



Alcohol consumption patterns and unhealthy aging among older lifetime drinkers from Spain

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ABSTRACT

Background: The protective health effects of light alcohol consumption are debated due to potential selection biases, reverse causation and confounding. We examined cross-sectional and prospective associations of alcohol consumption patterns with unhealthy aging among older drinkers addressing these methodological issues.

Methods: 2081 lifetime drinkers aged 65 + years from the Seniors-ENRICA-2 cohort followed-up for 2.4 years were classified as occasional (average lifetime alcohol intake [g/day] ≤ 1.43), low-risk (men: >1.43 –20; women: >1.43 –10), moderate-risk (men: >20 –40; women: >10 –20) and high-risk drinkers (men: >40 ; women: >20 ; or binge drinkers). A Mediterranean drinking pattern (MDP) was defined as occasional/low-risk drinking, wine preference and drinking only with meals. Unhealthy aging was measured with a 52-item health deficit accumulation index (DAI), with higher values indicating more health deficits.

Results: A 10-g/day increment in lifetime average alcohol intake was cross-sectionally associated with a higher DAI among all drinkers (mean difference [95% confidence interval] = 0.35 [0.16, 0.53]) and moderate-/high-risk drinkers (0.41 [0.17, 0.65]), but not among occasional/low-risk drinkers. Also, the DAI was 1.35 (0.06, 2.65) points higher in high-risk versus low-risk drinkers and 2.07 (0.59, 3.60) points higher in non-adherers versus adherers to the MDP. Most associations strengthened when restricting analyses to individuals with lower disease burden and did not generally remain after 2.4 years.

Conclusions: We found no evidence of a beneficial association between low-risk alcohol consumption and unhealthy aging, but a detrimental one for high-risk drinking, which strengthened when accounting for reverse causation, although attenuated over the follow-up likely due to selective attrition of those less resilient to the harmful effects of alcohol.

1. Introduction

Aging has emerged as a crucial policy issue due to the burdensome consequences for health and health systems of the dramatic rise in both the number and proportion of older persons, with projections showing that, by 2050, people aged 60 + years will amount to about 2 billion globally and will represent about 20% of the world's population ("World Population Ageing, 2019: Highlights (ST/ESA/SER.A/430)," 2019). To establish a framework for public health action in response to population

aging, the World Health Organization published in 2015 the World report on aging and health, which emphasized the importance of fostering healthy aging, defined as "the process of developing and maintaining the functional ability that enables wellbeing in older age" (World report on ageing and health WWW Document, 2015). Since then, considerable efforts have been devoted to better comprehend healthy aging and build the evidence to support a Decade of Healthy Ageing from 2020 to 2030 aimed to improve the wellbeing of older people ("Global strategy and action plan on ageing and health WWW

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Document, 2017; The decade of healthy ageing WWW Document, 2020; Kralj et al., 2018). In this context, it is essential to keep identifying its determinants, not only to improve older adults' health and quality of life, but also to reduce the approaching increase in the socioeconomic burden associated with disease in old age (Kralj et al., 2018).

Although the harmful health effects of heavy alcohol drinking are well known (Griswold et al., 2018), epidemiological research has suggested protective effects of drinking low amounts of alcohol, mainly on all-cause (Di Castelnuovo, 2006; Jayasekara et al., 2014; Kunzmann et al., 2018; Ronksley et al., 2011) and cardiovascular mortality (Di Castelnuovo et al., 2021; Kunzmann et al., 2018; Ronksley et al., 2011), ischemic heart disease (Griswold et al., 2018; Ronksley et al., 2011; Wood et al., 2018), and diabetes (Griswold et al., 2018). However, the results from some of these studies have been questioned due to several selection biases, potential reverse causation and residual confounding (Naimi et al., 2017). On the one hand, this has led to methodological improvements in research on alcohol and health (Griswold et al., 2018; Kunzmann et al., 2018; Wood et al., 2018), but on the other one, alongside the increased risk for cancer mortality (Di Castelnuovo et al., 2021) and cancer, injuries and communicable diseases (Griswold et al., 2018) observed even with small quantities of alcohol intake, it has cast doubt on the existence of a non-zero threshold for a safe level of drinking (Griswold et al., 2018).

The relationship between light alcohol consumption and healthy aging is also unclear. A systematic review of risk factors for unhealthy ageing (Kralj et al., 2018) showed inconsistent results: a positive association with healthy aging of moderate alcohol intake versus abstention in 12 studies, a negative association in 1, and lack of association in 9. This, and the methodological issues found, mainly the heterogeneity across studies in alcohol intake measurements, drinking categories and reference group, precludes drawing definite conclusions. Therefore, the purpose of this work was to examine the relationship of alcohol intake with unhealthy aging in older drinkers from Spain, while addressing the main methodological issues deemed to bias such association. In addition, because healthy aging might be affected not only by the drinking volume, but also by the type of alcoholic beverage or the context of drinking, we examined its association with several patterns of alcohol consumption typical of Mediterranean countries.

