International Journal of Mental Health and Addiction
https://doi.org/10.1007/s11469-023-01112-z

ORIGINAL ARTICLE

Sex differences in the comorbidity of patients seeking a first treatment for Alcohol Use Disorder

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Accepted: 2 July 2023

Abstract

Background The CohRTA multicenter study aims to characterize patients undergoing a first treatment for alcohol use disorder (AUD). The objective is to analyze sex-specific differences in the comorbidity of AUD when starting the first treatment for the disorder.

Methods A multicenter study was carried out between 2014 and 2021 in 6 public centers in Spain. Sociodemographic characteristics were collected, variables related to alcohol consumption, medical comorbidity according to *Cumulative Illness Rating Scale-Substance Abuse* (CIRS-SA), antecedent of psychiatric comorbidity, general blood test and screening for drugs in urine. Logistic regression models were used to establish associations.

Results A total of 896 patients (634 M, 262 W) were included. Median age at admission was 48 years [IQR:41–56 years]. Men reported beginning regular alcohol consumption at an earlier age and drank more alcohol. The most frequent medical comorbidities were hepatic, respiratory, vascular and neurological. The median number of affected systems was three, with no differences between men and women. However, depressive disorder was more frequent in women. In the multivariate analysis, women were up to 4 times more likely to have a major depressive disorder, elevated ESR and elevated total cholesterol than men. Men started alcohol consumption earlier, had a higher body mass index (BMI), a higher probability of using cocaine and a higher frequency of GGT and bilirubin alteration than women.

Conclusion Differences by sex were found among individuals beginning first treatment for AUD. These differences must be taken into account when designing specific therapeutic strategies for men and women.

Keywords Alcohol · Sex differences · Clinical variables · Comorbid disorders

Alcohol use disorder (AUD) is a disease characterized by the problematic use of alcohol. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the disorder is diagnosed when two or more criteria are presented out of eleven that are evaluated, including the amount of alcohol ingested and the appearance of withdrawal symptoms

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when discontinuing consumption. AUD is considered severe if six or more diagnostic criteria are detected (APA, 2013).

The prevalence of AUD in the Western world is high, affecting 12% of the European adult population. In 2016, alcohol consumption was responsible for 3% and 8% of mortality in women and men, respectively (WHO, 2018).

The prevalence of alcohol consumption and amount has historically been higher in men than in women (Slade et al., 2016). However, these differences have been narrowing in recent years (Slade et al., 2016; White, 2020). The frequency and amount of consumption is increasing among women, while in men, these patterns remain stable (Grucza et al., 2018). In adolescents, the pattern of binge drinking has declined more rapidly in men than in women, causing sex differences to narrow and even reverse (Johnston et al., 2016).

In the older population, an increase in the prevalence of alcohol consumption and in the binge drinking pattern is described, especially among women (Han et al., 2017). However, men over 50 years of age show a higher prevalence of consumption and standard drink units per day, although with geographic variations among the 21 countries analyzed (Calvo et al., 2020).

There are sex-specific differences in the risk factors for developing AUD, as well as in the medical and psychiatric comorbidity of individuals who are dependent or abuse alcohol (Erol & Karpyak, 2015). For example, in women, anxiety disorder, childhood trauma and disturbances in mood or emotions (internalizing symptoms) have been described as risk factors (Guinle & Sinha, 2020; McHugh & Weiss, 2019). In men, developing AUD has been linked to novelty seeking, conduct disorder, parental loss and low self-esteem (Kendler et al., 2015).

In relation to the medical comorbidities associated with AUD, a greater vulnerability to the neurotoxic effects of ethanol, liver disease, cardiovascular disease, breast cancer, infertility and early menopause has been reported (Nolen-Hoeksema, 2004). Psychiatric comorbidities such as major depression, dysthymia and anxiety disorders occur more frequently in women, while in men, antisocial personality disorder is more frequent (Boykoff et al., 2010; Kendler et al., 2015; McHugh & Weiss, 2019; Nolen-Hoeksema, 2004). In addition, depressive symptoms seem to be associated with relapses in alcohol consumption, mainly in women (Schutte et al., 1997).

