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ORIGINAL ARTICLE

Factors associated with mortality in women with decompensated alcohol-related cirrhosis

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Alcoholic hepatitis;
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Mortality;
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Abstract
Introduction and aims: Alcohol-related liver disease is becoming more common worldwide. Recently, alcohol consumption in women has increased significantly, raising the risk of developing alcohol-associated hepatitis, cirrhosis, and hepatocellular carcinoma. Greater susceptibility to alcohol-related liver damage appears to confer a higher mortality and decompensation risk on women. Our study aimed to assess alcohol consumption patterns and mortality rates in female patients with alcohol-related cirrhosis.
Material and methods: We conducted a single-center retrospective cohort study of patients hospitalized for cirrhosis due to chronic alcohol consumption at the *Hospital General de Mexico, "Dr. Eduardo Liceaga"* between 2018 and 2021. Utilizing the patients' electronic medical records, alcohol consumption patterns were identified and the survival rate for women and men after their first hospitalization was calculated through the Kaplan-Meier curve.
Results: A final total of 192 electronic medical records (50% women) were included. We classified the patients according to alcohol consumption into a) excessive consumption or b) binge drinking. The median age for the onset of chronic alcohol consumption was higher in women than in men (18 vs. 16.5 years of age; $p < 0.001$). The median for alcohol consumption in g/occasion was lower in women than in men (140 vs. 275 in excessive alcohol consumption and 196 vs 320 in binge drinking; $p < 0.0001$), as was the length of time of chronic alcohol consumption (24.5 vs. 30 years; $p < 0.001$)

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The mortality rate during the first hospitalization was 32.8% (61.9% for women and 38.9% for men). The mean age for survival was lower for women (33.8 ± 1.6 years of age, 95% CI 30.5–37.1), compared with men (37.0 ± 1.2 years of age, 95% CI 35.4–38.6) (p = 0.002). The factors associated with mortality in the Cox proportional hazards models were women vs men (OR = 4.1, 95% CI 2.1–7.9) and excessive consumption vs binge drinking (OR = 1.9, 95% CI 1.1–3.5).

Conclusions: Alcohol-related mortality is higher in women than in men and is associated with lower alcohol consumption, a shorter period of continued chronic consumption, and an older age at consumption onset.

PALABRAS CLAVE
Hepatitis alcohólica;
Cirrosis alcohólica;
Mortalidad;
Descompensación hepática;
Patrón de consumo de alcohol

Factores asociados con mortalidad en mujeres con cirrosis descompensada alcohólica

Resumen

Introducción y objetivos: La enfermedad hepática alcohólica se ha vuelto más común a nivel mundial. Recientemente, el consumo de alcohol en mujeres se ha incrementado de manera significativa, elevando el riesgo de desarrollar hepatitis asociada con alcoholismo, cirrosis y carcinoma hepatocelular. En las mujeres hay una mayor susceptibilidad a daño hepático relacionado con el alcohol y esto parece elevar el riesgo de mortalidad y descompensación en mujeres. Nuestro estudio tuvo como objetivo evaluar los patrones de consumo de alcohol y las tasas de mortalidad en pacientes femeninas con cirrosis alcohólica.

Materiales y métodos: Realizamos un estudio de cohorte retrospectiva de un solo centro con pacientes hospitalizados por cirrosis debida al consumo de alcohol, en el Hospital General de México ''Dr. Eduardo Liceaga'', entre 2018 y 2021. Por medio de los expedientes médicos electrónicos se identificaron los patrones de consumo de alcohol y se calculó la tasa de supervivencia para hombres y mujeres posterior a su primera hospitalización utilizando la curva de Kaplan–Meier.

Resultados: Se incluyó un total de 192 expedientes médicos electrónicos (50% mujeres). Clasificamos a los pacientes de acuerdo con su consumo alcohólico como a) C*onsumo Excesivo* o b) Consumo *por* Atracón. La edad mediana para el comienzo del consumo crónico de alcohol fue mayor en mujeres que en hombres (18 vs 16.5 años; p < 0.001). La mediana de consumo de alcohol en g/ocasión fue menor en mujeres que en hombres (140 vs 275 en Consumo Excesivo y 196 vs 320 Atracón; p < 0.001), al igual que el tiempo de consumo crónico de alcohol (24.5 vs 30 años; p < 0.001).

