early in life and that a significant percentage of alcohol-related deaths is premature due to acute conditions with short latency periods, studying older individuals may very likely introduce a survival bias (Naimi et al., 2019). The over-representation of older age groups may underestimate short-term mortality among younger individuals and, thus, drinkeŕs real risk of death compared to never-drinkers (Naimi et al., 2019).

The vast majority of population-based studies come from North America. The U.S. leads in publications linking mortality data with datasets from National Health Interview Survey (NHIS, ≥18 years) (Fuller, 2011; Plunk et al., 2014; Rostron, 2012; Tian et al., 2023; Xi et al., 2017), the National Health and Nutrition Examination Survey (1999–2014 NHANES ≥ 18 years) (Ricci et al., 2020), and the National Alcohol Survey (1984, 1995 NAS ≥ 18 years) (Kerr et al., 2011), followed by Canada linking data from the 2000–2010 Canadian Community Health Survey (≥18 years) with mortality data to estimate alcohol-mortality associations (Rosella et al., 2019). Our results support these studieś findings regarding the higher mortality risk among never- and former drinkers when compared to occasional or low-risk drinkers, as well as in terms of the increasing mortality risk associated to higher alcohol intakes.

Of these population-based studies, only one quantified alcohol intake in g/day, observing an increase in mortality risk starting at 15 g/day, an increase that became statistically significant when intakes reached 28 g/day (Ricci et al., 2020). Systematic reviews estimating the dose–response relationship with all-cause mortality also observed a curvilinear relationship depending on the reference category used. Wood and colleagues analyzed 83 studies, including current drinkers in the analysis, and observed an increased risk with intakes ranging between 100–150 g/week (Wood et al., 2018). Jayasekara and colleagues looked at alcohol consumption over the lifespan based on 8 studies and using non-drinkers as the reference category. They also observed a nonlinear relationship with an increase in mortality in men (no enough data on women) starting with intakes of 40 g/day (Jayasekara et al., 2014). One could argue that this threshold would likely be lower if the reference category was other than non-drinkers.

Regarding differences in the health impact by specific sociodemographic characteristics, some studies report that women reach a significant risk of mortality at lower alcohol intakes than men (Rehm et al., 2021), but others do not report any differences (Wood et al., 2018). Our results support previous work reporting higher risk for women than men, but only at high consumption levels (Di Castelnuovo et al., 2006). There is more consensus in the literature regarding age, i.e., the higher risk in younger individuals compared to older ones (Rehm et al., 2021; Wood et al., 2018). Finally, data are scarce regarding the shape of the association by SES, even though the higher risk of alcohol-attributable mortality with decreasing SES is well-known (Probst et al., 2021). Our results conveying a higher mortality risk among low SES individuals in the face of this groups lower levels of alcohol consumption confirmed the well-known alcohol-harm paradox (Peña et al., 2021).

In contrast, the prognostic effect of HED is understudied, especially while adjusting for the total amount of alcohol consumed. As seen in our results, this adjustment is important because it moderately reduces the magnitude of the HED-mortality association. Findings in older populations (68–70 year-olds) found no effect (van den Brandt & Brandts, 2020), whereas evidence in younger groups aged 25–64 years (Laatikainen et al., 2003) and aged 20–62 years (Graff-Iversen et al., 2013) indicates an increased risk of mortality which may rise with the frequency of HED episodes (Graff-Iversen et al., 2013).

In fact, several studies have highlighted the importance of including the HED pattern in this line of research as mortality risks for moderate drinkers reporting HED were higher than for those not engaging in HED (Kerr et al., 2011; Plunk et al., 2014; Roerecke & Rehm, 2014). However, our results do not reproduce these findings.

Finally, the increased mortality risk observed in this study among never-drinkers regardless of age is not explained by the presence of poor health, even when morbidity is measured comprehensively through the combination of indicators included in the analysis. Therefore, further studies are needed to understand the causes behind this effect.

4.1. Strengths and limitations

To interpret our results correctly, the limitations of the study should be considered. First, alcohol consumption measures rely on self-reported data. Alcohol intake underreporting is well known, especially by sporadic and regular heavy drinkers (Boniface et al., 2014; Stockwell, Zhao, Greenfield, et al., 2016). This misclassification bias may lead to an underestimation of the observed associations for high consumption levels and an overestimation for moderate levels. Second, our study only collected alcohol consumption at baseline and evidence shows weak stability of drinking behaviors over time. For instance, another population-based study in Spain concluded that in three years 50 % of individuals changed their alcohol consumption pattern, tending to decrease their consumption, and that 30 % of non-drinkers started consuming alcohol in the same period (Soler-Vila, Galán, Donado-Campos, et al., 2014).

Third, we lacked the statistical power to conduct more detailed subgroup analyses or investigate the association by specific causes of mortality. Fourth, even adjusting for numerous confounding factors, the presence of residual confounding cannot be ruled out as it is inherent to the observational design of the study. Finally, the questionnaire did not include other consumption patterns such as consuming alcohol with meals (Jani et al., 2021).

Among the studýs strengths, we would like to underline that the sample is representative of the population residing in Spain, reinforcing the external validity of the associations. The data linkage to mortality records used the government-issued national personal identification document number as linking variable, thus reducing classification errors (Harron et al., 2017). To better adjust for potentially confounding variables, we included levels of intensity of key lifestyles or behaviors. Further, health status was addressed in a comprehensive manner by adjusting for perceived health, functional limitation, and history of chronic diseases. Finally, we conducted various sensitivity analyses to assess the consistency of the associations observed in the study.

5. Conclusion

Compared to infrequent occasional drinkers low-volume drinkers had a comparable mortality risk. However, mortality risks are significantly higher among never-drinkers, former drinkers, and regular consumers of over 20 g/day of alcohol. This risk further increases for individuals who also engaged in heavy episodic drinking (HED), especially for those reporting more frequent episodic drinking.

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Disclaimer

This article presents independent research. The views expressed are those of the authors and not necessarily those of the Institute of Health Carlos III.

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Iñaki Galán: Writing – review & editing, Writing – original draft, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Julia Fontán:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis. **Cristina Ortiz:** Writing – review & editing, Resources, Methodology, Formal analysis, Data curation. **Teresa López-Cuadrado:** Writing – review & editing, Resources. **María Téllez-Plaza:** Writing – review & editing, Supervision. **Esther García-Esquinas:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2024.108108.

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