The increase in the frequency and quantity of alcohol consumption among women could be reflected in the increasing morbidity and mortality of this population. In this sense, an increase in the number of visits to the emergency room and in alcohol-related mortality has been described (White et al., 2018, 2020).

It has been suggested that sex differences should be considered in the design of specific therapeutic interventions for AUD (Greenfield et al., 2007). However, a sufficient number of patients is needed to establish differential aspects of the disorder and the severity of medical and psychiatric complications (Agabio et al., 2017).

The CohRTA multicenter study has as its main objective to characterize AUD in men and women in Spain as they begin their first treatment for the disorder (Sanvisens et al., 2021). We aimed to analyze sex differences in the context of sociodemographic, clinical and disease burden aspects to better understand different treatment interventions in this population.

Material and Methods

Participants and Methods

From January 2014 to March 2021, 896 patients who began their first treatment for AUD in six public centers of the Spanish health system affiliated with the CohRTA study were

enrolled. The centers were Hospital Son Espases (Palma de Mallorca), Hospital Clinic (Barcelona), Hospital del Mar (Barcelona), Hospital 12 de Octubre (Madrid), Hospital Universitari Germans Trias i Pujol (Badalona) and Hospital Universitari de Bellvitge (Hospitalet de Llobregat).

The study was approved by the Clinical Research Ethics Committee (CEIC) of the coordinating center (Hospital Universitari Germans Trias i Pujol) and by the CEIC of each participating center. The patients signed an informed consent form that included the transfer of clinical data and biological samples. The methods used in this study have complied with the ethical standards for medical research, the principles of good clinical practice established by the Declaration of Helsinki, and Organic Law 3/2018 on Data Protection and Guarantee of Digital Rights (LOPD-GDR) and Law 14/2007 on Biomedical Research.

The diagnosis of AUD was made according to DSM-5 criteria (APA, 2013), and the patients followed the same clinical protocol in all participating centers. The CohRTA multicenter study has a database with 1) sociodemographic variables (i.e., age, sex, employment status, educational level, marital status); 2) alcohol consumption questionnaire: age at first alcohol exposure, age of onset of regular alcohol consumption (i.e. weekly drinking), duration of regular alcohol consumption (i.e. elapsed time between age of onset of regular alcohol consumption, and age at admission to treatment), amount of alcohol consumption (last 30 days) in Standard Drinks per day (SD/day), and number of alcohol intoxications (lifetime); 3) use of other substances (i.e., cocaine); 4) Cumulative Illness Rating Scale-Substance Abuse (CIRS-SA), which assesses the involvement of organs and systems and the severity of comorbidity; 5) psychiatric comorbidity; and 6) laboratory parameters with hemogram, biochemistry, viral serologies and screening for drugs of abuse in urine when entering the study.

The CIRS-SA scale is validated in the Spanish population (Castillo et al., 2004; Rivas et al., 2013) and analyzes comorbidities in the following organs/systems: (i) heart; (ii) vascular and hematopoietic; (iii) respiratory; (iv) eyes, ears, nose; (v) throat and larynx; (vi) gastrointestinal tract; (vii) liver, including hepatitis B and C viruses; (viii) renal; (ix) genitourinary; (x) musculoskeletal; (xi) neurological; (xii) endocrinology, breast and infectious diseases; and (xiii) HIV infection. Each category receives a score between 0 and 4 according to the severity of the illness, with 0 being the absence of comorbidity and 4 being a very severe manifestation. In addition, CIR-SA generates three indicators: (a) total score (range from 0 to 54), (b) number of organs or systems affected (range from 0 to 13) and (c) severity index (total score divided by the number of organs or systems affected).

Antecedent of psychiatric comorbidity might be established following a review of the medical records to obtain diagnoses from specialists in Psychiatry: major depression, psychosis, attention and hyperactivity disorder, posttraumatic stress disorder, generalized anxiety disorder, panic disorder, social phobia and mania.