2. Methods

2.1. Study design and participants

Participants in the Seniors-ENRICA-2 cohort (Ortolá et al., 2021a) were recruited between 2015 and 2017 by stratified random sampling of all community-dwelling individuals aged 65 and older holding a national healthcare card and living in the Madrid area in Spain (note that access to the Spanish healthcare system is universal and cost-free for all residents in Spain, and all of them are entitled to a healthcare card). At baseline, a computer-assisted telephone interview was used to obtain information on socio-demographic data, lifestyles and morbidity, and home visits were conducted to collect biological samples, perform a physical examination, and record a diet history. Participants were followed-up for a median of 2.4 years (range: 1.6–3.1 years) up to 2019 to update the study information. The Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study and all participants provided written informed consent.

2.2. Study variables

2.2.1. Alcohol consumption patterns

At baseline, study participants were asked about the amount and frequency of the main types of alcoholic beverages that they had consumed during each decade of their lives, and alcohol content of each drink was estimated using standard composition tables (León-Muñoz et al., 2015; Rodríguez-Artalejo et al., 2011). They were also asked if

they had drunk ≥ 8 for men or ≥ 6 standard units (SU) for women during any drinking session in the preceding 30 days (León-Muñoz et al., 2015), and if so, they were considered as binge drinkers. Note that, in Spain, the estimated alcohol SU is 10 g of pure alcohol (Rodríguez-Martos Dauer et al., 1999). According to their average lifetime alcohol intake, participants were classified into occasional drinkers (≤ 1.43 g/day, equivalent to ≤ 1 SU/week), low-risk drinkers (> 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women), moderate-risk drinkers (> 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women), and high-risk drinkers (> 40 g/day for men and > 20 g/day for women). Binge drinkers were included in this last category (Ortolá et al., 2019a). This classification was based in a recent update on the risks related to alcohol consumption levels published by the Spanish Ministry of Health, which sets the thresholds of low-risk alcohol consumption at 20 g/day for men and 10 g/day for women, and those of high-risk alcohol consumption at 40 g/day for men and 20 g/day for women, and considers binge drinking as a high-risk behavior (Spanish Ministry of Health, 2020). According to their lifetime preference for a specific type of beverage (when more than 80% of lifetime alcohol intake was derived from such drink), participants were classified into those with preference for wine, and those with preference for other drinks or with no preference whatsoever.

Additionally, information on habitual food and beverage consumption in the previous year by occasion of intake was obtained through a validated diet history developed from the one used in the EPIC cohort study in Spain (Guallar-Castillón et al., 2014). Based on the occasion of alcohol intake, participants were classified into those who drank only with meals (lunch and dinner) and those who drank either only outside of meals or at any time. Lastly, we ascertained whether they adhered or not to a Mediterranean drinking pattern (MDP), defined as occasional/low-risk drinking with preference for wine and drinking only with meals (León-Muñoz et al., 2014).

2.2.2. Unhealthy aging

To assess unhealthy aging both at baseline and follow-up, we calculated a 52-item health deficit accumulation index (DAI) with four domains: physical and cognitive functional impairments (22 items), self-reported health/vitality (7 items), mental health (6 items), and morbidities/use of health services (17 items) (García-Esquinas et al., 2019), based on the procedure used by Rockwood et al. (Rockwood and Mitnitski, 2007). This index is robustly associated with age and mortality, and its trajectories do not depend on the nature or the number of the variables included in it (Mitnitski and Rockwood, 2014). The complete list of health deficits and associated scores is presented in Supplementary Table 1. The overall and domain-specific DAI scores were computed as the total sum of points assigned to each deficit divided by the number of deficits considered and further multiplied by 100 to obtain a range from 0 (lowest) to 100 (highest deficit accumulation). We then calculated changes from baseline to follow-up in the overall and domain-specific DAI scores, so that positive changes denote more health deficit accumulation.

2.2.3. Potential confounders of the study associations

At baseline, we also collected information on sociodemographic and lifestyle characteristics including sex, age, education (primary or less, secondary, or university), tobacco smoking (never, former, or current), leisure-time physical activity (metabolic equivalents of task-hour/week) (Ortolá et al., 2021b) and time spent watching TV (hours/day) (Ortolá et al., 2021b). Food and beverage consumption in the previous year obtained from the diet history was used to estimate energy intake (kcal/day) using standard composition tables (Guallar-Castillón et al., 2014), and diet quality was assessed with the Mediterranean Diet Adherence Screener (MEDAS) excluding the wine component, thus ranging from 0 (lowest) to 13 (highest adherence) (Schröder et al., 2011). Also, the body mass index (BMI) was calculated as the weight (in kg) divided by the squared height (in m), both measured by standardized procedures (Gutiérrez-Fisac et al., 2012). Lastly, serum growth

differentiation factor 15 (GDF-15) was measured by an electrochemiluminescence Elecsys® immunoassay method using a cobas® 6000 analyzer (Roche Diagnostics).