La tasa de mortalidad durante la primera hospitalización fue 32.8% (61.9% en mujeres y 38.9% en hombres). La edad media de supervivencia fue menor en mujeres (33.8 ± 1.6 años, IC 95% 30.5–37.1) en comparación con los hombres (37.0 ± 1.2 años, IC 95% 35.4–38.6) (p = 0.002). Los factores asociados con la mortalidad en los modelos de regresión de Cox fueron mujeres vs hombres (OR = 4.1, IC 95% 2.1–7.9) y Consumo Excesivo vs Atracón (OR = 1.9, IC 95% 1.1–3.5).

Conclusiones: La mortalidad asociada con alcoholismo es mayor en mujeres que en hombres y está asociada con menor consumo de alcohol, un periodo más corto de consumo crónico y un inicio de consumo a mayor edad.

Introduction

Liver disease due to alcohol consumption is becoming more frequent worldwide. In North America and Europe, it is the fifth leading cause of death in the young population and is a frequent cause of disability.[1,2] In Mexico, liver cirrhosis due to alcohol consumption represents approximately 50% of cases, constituting a public health problem.[3] A significant increase in alcohol consumption during the COVID-19 pandemic could have impacted the development of liver disease,[4] with a substantial increase in Mexican women.

According to the Mexican National Survey of Addictions, *ENCODAT* 2016, the prevalence of excessive alcohol consumption increased by 5% (19.7–24.4%) and regular consumption increased up to 3 times, from 1.4 to 3.5%.[5] The

same *ENCODAT* survey showed that younger women drank more alcohol and started consuming it at earlier ages. Mellinger et al.[6] found that liver disease due to alcohol consumption in women in the United States increased by 50% from 2009 to 2015, compared with 30% in men, over the same period. Grant et al.[7] reported an 80% increase in heavy alcohol consumption in women, compared with 30% in men between 2001–2003 and 2012—2013. A similar pattern has been observed globally, with a two to four-fold increase in alcohol consumption among Japanese women.[8]

The increase in alcohol consumption in both sexes and at younger ages increases the toxic exposure time, which favors liver damage from alcohol-associated steatohepatitis and its progression to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[9] The complications of cirrhosis include portal hypertension with increased variceal hemorrhage risk; splanchnic vasodilatation, which induces activation of the renin-angiotensin-aldosterone system and development of ascites; hepatic encephalopathy; and liver cancer. Some patients develop alcoholic hepatitis (AH), with a 3-month mortality risk of 20–50%.[10] The leading causes of AH hospital admission are variceal hemorrhage, aggregate infectious processes, grade III ascites, renal failure, and multiple organ dysfunction. Decompensation causes and mortality rates differ between sexes and are higher in women due to their greater susceptibility to alcohol-related liver damage.[11–13]

Our aim was to evaluate the quantity and duration of alcohol consumption and its relation to mortality in patients with alcohol-related cirrhosis during their first hospital admission.

Material and methods

We conducted a retrospective cohort study on patients hospitalized for the first time at the Gastroenterology and Hepatology Service of the *Hospital General de Mexico "Dr. Eduardo Liceaga"* (*HGMEL*) and diagnosed with alcohol-related cirrhosis between 2018 and 2021. The *HGMEL* Research Ethics Committee approved this study. Patients with a different cause of cirrhosis (chronic viral hepatitis, autoimmunity, and metabolic syndrome, among others) and patients over 70 years of age (with possible associated geriatric syndromes) were excluded. From the records of patients who met the selection criteria, we collected data regarding their survival status (yes/no), liver complications at hospital admission (digestive tract bleeding, jaundice, ascites, encephalopathy, alcoholic hepatitis, renal failure, and acute-on-chronic liver failure), together with liver disease severity scores (Child-Turcotte-Pugh and MELD scores). The onset of alcohol consumption and its duration until diagnosis were also collected.

From the routine questionnaire applied to patients at hospital admission, we obtained data on the usual type of alcoholic beverage consumed (fermented, distilled, or mixed) and the frequency of alcohol intake. We identified two patterns of alcohol consumption: excessive (>60 g/day for men and >50 g/day for women) and binge drinking (>60 g/occasion for men and >50 g/occasion for women).[14,15] The average drink for both types of alcohol consumption was estimated by the formula: grams/day of alcohol = (amount consumed in milliliters) (alcohol content of the ingested drink) (0.8)/100.