Upon entry into the study, blood samples were obtained for hematological parameters (i.e., hemogram), liver function (i.e., aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and acute phase reactants, such as erythrocyte sedimentation rate (ESR). Serologies were performed to detect antibodies against HIV, HCV and HBV. In addition, a urine drug screen was carried out.

Statistical analysis

Categorical variables are expressed as relative frequencies, and continuous variables are expressed as the median and interquartile range (IQR). Sex differences in categorical

variables were determined using Fisher's exact test or the chi-square test. Mann−Whitney U test was applied as a nonparametric test for continuous variables.

A logistic regression model was used to analyze sex differences, with men being the reference category. For the regression model, some variables with various categories were dichotomized (i.e., oropharynx and larynx). The multivariate analysis included those variables that were statistically significant in the univariate analysis; specifically, laboratory parameters were included in the model when statistically significant globally and pathologically. Results with a p value < 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA).

Results

A total of 896 patients (634 men) were included in the study. The age at the first treatment (median [IQR]: 48 years [41–56]) was similar in men and women. However, statistically significant differences ($p < 0.001$) were observed in work and family situations: women were more dedicated to household chores (5.9% vs. 0.2%), they had a lower prevalence of disability (13% vs. 19.7%) and they were divorced more frequently (36.8% vs. 30.6%), while men tended to be single (36.8% vs. 24%).

Regarding educational level, 21% of the men and 13% of the women had a primary school education; 56% of both genders had secondary education, and women had a higher frequency of university studies than men (25.3% vs. 16.3%, respectively) ($p = 0.002$).

Alcohol consumption

Table 1 shows the characteristics of alcohol consumption. Men started drinking, on average, one year earlier than women (median [IQR]: 15 [13–17] years vs. 16 [14–18] years; $p = 0.002$) and tended to consume alcohol regularly from an earlier age (median [IQR]: 20 [17–26] years vs. 26 [20–37] years; $p < 0.001$). In addition, men consumed a greater amount of alcohol than women (median [IQR]: 15 [10–24] SU/day vs. 12 [8–20] SU/day; $p < 0.001$).

In addition, a family history of AUD was more frequent among women ($p = 0.004$), and in relation to the consumption of other substances, men showed a higher prevalence of cocaine use than women ($p = 0.003$).

Medical comorbidity

Table 2 shows the sex differences in baseline medical comorbidities. Overall, the most frequent organ or system involvement was the liver (73%), followed by respiratory (55%) and vascular (52%) systems. Compared with women, men showed a higher prevalence of severe or very severe medical comorbidities in most organs or systems, although statistically significant differences were observed only in oropharynx and larynx ($p < 0.05$). In addition, the severity index score of the CIRS-SA scale was higher for men ($p < 0.05$).

Table 1 Characteristics of 634 men and 262 women requesting a first treatment for AUD in the CohRTA Study

Variables	Men N = 634 n (%)	Women N = 262 n (%)	p value
Age at first alcohol use Median (IQR)(n = 858)	15 (13–17)	16 (14–18)	**0.002**[(1)]
Age of onset of regular alcohol consumption Median (IQR)(n = 890)	20 (17–26)	26 (20–37)	**< 0.001**[(1)]
Duration of regular alcohol consumption (years) Median (IQR)(n = 888)	26 (14–35)	17 (9–29)	**< 0.001**[(1)]
DSM-5 criteria Median (IQR)	10 (8–13)	10 (8–12)	0.328[(1)]
Amount of alcohol consumption (Standard Drink/day) Median (IQR) (n = 841)	15 (10–24)	12 (8–20)	**< 0.001**[(1)]
AUD family history (n = 843)			
No	232 (39.0)	72 (28.9)	
Yes	349 (58.8)	173 (69.5)	**0.014**[(2)]
Unknown	13 (2.2)	4 (1.6)	
Number of alcohol intoxications (lifetime) (n = 796)			
None	404 (72.8)	163 (67.6)	
1–5	132 (23.8)	67 (27.8)	0.318[(2)]
> 5	19 (3.4)	11 (4.6)	
Tobacco Smokers (n = 684)	454 (94.2)	195 (96.5)	0.139[(2)]
Detection of drugs in urine			
Amphetamines (n = 725)	8 (1.6)	1 (0.5)	0.443[(2)]
Cannabis (n = 725)	99 (19.4)	33 (15.3)	0.221[(2)]
Cocaine (n = 725)	49 (9.6)	7 (3.2)	**0.003**[(2)]