2.3. Statistical analysis

From the 3273 participants in the Seniors-ENRICA-2 cohort, we selected 2293 who were or had been alcohol drinkers at some point in their lives. From these, we excluded 1 with no information on the baseline DAI score, 195 without GDF-15 measures, and 16 with missing data on potential confounders of the study association at baseline. Thus, the analytical sample for the cross-sectional association comprised 2081 individuals. From these, 30 participants died and 618 were lost over the follow-up period, whereas 3 had no data on the follow-up DAI score. Thus, the analytical sample for the prospective association comprised 1430 individuals.

The cross-sectional associations between the average amount of alcohol consumed by drinkers over their lifetime and the baseline overall and domain-specific DAI scores were summarized with mean differences per 1-SU/day increment in alcohol intake and their 95% confidence intervals (CIs), obtained from linear regression in the total sample and separately in two categories of lifetime alcohol consumption status: occasional/low-risk drinkers, and moderate-/high-risk drinkers. We built two models: Model 1 adjusted for sex, age, and education; and Model 2 further adjusted for tobacco smoking, energy intake excluding alcohol from alcoholic beverages, MEDAS score excluding the wine component, leisure-time physical activity, and time watching TV. Also, dose-response associations were evaluated by modeling the average lifetime alcohol intake as restricted cubic splines with knots at the 10th, 50th and 90th percentiles, and using as reference the median alcohol intake for occasional drinkers. P-values for non-linearity were calculated by testing the null hypothesis that the coefficient for the second spline is equal to 0 using Wald tests.

The same analyses were performed to assess prospective associations between the average amount of alcohol consumed by drinkers over their lifetime and changes in the overall and domain-specific DAI scores over the follow-up, though in this case the analyses were additionally adjusted for the corresponding baseline overall or domain-specific DAI score.

Cross-sectional and prospective associations of lifetime alcohol consumption status, lifetime beverage preference, drinking with meals, and adherence to the MDP with the baseline overall and domain-specific DAI scores or changes over the follow-up were also summarized with

mean differences (95% CI) across categories of these variables obtained using the same statistical methods.

To assess the robustness of our results, we performed two sensitivity analyses: (1) excluding participants who had quit alcohol in the previous decade, and (2) using the maximum amount of alcohol consumed over the lifetime instead of the average amount. Additionally, to examine the potential for reverse causation, we replicated the analyses excluding individuals with GDF-15 levels above the study median (1156 pg/mL), as GDF-15 is a biomarker of chronic disease burden (Fujita et al., 2016). Finally, we assessed whether sociodemographic and lifestyle variables modified the study associations by testing interaction terms defined as the product of average lifetime alcohol consumption and alcohol consumption patterns by categories of such variables. Since no significant interactions were found, results are presented for the total sample.

Statistical significance was set at two-sided p value < 0.05. Analyses were performed with Stata®, version 15 (College Station, TX: StataCorp LLC).

3. Results

Study participants had a mean age of 71.4 years at baseline and 55.4% were men. High-risk drinkers were younger, more frequently men, less frequently never smokers, and had a higher BMI and a higher prevalence of diabetes, whereas occasional drinkers had a lower educational level, were more frequently never smokers, did less physical activity, and had a lower energy intake and a higher DAI score at baseline (Table 1).

The average lifetime amount of alcohol consumed was associated with more baseline deficit accumulation, with a mean increase (95% CI) in the overall DAI score per 1-SU/day increment in alcohol intake of 0.35 (0.16, 0.53) in the fully-adjusted model (Table 2). Although there was no evidence of a departure from linearity ($p = 0.07$), the overall DAI score increased by 0.41 (0.17, 0.65) per 1-SU/day increment in alcohol intake among moderate-/high-risk drinkers, but did not appear to be related to alcohol intake among occasional/low-risk drinkers (Fig. 1, Table 2). As a result, low-risk drinkers had a mean DAI score (95% CI) 1.35 (0.06, 2.65) points lower than high-risk drinkers, and a tendency to lower deficit accumulation compared to occasional drinkers, which was not statistically significant in the fully adjusted model (Table 2). The observed associations were mainly driven by the morbidities/use of health services and the functional impairments domains of the DAI (Figure S1, Table S2). The self-rated health/vitality domain also contributed to the increased deficit accumulation found in moderate-/

Table 1

Baseline characteristics of older lifetime drinkers by categories of lifetime alcohol consumption status ($n = 2081$).