Statistical analysis

The quantitative variables: age at admission, age at alcohol consumption onset, MELD score, length of time of chronic alcohol consumption (calculated by subtracting age at alcohol consumption onset from age at cirrhosis diagnosis), grams of alcohol consumption for excessive consumption and binge drinking, and number of liver complications at first hospitalization due to chronic alcohol consumption were expressed as mean and standard deviation.

The non-quantitative variables were expressed as median and interquartile range. Sex, alcohol consumption pattern, preferred alcoholic beverage, and Child-Turcotte-Pugh classification were expressed as percentages. Associations between categorical variables were determined using the chi-square test with the Bonferroni correction, when there were more than two categories.

We used the Kaplan–Meier survival curve log-rank test to assess mortality in men and women. To identify the factors associated with mortality, we employed the multivariate predictive models with a Cox regression for the length of time of chronic alcohol consumption. Predictors were age at hospital admission, grams of alcohol consumption per occasion, MELD score, type of drink, alcohol consumption pattern, and sex. To independently identify the factors associated with mortality between men and women, a second Cox regression model was used that included age at first hospital admission, alcohol consumption pattern, number of liver complications, type of alcoholic beverage consumed, the Child-Turcotte-Pugh classification, and content in grams of alcohol consumption per occasion as predictors. All statistical analyses were performed using the IBM SPSS 26.0 statistical package. In all comparisons, $p \leq 0.05$ was considered statistically significant.

Results

We reviewed a total of 220 medical records of patients diagnosed with alcohol-related cirrhosis; we excluded 28 patients who did not meet the inclusion criteria. Ninety-six women (50%) and 96 men (50%) were finally included (n = 192) in the study.

Reaching statistical significance, age at chronic alcohol intake onset was 1.5 years lower in men than in women (16.5 vs 18 years of age, respectively) (p = 0.0001), excessive alcohol consumption was lower in women (140 g/day) than in men (275 g/day) (p = 0.0001), and binge drinking was lower in women (196 g/occasion) than in men (320 g/occasion) (p = 0.0001). The number of years of chronic alcohol consumption was also statistically significant and was 5.5 years lower in women than in men. Women had a higher frequency of complications than men (p = 0.0001) (Table 1).

There were no statistically significant differences between women and men, with respect to the MELD score at

Table 1 Clinical manifestations, age of onset, and consumption of alcohol in men vs women.

	Women		Men		
	Median (Q3, Q1)	Min, Max	Median (Q3, Q1)	Min, Max	p
Age at first hospitalization (years)	50 (61.7, 41)	(25, 69)			
Age at onset of alcohol consumption (years)	18 (22, 17)	(13, 35)	16.5 (18, 15)	(12, 22)	0.0001
Alcohol consumption per day (grams) for Excessive alcohol consumption	140 (180, 110)	(80, 362)	275 (336, 217)	(160, 440)	0.0001
Alcohol consumption per occasion (grams) for Binge drinking	196 (280, 136)	(80, 460)	320 (360, 230)	(160, 460)	0.0001
Age at diagnosis of cirrhosis (years)	44 (50, 38.2)	(25, 65)	46 (50, 40.5)	(25, 60)	0.063
Length of time of alcohol consumption (years)	24.5 (30, 18)	(9, 49)	30 (34.7, 25.5)	(11, 42)	0.0001
MELD score	17.5 (24.7, 12)	(7, 42)	22 (28, 13)	(10, 44)	0.097
Number of complications at first hospitalization*	3 (4, 2)	(1, 6)	2 (2, 1)	(1, 4)	0.0001

* Complications: acute kidney injury (AKI), gastrointestinal bleeding, ascites, acute-on-chronic liver failure (ACLF), and hepatic encephalopathy.

admission, age at first hospital admission (50 and 51 years), and age at cirrhosis diagnosis (Table 1).