[(1)]Statistical analysis was conducted using the Mann–Whitney U test

[(2)]Statistical analysis was conducted using Fisher's exact test or chi-square test

Psychiatric comorbidity

Table 3 shows the prevalence of psychiatric comorbidities. The most frequent disorders were major depression (MDD) (24.0%), generalized anxiety (6.1%) and psychotic disorder (2.5%). The prevalence of MDD was significantly higher in women than in men (46.7% vs. 22.0%, $p < 0.001$).

Anthropometric and blood parameters

The BMI and general laboratory parameters are described in Table 4. Men had a higher BMI than women (25.6 vs. 24.0 kg/m^2, $p < 0.001$). Men also showed a higher median leukocyte count and hemoglobin level than women ($p = 0.018$ and $p < 0.001$,

Table 2 Characteristics of comorbidity in 483 men and 213 women requesting a first treatment of AUD in CohRTA Study

Organ/System	Severity	Men N = 483 n (%)	Women N = 213 n (%)	p value
Heart	Absent	439 (90.9)	202 (94.8)	0.154[(1)]
	Mild	19 (3.9)	3 (1.4)	
	Moderate	17 (3.5)	5 (2.3)	
	Severe	8 (1.7)	2 (0.9)	
	Very severe	0	1 (0.5)	
Vascular and hematopoietic	Absent	234 (48.4)	98 (46.0)	0.203[(1)]
	Mild	153 (31.7)	84 (39.4)	
	Moderate	84 (17.4)	28 (13.1)	
	Severe	9 (1.9)	3 (1.4)	
	Very severe	3 (0.6)	0	
Respiratory	Absent	218 (45.1)	93 (43.7)	0.480[(1)]
	Mild	176 (36.4)	87 (40.8)	
	Moderate	77 (15.9)	25 (11.7)	
	Severe	8 (1.7)	5 (2.3)	
	Very severe	4 (0.8)	3 (1.4)	
Eyes, ears, nose	Absent	455 (94.2)	203 (95.3)	0.526[(1)]
	Mild	16 (3.3)	6 (2.8)	
	Moderate	6 (1.2)	4 (1.9)	
	Severe	3 (0.6)	0	
	Very severe	3 (0.6)	0	
Oropharynx and larynx	Absent	405 (83.9)	184 (86.4)	**0.047**[(1)]
	Mild	35 (7.2)	16 (7.5)	
	Moderate	19 (3.9)	12 (5.6)	
	Severe	11 (2.3)	1 (0.5)	
	Very severe	13 (2.7)	0	
Gastrointestinal tract (upper and lower)	Absent	444 (91.9)	201 (94.4)	0.557[(1)]
	Mild	29 (6.0)	7 (3.3)	
	Moderate	5 (1.0)	3 (1.4)	
	Severe	1 (0.2)	1 (0.5)	
	Very severe	4 (0.8)	1 (0.5)	
Liver, including hepatitis B and C viruses	Absent	123 (25.4)	63 (29.6)	0.203[(1)]
	Mild	14 (2.9)	6 (2.8)	
	Moderate	294 (60.7)	131 (61.5)	
	Severe	35 (7.2)	6 (2.8)	
	Very severe	18 (3.7)	7 (3.3)	
Renal	Absent	470 (97.3)	204 (95.8)	0.173[(1)]
	Mild	10 (2.1)	6 (2.8)	
	Moderate	1 (0.2)	3 (1.4)	
	Severe	0	0	
	Very severe	2 (0.4)	0	
Genitourinary	Absent	456 (94.4)	194 (91.1)	0.344[(1)]
	Mild	13 (2.7)	12 (5.6)	
	Moderate	10 (2.1)	4 (1.9)	
	Severe	2 (0.4)	1 (0.5)	
	Very severe	2 (0.4)	2 (0.9)	
Musculoskeletal	Absent	429 (88.8)	191 (89.7)	0.202[(1)]
	Mild	23 (4.8)	15 (7.0)	
	Moderate	22 (4.6)	7 (3.3)	
	Severe	7 (1.4)	0	
	Very severe	2 (0.4)	0	