	Occasional drinkers $n = 364$	Low-risk drinkers $n = 1163$	Moderate-risk drinkers $n = 357$	High-risk drinkers $n = 197$
Sex - men; No. (%)	67 (18.4)	675 (58.0)	235 (65.8)	175 (88.8)*
Age (years)	71.8 (4.4)	71.4 (4.2)	71.6 (4.3)	70.3 (3.9)*
Education - primary or less; No. (%)	249 (68.4)	673 (57.9)	231 (64.7)	122 (61.9)*
Tobacco smoking - never smoker; No. (%)	248 (68.1)	545 (46.9)	143 (40.1)	39 (19.8)*
Leisure-time physical activity (MET-h/week)	24.7 (16.3)	29.8 (19.8)	30.0 (18.9)	31.5 (21.5)*
Time watching TV (h/day)	3.1 (1.6)	3.1 (1.5)	3.2 (1.5)	3.3 (1.7)
Energy intake excluding alcohol from alcoholic beverages (kcal/day)	1787 (264)	1905 (306)	1962 (346)	2089 (399)*
MEDAS score excluding the wine component	6.9 (1.6)	6.9 (1.7)	6.9 (1.8)	6.8 (1.6)
Body mass index (kg/m^2)	27.8 (4.9)	27.4 (4.0)	28.0 (4.6)	28.6 (4.2)*
Alcohol intake (SU/day)	0.1 (0.0)	0.7 (0.5)	2.3 (0.8)	6.6 (3.5)*
DAI score	16.7 (10.5)	13.6 (8.7)	14.5 (9.3)	13.7 (8.7)*
Cardiovascular disease ^a ; No. (%)	16 (4.4)	32 (2.8)	12 (3.4)	9 (4.6)
Diabetes; No. (%)	75 (20.8)	211 (18.2)	72 (20.2)	57 (28.9)*
Cancer; No. (%)	10 (2.8)	35 (4.1)	11 (3.1)	8 (4.1)

Values are means (standard deviations) unless indicated. * $p < 0.05$ across categories of lifetime alcohol consumption status.

DAI = deficit accumulation index; MEDAS = Mediterranean Diet Adherence Screener score; MET = metabolic equivalent of task; SU = standard unit (10 g of pure alcohol).

Occasional drinkers ≤ 1.43 g/day; low-risk drinkers > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; moderate-risk drinkers > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; high-risk drinkers > 40 g/day for men and > 20 g/day for women, or binge drinkers.

^aIncluding ischemic heart disease, stroke and chronic heart failure,

Table 2

Cross-sectional association of the average lifetime amount of alcohol consumed by older lifetime drinkers and alcohol consumption patterns with unhealthy aging measured with the DAI score (n = 2081).

Average lifetime alcohol intake	n	Mean differences in the baseline DAI score per 1-SU/day increment in alcohol intake (95% CI)	
		Model 1	Model 2
All drinkers	2081	0.41 (0.22, 0.60)***	0.35 (0.16, 0.53)***
Occasional/low-risk drinkers	1527	−0.74 (−1.74, 0.26)	−0.52 (−1.48, 0.45)
Moderate-/high-risk drinkers	554	0.49 (0.25, 0.74)***	0.41 (0.17, 0.65)***

Alcohol consumption patterns	n	Mean differences in the baseline DAI score (95% CI)	
		Model 1	Model 2
<i>Lifetime alcohol consumption^a</i>			
Occasional drinkers	364	1.09 (0.02, 2.16)*	0.91 (−0.12, 1.93)
Low-risk drinkers	1163	Ref.	Ref.
Moderate-risk drinkers	357	0.96 (−0.08, 1.99)	0.85 (−0.14, 1.84)
High-risk drinkers	197	1.68 (0.34, 3.02)*	1.35 (0.06, 2.65)*
<i>Lifetime beverage preference</i>			
Other	1661	Ref.	Ref.
Wine	420	−0.62 (−1.57, 0.32)	−0.27 (−1.18, 0.64)
<i>Current drinking with meals</i>			
Other	1239	Ref.	Ref.
Drinking only with meals	528	−0.23 (−1.08, 0.63)	−0.15 (−0.98, 0.67)
<i>MDP^b</i>			
No MDP	1922	Ref.	Ref.
MDP	124	−2.29 (−3.86, −0.73)**	−2.07 (−3.60, −0.59)**

*p < 0.05; **p < 0.01; *** p < 0.001. CI = confidence interval; DAI = deficit accumulation index; MDP = Mediterranean drinking pattern; SU = standard unit (10 g of pure alcohol).