Excessive consumption patterns were more frequent in men than in women (60 vs 51%, with no statistical association regarding drinking pattern (p = 0.191). In the excessive consumption and binge drinking patterns, there was an independent association with the type of drink, for women and for men. There was a higher percentage of distilled and fermented drink intake in women with excessive alcohol consumption (p = 0.001), whereas the percentage of distilled drink intake and binge drinking was higher in men. The percentage for mixed drink intake was high in both sexes (p = 0.005) (Table 2).

The total mortality rate during first hospital admission was 32.8% (n = 63), of which 61.9% (39) were women and 38.1% (24) were men.

Regarding liver disease severity, the Child-Turcotte-Pugh score in women was A: 9 (10%), B: 32 (33%), and C: 55 (57%). In men, the Child-Turcotte-Pugh score was A: 4 (4%), B: 25 (26%), and C: 67 (70%). The chi-square test did not reflect statistical significance: (2) = 3.96; p = 0.138.

Mean survival in women and men was 33.8 ± 1.6 years (95% CI 30.5–37.1) and 37.0 ± 1.2 years (95% CI 35.4–38.6), respectively (log-rank test [chi-square = 9.688; p = 0.002]).

The multivariate analysis conducted with a Cox proportional hazards regression produced an association between mortality and lower age at hospital admission; a 98% increase in mortality with excessive alcohol consumption, compared with binge drinking; a 6% increase in mortality with a higher MELD score; and a 4.2% increase in mortality for women, compared with men (Table 3 and Fig. 1).

Fig. 2 and Table 4 showed a lower survival curve for women than for men. The independent Cox proportional hazards regression for men and women produced an association between age and a higher mortality rate, in women and men (p = 0.0001), whereas only the MELD score was associated with mortality in women.

Age at hospital admission was 15.6% lower in women, as a mortality factor for chronic alcohol consumption duration. The average age at death was 49.9 and 50.9 years for women and men, respectively. The MELD score was 4% higher in women, but the difference from men was not statistically significant. Grams of alcohol consumption per occasion, the number of symptom manifestations during hospitalization, consumption pattern, and drink type were not significantly associated with mortality and the length of time of continued chronic alcohol consumption (Table 3).

Discussion

Alcohol consumption has become a significant concern, both in Mexico and worldwide. Increased alcohol consumption in women, particularly young women, is a public health problem.[15] In our results, we found that women started drinking alcohol two years later than men. This behavior in women could have a cultural and social explanation or be due to a higher prevalence of anxiety and depression or to social pressure from peers to drink alcoholic beverages. In our study group, the mean amount of alcohol consumed by women was significantly less than that of men (160 g, when compared between groups, and 290 g per occasion, respectively). However, this was not reflected in the consumption pattern, in which no statistical difference was found throughout the time of active consumption. Although patients required hospitalization, it did not contribute to

Table 2 Type of alcohol consumption and differences between men and women.

	Women n = 96					Men n = 96				
Type of drink	Overall n(%)	Excessive alcohol consumption n(%) 49 (51)	Binge dinking n(%) 47 (49)	χ^2	p value	Overall n(%)	Excessive alcohol consumption n(%) 58 (60)	Binge drinking n(%) 38 (40)	χ^2	p value
Fermented	23 (24)	19 (19.8)	4 (4.2)	14.934	001	17 (17.7)	11 (11.5)	6 (6.3)	10.537	0.005
Distilled	35 (36.4)	18 (18.8)	17 (17.8)			37 (38.5)	29 (30.2)	8 (8.3)		
Mixed	38 (39.6)	12 (12.5)	26 (20.1)			42 (43.8)	18 (18.8)	24 (25)		

Table 3 Association with mortality by age at the time of first hospitalization, alcohol consumption per occasion in grams, MELD score, pattern of alcohol consumption, type of drink, and sex.