Table 2 (continued)

Organ/System	Severity	Men N = 483 n (%)	Women N = 213 n (%)	p value
Neurological	Absent	413 (85.5)	188 (88.3)	0.056[(1)]
	Mild	31 (6.4)	9 (4.2)	
	Moderate	18 (3.7)	14 (6.6)	
	Severe	20 (4.1)	2 (0.9)	
	Very severe	1 (0.2)	0	
Endocrine, breast and infectious diseases	Absent	356 (73.7)	164 (77.0)	0.236[(1)]
	Mild	82 (17.0)	31 (14.6)	
	Moderate	35 (7.2)	13 (6.1)	
	Severe	9 (1.9)	2 (0.9)	
	Very severe	1 (0.2)	3 (1.4)	
HIV Infection	Absent	462 (95.7)	207 (97.2)	0.692[(1)]
	Mild	8 (1.7)	1 (0.5)	
	Moderate	6 (1.2)	2 (0.9)	
	Severe	6 (1.2)	3 (1.4)	
	Very severe	1 (0.2)	0	
Total scores Median [IQR]		4.0 (3.0–7.0)	4.0 (2.5–6.0)	0.187[(2)]
Number of categories affected Median [IQR]		3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.564[(2)]
Severity index Median [IQR]		1.5 (1.3–2.0)	1.5 (1.3–1.8)	**0.014**[(2)]

Severity index = total score divided by number of categories affected

[(1)]Statistical analysis was conducted using Fisher´s exact test or chi-square test

[(2)]Statistical analysis was conducted using the Mann–Whitney U test

Table 3 Psychiatric comorbidity in 634 men and 262 women seeking a first AUD treatment in the CohRTA Study

Comorbidities	Men N = 634 n (%)	Women N = 262 n (%)	p value [(1)]
Major depression disorder (n = 722)	109 (22.0)	106 (46.7)	**< 0.001**
Psychosis (n = 714)	16 (3.3)	6 (2.7)	0.721
Attention and hyperactivity disorders (n = 711)	12 (2.5)	4 (1.8)	0.787
Post-traumatic stress disorder (n = 712)	5 (1.0)	5 (2.2)	0.302
Generalized anxiety disorder (n = 714)	33 (6.7)	22 (9.8)	0.175
Panic disorder (n = 712)	7 (1.4)	7 (3.1)	0.151
Social phobia (n = 711)	2(0.4)	1 (0.4)	1.000
Maniac disorder (n = 712)	5 (1.0)	1 (0.4)	0.671

[(1)] Statistical analysis was conducted using Fisher's exact test or chi-square test

Table 4 Body mass index (BMI) and blood parameters in 896 patients at first AUD treatment in the CohRTA Study