^aOccasional drinkers: ≤ 1.43 g/day; low-risk drinkers: > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; moderate-risk drinkers: > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; high-risk drinkers: > 40 g/day for men and > 20 g/day for women, or binge drinkers.

^bOccasional/low-risk drinkers with preference for wine and drinking only with meals.

Model 1: Linear regression model adjusted for sex, age, and education (primary or less, secondary, or university).

Model 2: As Model 1 and further adjusted for smoking status (never, former, or current), energy intake excluding alcohol from alcoholic beverages (kcal/day), Mediterranean Diet Adherence Screener score excluding the wine component, leisure-time physical activity (METs-h/week), and TV-watching time (h/day).

high-risk drinkers, but the mental health domain did not appear to contribute much (Figure S1, Table S2).

Health deficit accumulation increased over the 2.4-year follow-up, with a mean change (95% CI) in the overall DAI score of 2.73 (2.38, 3.08). The average lifetime alcohol intake was not associated with

change in the overall DAI score in the total sample of drinkers (mean change [95% CI] per 1-SU/day increment in alcohol = 0.04 [−0.13, 0.22]) (Table 3). However, although we did not find any differences across categories of lifetime alcohol consumption status (Table 3), there was evidence of a departure from linearity (p = 0.015), so that the overall DAI score tended to decrease among occasional/low-risk drinkers and to increase among moderate-/high-risk drinkers, reaching statistical significance for the self-rated health/vitality domain among moderate-/high-risk drinkers (Fig. 2, Table 3, Table S2, Figure S2).

As regards other alcohol consumption patterns, lifetime wine preference and current drinking with meals were not associated with baseline deficit accumulation, but the mean (95% CI) DAI score was 2.07 (0.59, 3.60) points lower in adherers to the MDP than in non-adherers (Table 2). Nevertheless, this association was not apparent after the 2.4 years of follow-up (Table 3).

Restricting analyses to individuals with lower GDF-15 strengthened most of the observed cross-sectional associations. Thus, the overall DAI score increased by 0.54 (0.25, 0.83) points per 1-SU/day increment in alcohol intake in all drinkers and by 0.60 (0.18, 1.01) among moderate-/high-risk drinkers; also, low-risk drinkers had a mean (95% CI) DAI score 1.89 (0.02, 3.86) points lower than high-risk drinkers. However, neither the lower baseline deficit accumulation among adherers to the MDP versus non-adherers nor the trend to a lower baseline DAI score in low-risk versus occasional drinkers remained. As with the main analyses, in general, no associations were apparent after the 2.4-year follow-up (Tables S3 and S4, Figure S3).

Analyses excluding individuals who had quit alcohol in the previous decade rendered very similar results, but now the prospective association of the average lifetime alcohol consumption with the DAI score became statistically significant among moderate-/high-risk drinkers (Tables S5 and S6). The associations of the maximum amount of alcohol consumed over the lifetime and the alcohol consumption status according to this amount with the DAI score were also consistent (Table S7).

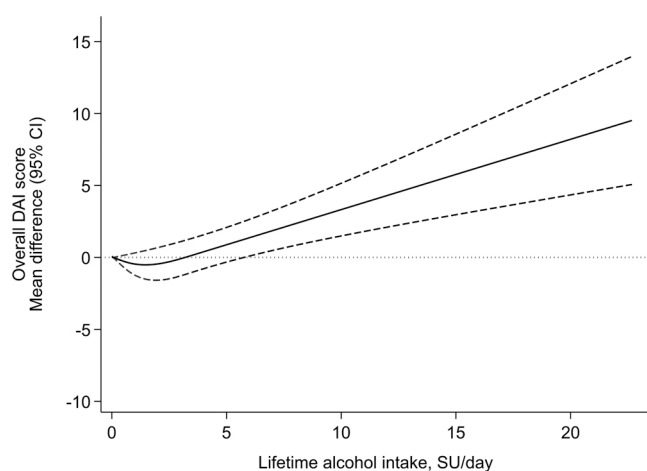


Fig. 1. Cross-sectional association of the average lifetime amount of alcohol consumed by older lifetime drinkers with the overall DAI score (n = 2081). DAI = deficit accumulation index; SU = standard unit (10 g of pure alcohol). Restricted cubic splines (knots at the 10th [0.067 SU/day, 50th [0.754 SU/day] and 90th percentile [3.499 SU/day]; reference at the median alcohol intake for occasional drinkers [0.062 SU/day]) from a linear regression model adjusted for sex, age, and education (primary or less, secondary, or university), smoking status (never, former, or current), energy intake excluding alcohol from alcoholic beverages (kcal/day), Mediterranean Diet Adherence Screener score excluding the wine component, leisure-time physical activity (METs-h/week), and TV-watching time (h/day).