	OR	95% CI	p
Age	0.875	0.839 - 0.913	0.0001
Alcohol consumption per occasion in grams	1.002	0.999 - 1.005	0.298
MELD score	1.054	1.023 - 1.085	0.0001
Consumption pattern excessive vs binge	1.985	1.113 - 3.541	0.02
Type of drink			
Fermented vs distilled	1.172	.549 - 2.502	0.682
Fermented vs mixed	1.403	.785 - 2.505	0.253
Mixed vs distilled	1.197	.577 - 2.482	0.629
Sex: women vs men	4.137	2.154 - 7.948	0.0001

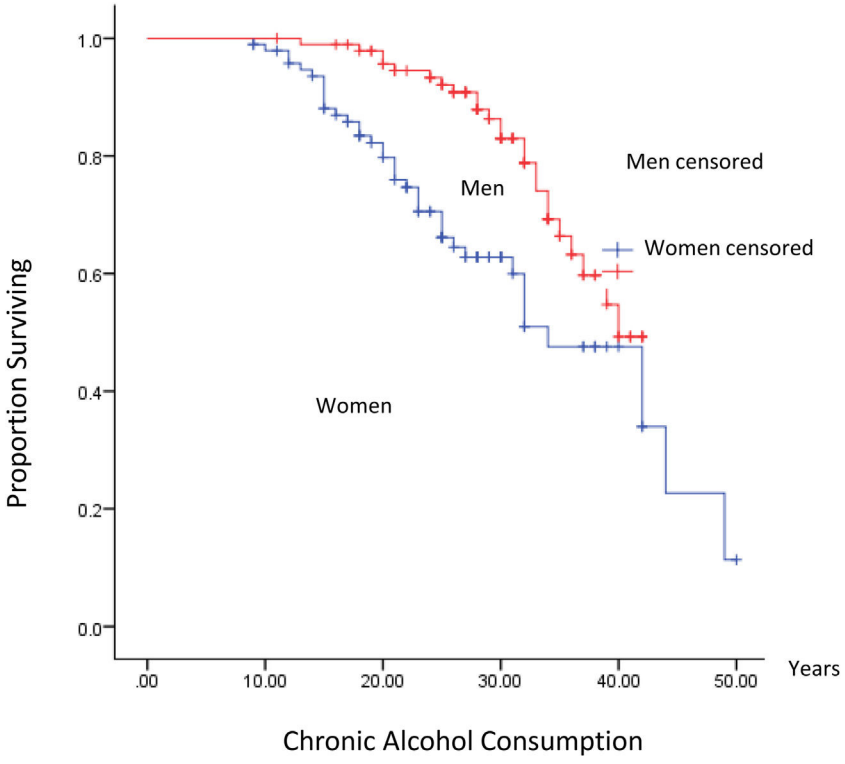

Figure 1 Kaplan–Meier survival curve at 50 months from 192 patient records (50% women and 50% men) with alcohol-related cirrhosis at first hospital admission.

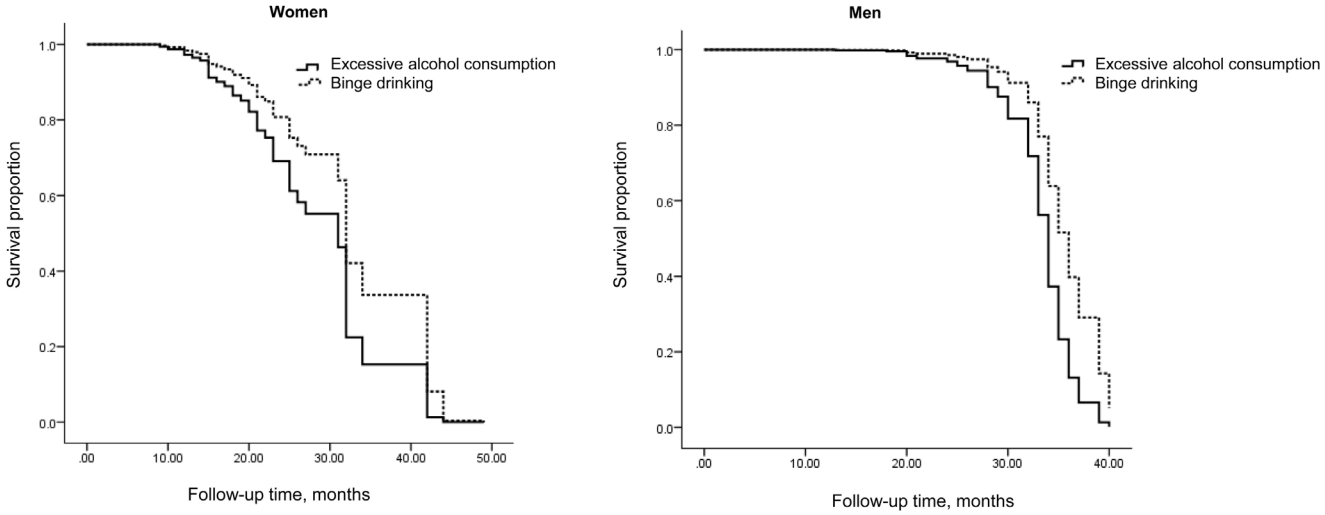

Figure 2 Unadjusted Kaplan–Meier survival curves for the effect of the alcohol consumption pattern on mortality, separated for women and men.