Variables	Men N = 634	Women N = 262	p value
BMI (kg/m^2) (n = 623)	25.6	24.0	
Median (IQR)	(23.5–29.1)	(20.6–27.7)	**< 0.001**$^{(1)}$
> 25 (kg/m2), n (%)	240 (58.1)	87 (42.4)	**0.001**$^{(2)}$
Blood count			
Leukocytes (× 10^9/L) (n = 789)	7.1	6.8	
Median (IQR)	(5.9–8.8)	(5.5–8.1)	**0.018**$^{(1)}$
< 4.0 (× 109/L), n (%)	29 (5.2)	13 (5.7)	0.861$^{(2)}$
Hemoglobin (g/dL) (n = 791)	15.1	13.8	
Median (IQR)	(13.8–16.3)	(12.8–14.9)	**< 0.001**$^{(1)}$
< 13 men < 12 women (g/dL), n (%)	91 (16.2)	31 (13.5)	0.386$^{(2)}$
MCV (fL) (n = 789)	95.9	98.0	
Median (IQR)	(92.3–100.0)	(93.4–102)	**< 0.001**$^{(1)}$
≥ 95 (fL), n (%)	325 (58.1)	158 (68.7)	0.006$^{(2)}$
Platelets (× 10^9/L) (n = 783)	218.5	232.0	
Median (IQR)	(169.8–272.3)	(188.0–287.0)	**0.012**$^{(1)}$
< 150 (× 109/L), n (%)	92 (16.6)	29 (12.7)	0.192$^{(2)}$
ESR (mm) (n = 682)	8.0	14.0	
Median (IQR)	(5.0–19.0)	(7.0–26.0)	**< 0.001**$^{(1)}$
> 20 (mm), n (%)	116 (24.1)	73 (36.3)	**0.001**$^{(2)}$
Biochemistry			
Total cholesterol (mg/dL) (n = 772)	194.0	210.0	
Median (IQR)	(165.0–229.0)	(181.0–250.5)	**< 0.001**$^{(1)}$
> 200 (mg/dL), n (%)	246 (45.0)	131 (58.2)	**0.001**$^{(2)}$
Triglycerides (mg/dL) (n = 761)	129.0	103.5	
Median (IQR)	(84.0–206.5)	(76.0–159.8)	**0.001**$^{(1)}$
> 150 (mg/dL), n (%)	222 (41.0)	66 (30.0)	**0.005**$^{(2)}$
Albumin (g/L) (n = 735)	41.8	42.3	
Median (IQR)	(29.9–45.0)	(37.9–45.0)	0.158$^{(1)}$
< 35 (g/L), n (%)	148 (28.5)	41 (19.0)	**0.007**$^{(2)}$
Basal glucose (mg/dL) (n = 778)	95.0	91.0	
Median (IQR)	(86.0–106.0)	(82.0–101.8)	**< 0.001**$^{(1)}$
> 110 (mg/dL), n (%)	116 (21.1)	36 (15.8)	0.092$^{(2)}$
Total bilirubin (mg/dL) (n = 736)	0.7	0.7	
Median (IQR)	(0.5–1.0)	(0.4–1.0)	**0.029**$^{(1)}$
> 1.2 (mg/dL), n (%)	90 (17.2)	18 (8.5)	**0.003**$^{2)}$
AST (U/L) (n = 706)	35.0	32.0	
Median (IQR)	(24.0–71.0)	(20.0–64.0)	**0.027**$^{(1)}$
> 50 (U/L), n (%)	174 (34.6)	69 (34.0)	0.930$^{(2)}$
ALT (U/L) (n = 732)	31.0	26.5	
Median (IQR)	(20.0–57.8)	(17.0–50.8)	**0.004**$^{(1)}$
> 50 (U/L), n (%)	158 (30.2)	53 (25.5)	0.240$^{(2)}$
GGT (U/L) (n = 778)	91.0	52.0	
Median (IQR)	(41.0–258.5)	(24.0–221.5)	**< 0.001**$^{(1)}$

Table 4 (continued)

Variables	Men N = 634	Women N = 262	p value
> 55 (U/L), n (%)	360 (65.6)	113 (49.3)	**< 0.001**[(2)]
Creatinine (U/L) (n = 780)	0.8	0.7	
Median (IQR)	(0.7–0.9)	(0.6–0.8)	**< 0.001**[(1)]
> 1.18 (U/L), n (%)	19 (3.4)	4 (1.7)	0.250[(2)]

AST = aspartate aminotransferase; ALT = alanine aminotransferase; BMI = body mass index; ESR = erythrocyte sedimentation rate; GGT = gamma-glutamyl transferase; MCV = mean corpuscular volume

[(1)]Statistical analysis was conducted using the Mann–Whitney U test

[(2)]Statistical analysis was conducted using Fisher's exact test or chi-square test

respectively), while women showed a higher frequency of mean corpuscular volume (MCV) > 95 fl ($p < 0.001$), and ESR > 20 mm ($p = 0.001$) than men.