Table 3

Prospective association of the average lifetime amount of alcohol consumed by older lifetime drinkers and alcohol consumption patterns with changes in the DAI score over 2.4 years (n = 1430).

Average lifetime alcohol intake	n	Mean changes in the DAI score over 2.4 years per 1-SU/day increment in alcohol intake (95% CI)	
		Model 1	Model 2
All drinkers	1430	0.08 (−0.09, 0.25)	0.04 (−0.13, 0.22)
Occasional/low-risk drinkers	1056	−0.46 (−1.37, 0.45)	−0.51 (−1.42, 0.41)
Moderate-/high-risk drinkers	374	0.26 (0.03, 0.48)*	0.23 (−0.00, 0.45)

Alcohol consumption patterns	n	Mean change in the DAI score over 2.4 years (95% CI)	
		Model 1	Model 2
<i>Lifetime alcohol consumption^a</i>			
Occasional drinkers	245	0.42 (−0.57, 1.42)	0.48 (−0.51, 1.48)
Low-risk drinkers	811	Ref.	Ref.
Moderate-risk drinkers	237	−0.66 (−1.62, 0.30)	−0.74 (−1.71, 0.22)
High-risk drinkers	137	0.19 (−1.03, 1.41)	−0.05 (−1.28, 1.19)
<i>Lifetime beverage preference</i>			
Other	1152	Ref.	Ref.
Wine	278	0.24 (−0.64, 1.12)	0.34 (−0.54, 1.23)
<i>Current drinking with meals</i>			
Other	864	Ref.	Ref.
Drinking only with meals	364	0.04 (−0.76, 0.84)	0.11 (−0.69, 0.91)
<i>MDP^b</i>			
No MDP	1325	Ref.	Ref.
MDP	86	0.69 (−0.74, 2.12)	0.71 (−0.72, 2.14)

*p < 0.05. CI = confidence interval; DAI = deficit accumulation index; MDP = Mediterranean drinking pattern; SU = standard unit (10 g of pure alcohol).

^aOccasional drinkers: ≤ 1.43 g/day; low-risk drinkers: > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; moderate-risk drinkers: > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; high-risk drinkers: > 40 g/day for men and > 20 g/day for women, or binge drinkers.

^bOccasional/low-risk drinkers with preference for wine and drinking only with meals.

Model 1: Linear regression model adjusted for the baseline DAI score, sex, age, and education (primary or less, secondary, or university).

Model 2: As Model 1 and further adjusted for smoking status (never, former, or current), energy intake excluding alcohol from alcoholic beverages (kcal/day), Mediterranean Diet Adherence Screener score excluding the wine component, leisure-time physical activity (METs-h/week), and TV-watching time (h/day).

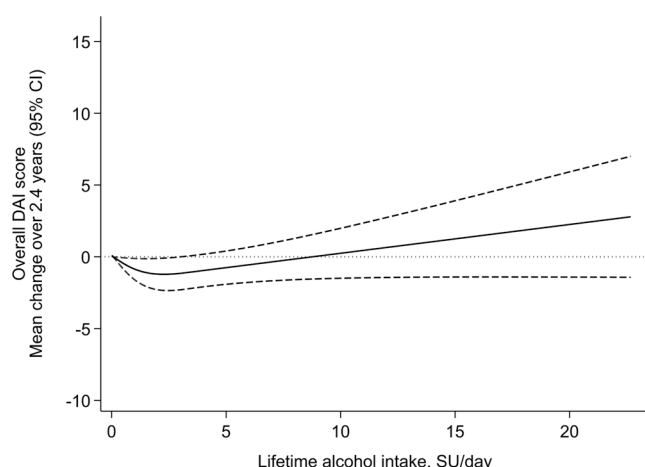


Fig. 2. Prospective association of the average lifetime amount of alcohol consumed by older lifetime drinkers with changes in the overall DAI score over 2.4 years (n = 1430). DAI = deficit accumulation index; SU = standard unit (10 g of pure alcohol). Restricted cubic splines (knots at the 10th [0.070 SU/day], 50th [0.762 SU/day] and 90th percentile [3.499 SU/day]; reference at the median alcohol intake for occasional drinkers [0.067 SU/day]) from a linear regression model adjusted for the baseline overall DAI score, sex, age, and education (primary or less, secondary, or university), smoking status (never, former, or current), energy intake excluding alcohol from alcoholic beverages (kcal/day), Mediterranean Diet Adherence Screener score excluding the wine component, leisure-time physical activity (METs-h/week), and TV-watching time (h/day).