Table 4 Variables associated with mortality by type of consumption for men and women at first hospitalization.

	Women			Men		
	OR	95% CI	p	OR	95% CI	p
Age	0.918	0.876—0.963	0.0001	0.768	0.692—0.852	0.0001
Alcohol consumption per occasion in grams	0.999	0.995—1.004	0.732	1.001	1.995—1.007	0.751
MELD score	1.08	1.004—1.161	0.038	1.045	0.973—1.122	0.223
Consumption pattern excessive vs binge	0.676	0.288—1.587	0.369	0.425	0.160—1.128	0.086
Type of drink						
Fermented vs distilled	2.135	0.792—5.759	0.135	0.675	0.172—2.650	0.573
Fermented vs mixed	1.341	0.476—3.779	0.579	0.647	0.160—2.626	0.543
Number of complications at first hospitalization[a]	0.731	0.472—1.132	0.16	0.798	0.422—1.511	0.489

[a] Manifestations: acute kidney injury (AKI), gastrointestinal bleeding, ascites, acute-on-chronic liver failure (ACLF), and hepatic encephalopathy.

mortality. It is noteworthy that the different patterns of alcohol consumption and the type of beverage (fermented or distilled) showed no significant difference, when compared between groups. Conceivably, the accuracy of answering the questionnaire could be biased. Nevertheless, in other studies, alcoholic beverage type and consumption pattern have shown distinct toxic liver effects and are related to mortality.[16] In our cohort, mortality in women was higher, at 40%, compared with 25% in men.

The survival curve showed a disadvantage for women with chronic excessive alcohol consumption. Age was a significant factor for mortality in both sexes and was less protective for women. The lower alcohol consumption and shorter duration in women, compared with men, suggest a greater predisposition to liver damage in women, with a 3-year difference in mean survival, in favor of men. This result was also reflected in increased complications at hospital admission, and the MELD score was only significant in women as a factor associated with mortality. Alcohol-related mortality is known to be potentially higher in women and can be explained by the effect of sex hormones on the oxidative and metabolic pathways and the differential transcription of genes, resulting in a greater susceptibility to alcohol-induced toxicity,[17,18] as well as by the absence of a gastric first pathway of alcohol metabolism.

Other factors that negatively impact women who consume alcohol are slower gastric emptying time, lower lean body mass that induces greater plasma volume of circulating alcohol, and low activity of the cytochrome P450 enzyme, which generates a difference in the rate of alcohol metabolism.[19,20] Paradoxically, however, progesterone is associated with faster alcohol elimination rates in women.[21,22]

Chronic alcohol consumption (in two patterns of alcohol consumption: daily or per occasion) increases dysbiosis and bacterial overgrowth by increasing the intestinal bacterial load. In addition, it modifies the composition of the existing microbiota, with increased intestinal permeability and translocation of pathogen-associated molecular patterns (PAMPs) derived from the intestinal microbiome and bacterial DNA, activating the innate and adaptive immune response, thus causing an excessive synthesis of

pro-inflammatory cytokines and chemokines. In women, this response is much greater at lower blood alcohol concentrations.[23,24]

The limitations of our study include the fact that inquiring about alcohol consumption is complicated by sociocultural taboos, and women may have a more significant response bias. Other factors, such as the coexistence of women with eating disorders (e.g., bulimia or anorexia) was not considered, and said conditions could have a more significant harmful effect due to poor food intake in those patients.

Conclusions

Mortality due to alcohol-related liver damage is higher in women than in men; it is associated with a lower amount of g/day alcohol consumption, a shorter period of continued chronic consumption, and a higher age at the onset of drinking. Mortality in women in the coming years could increase because there is evidence of a prevalent increase in female alcohol consumption.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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