4. Discussion

In older lifetime alcohol drinkers from Spain, an increase in the average amount of alcohol consumed over their lifetime was associated with more baseline health deficit accumulation, especially more morbidities and functional impairments. Such association was not evident among occasional/low-risk drinkers, but was rather strong among moderate-/high-risk drinkers, where higher alcohol intakes were also related to poor perceived health. Besides, baseline deficit accumulation was lower in low-risk versus high-risk drinkers (but not versus occasional drinkers). The found associations have clinical relevance because, using linear mixed models for repeated measurements over time that included interactions between linear age trends and sex, and adjusted for educational level, baseline dietary pattern, and changes over time in smoking status, alcohol drinking, physical activity, sedentary behavior and BMI, we have previously estimated in a very similar cohort (Seniors-ENRICA-1) an annual increase in the DAI score of 0.74 points, which was associated with a 2% increased death risk (García-Esquinas et al., 2019). Thus, drinking 1 SU/day less over the lifetime would delay unhealthy aging by about 5 months among all drinkers, and by 6 months among moderate-/high-risk drinkers; and low-risk drinkers would have a delay of almost 2 years compared with high-risk drinkers. However, these associations did not remain after 2.4 years of follow-up, although there was a tendency to increased deficit accumulation among moderate-/high-risk drinkers, especially to worsening self-rated health and mental health. Whereas wine preference and drinking with meals did not seem to have much influence on unhealthy aging, baseline deficit accumulation was lower in adherers to the MDP versus non-adherers, although this association disappeared in analyses restricted to healthier individuals.

Interventional studies, in particular, randomized controlled trials, are the gold standard for causal inference, but they may be impractical when the health effects of an exposure have long induction periods, which may be the case for alcohol, and even unethical when the exposure may pose health risks. However, well-designed observational studies, such as large longitudinal studies with good measurements, control for the outcome and potential confounders at baseline, and sensitivity analyses showing consistent results, may provide sufficient evidence for causal inference. Cross-sectional studies where data on exposure have been obtained retrospectively and share the above-mentioned characteristics can also have some value (VanderWeele, 2021). In our study, we collected information on alcohol intake during each decade of the participants' lives and examined the associations between alcohol consumption patterns and unhealthy aging both at baseline and after a 2.4-year follow-up. We also adjusted analyses for many socio-demographic, lifestyle and clinical variables to palliate residual confounding and, to assess the potential for reverse causation, we conducted additional analyses excluding individuals with a higher degree of chronic disease burden estimated with a serum biomarker.

In addition, our analyses tried also to address the potential selection biases inherent to the relationship between alcohol and health. Thus, we used lifetime alcohol intake as a measure of alcohol intake, thus preventing the "abstainer" bias by not removing former drinkers from the drinking categories, but rather including them in their corresponding categories according to their lifetime alcohol intake. Moreover, we restricted analyses to lifetime drinkers to palliate the potential "healthy drinker/survivor" bias that may occur in studies of older adults, where only healthier drinkers who have survived the harmful effects of alcohol are able to participate, resulting in an underestimation of the risk of poor health outcomes among drinkers versus non-drinkers (Naimi et al., 2017); and also to avoid potential confounding due the poorer lifestyles and health reported in lifetime abstainers compared to regular drinkers (Ng Fat and Shelton, 2012), which may also underestimate the risk among never drinkers.

In line with recent research on the relationship between alcohol and health (Griswold et al., 2018; Ortola et al., 2019a; Wood et al., 2018), our results corroborated the detrimental health effects of heavy drinking in older adults as shown by the higher baseline health deficit accumulation in high-risk drinkers versus low-risk drinkers as well as the higher lifetime amounts of alcohol in the total sample of drinkers and also among moderate-/high-risk drinkers. The fact that these associations attenuated over the follow-up may be explained by selective attrition, as participants who remain in the study are probably healthier drinkers who could have survived the harmful effects of alcohol, which would bias the associations towards the null. In fact, individuals who were lost to follow-up were older, less educated, less physically active, had a higher prevalence of diabetes and a higher DAI score at baseline, and had a greater mean reduction in alcohol intake from when they were in their 40 s to their 60 s than those who were followed-up (6.1 g/day [95% CI: 4.4, 7.7] versus 4.1 [3.1, 5.0], $p = 0.03$), suggesting a higher resilience in participants who remained in the study. Therefore, in this case, the cross-sectional estimates may be less biased than the longitudinal ones. Besides, even though there is evidence of reverse causation in prospective research on the relationship between alcohol and health (Holdsworth et al., 2016; Ortola et al., 2019b), there was no indication of a substantial amount in our cross-sectional analyses, as most associations strengthened when excluding participants with more chronic disease burden. This may be explained by the fact that the time points of alcohol consumption preceded the assessments of unhealthy aging. Exclusion of non-community dwellers from the study may have also contributed to mitigate reverse causation. Notwithstanding this, we acknowledge that a cross-sectional design cannot entirely rule out reverse causation despite the methodological improvements that we adopted to limit its effects. Finally, although it has been suggested that occasional drinkers may be a better comparison group than never drinkers because they share more characteristics with regular drinkers

than with never drinkers (Naimi et al., 2017), in our study, habits and health of occasional drinkers were more similar to those of never drinkers (Ortola et al., 2022); they were more frequently women, older, less educated, less physically active, had a lower energy intake and a higher DAI score at baseline than the other drinker categories (Table 1). This may have resulted in a tendency to less unhealthy aging in low-risk drinkers.

On the other hand, average lifetime consumption of low amounts of alcohol did not seem to confer any benefits on unhealthy aging in our study, as evidenced by the lack of association of both the baseline DAI score and its changes over follow-up with increasing alcohol intake among occasional/low-risk drinkers and with low-risk versus occasional drinking. Given the heterogeneity of results from studies on alcohol and healthy aging and their associated methodological problems, including the choice of the reference group (Knott et al., 2015; Kralj et al., 2018; Park et al., 2017), we think our work makes a valuable contribution to the research in this field.

As regards alcohol consumption patterns, wine drinking was not related to unhealthy aging in our study, in line with a recent pool of studies reporting a non-differential effect of specific types of alcoholic drinks on all-cause mortality and several cardiovascular outcomes (Wood et al., 2018). Drinking with meals was not related to unhealthy aging either, unlike other studies reporting an association with lower risk of mortality (Trevisan et al., 2001) or frailty (Ortola et al., 2016). Lastly, in line with previous research where a MDP was associated with reduced mortality in younger individuals (Gea et al., 2014; Morales et al., 2021), and with a lower risk of frailty and falls in older adults (Ortola et al., 2017, 2016), adherers to the MDP in our study had lower baseline deficit accumulation than non-adherers, although this association disappeared in analyses restricted to healthier individuals, so it is probably not causal.

Despite our efforts to overcome most of the potential methodological issues of epidemiological research on alcohol and health, and the use of several standardized scales and validated measures to assess unhealthy aging (García-Esquinas et al., 2019), our study still has some limitations. First, alcohol intake was self-reported and obtained retrospectively, and therefore prone to recall error and some degree of misclassification. However, there was a good correlation (Spearman correlation coefficient of 0.82) between the self-reported intake during the current decade and the current intake derived from the diet history, an instrument with a Pearson correlation coefficient with seven 24-hour recalls during 1 year for alcohol consumption of 0.65. Also, recalled alcohol intake, even over long periods, is reliable, with observed differences between recalled intake and the actual amount consumed up to 23 years back of less than one drink per week (Chu et al., 2010). It also provides better estimates of past drinking than measures of current alcohol intake (Russell and Welte, 1996). Besides, since heavier drinkers are the only ones that appear to substantially underestimate past alcohol intake (Russell and Welte, 1996) and might have been misclassified as moderate-risk drinkers, the differences in the DAI score between high-risk and low-risk drinkers found in our study might be even larger (for example, 1.48 [0.40, 2.56] and 0.11 [-0.93, 1.15] for the cross-sectional and prospective associations, respectively, when moderate-risk drinkers consuming >30 g/day for men and >15 g/day for women were classified as high-risk drinkers). Second, as in any observational study, we cannot entirely rule out residual confounding, despite adjusting for many potential confounders. And third, this study was conducted in older adults of a Mediterranean country, with distinct lifestyles and drinking patterns (León-Muñoz et al., 2014; Sotos-Prieto et al., 2015), so our results may not be generalizable to other populations.

5. Conclusions

This study on older lifetime drinkers from Spain did not find evidence of a beneficial association between low-risk alcohol consumption and unhealthy aging, but it observed a detrimental one for high-risk

drinking, which strengthened when accounting for reverse causation, although attenuated over the follow-up probably due to attrition bias. Baseline deficit accumulation was also lower in adherers to the MDP versus non-adherers, although this association disappeared in analyses restricted to healthier individuals, so it is probably not causal. These results may have important practical implications because they suggest that older adults cannot gain any health benefits from low alcohol intake, but their associated chronic conditions might be aggravated by heavy drinking.

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CRediT authorship contribution statement

Rosario Ortola and Fernando Rodríguez-Artalejo designed the research. Rosario Ortola performed the statistical analyses. All authors contributed to results interpretation. Rosario Ortola and Fernando Rodríguez-Artalejo drafted the manuscript. Rosario Ortola and Fernando Rodríguez-Artalejo had primary responsibility for final content. All authors reviewed the manuscript for important intellectual content, read and approved the final manuscript.

Conflict of interest

No conflict declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.drugalcdep.2022.109444](https://doi.org/10.1016/j.drugalcdep.2022.109444).

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