In relation to biochemistry markers, women showed higher total cholesterol levels ($p < 0.001$). However, men had higher concentrations of triglycerides ($p = 0.001$), basal glucose ($p < 0.001$), creatinine ($p < 0.001$), AST ($p = 0.027$), and ALT ($p = 0.004$), as well as higher prevalence of albumin < 35 g/L ($p = 0.007$), total bilirubin > 1.2 mg/dL ($p = 0.003$), and GGT > 55 U/L ($p < 0.001$).

Sex-specific associations

Multivariate analysis (described in Table 5) showed that the diagnosis of MDD was four times more likely in women than men (OR = 4,29, 95% CI: 2,57–7,16), as was elevated ESR levels (> 20 mm) (OR = 2,55, 95% CI: 1,54–4,22) and total cholesterol (> 200 mg/dL) (OR = 1,61, 95% CI: 0.99–2.58).

Age of onset of alcohol consumption (OR = 0.94, 95% CI = 0.90–0.99), BMI > 25 kg/m^2 (OR = 0.56, 95% CI: 0.35–0.89), cocaine use (OR = 0.11, 95% CI = 0.03–0.46), elevated levels of total bilirubin (> 1.2 mg/dL) (OR = 0.47, 95% CI = 0.24–0.94) and GGT > 55 U/L (OR = 0.54, 95% CI = 0.33–0.88) were more likely in men than in women.

Discussion

The results of this study show sex differences when starting the first treatment for AUD. Men and women begin their first treatment at a similar age, although women report fewer years of regular alcohol consumption. Although women would be less likely to seek treatment for AUD (Agabio et al., 2017), these results indicate that when they do it for the first time, they have been exposed to excessive alcohol consumption for fewer years.

If women show less time of excessive alcohol use, the expected comorbidity could be less than that of men. However, in our results the expected comorbidity is similar for both sexes in most organs or systems; previous studies show a greater vulnerability of women to the harmful effects of alcohol after fewer years of excessive alcohol use in comparison with men (Mumenthaler et al., 1999; Randall et al., 1999).

Table 5 Logistic regression model in the AUD sample

Variables	Univariate		Multivariate	
	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Age at first alcohol use	0.95 (0.92–0.98)	**< 0.001**	0.94 (0.90–0.99)	**0.014**
Age of onset of regular alcohol consumption	0.95 (0.94–0.96)	**< 0.001**	-	
Duration of regular alcohol consumption (years)	1.03 (1.02–1.05)	**< 0.001**	1.02 (0.99–1.03)	0.058
Amount of alcohol consumption (SD/day)	1.03 (1.01–1.04)	**< 0.001**	1.01 (0.99–1.03)	0.158
AUD Family history	1.59 (1.18–2.14)	**0.003**	1.43 (0.88–2.33)	0.150
Cocaine in urine	0.31 (0.14–0.71)	**0.005**	0.11 (0.03–0.46)	**0.002**
BMI > 25 kg/m^2	0.53 (0.38–0.75)	**< 0.001**	0.56 (0.35–0.89)	**0.015**
Oropharynx and larynx pathology	0.82 (0.52–1.30)	0.394	-	
CIRS-SA severity index	1.60 (1.09–2.33)	**0.015**	1.37 (0.73–2.57)	0.320
MDD diagnosis	3.27 (2.37–4.51)	**< 0.001**	4.29 (2.57–7.16)	**< 0.001**
ESR > 20 mm	1.79 (1.26–2.56)	**0.001**	2.55 (1.54–4.22)	**< 0.001**
Total cholesterol > 200 mg/dL	1.70 (1.25–2.33)	**0.001**	1.61 (0.99–2.58)	0.051
Triglycerides > 150 mg/dL	0.62 (0.44–0.86)	**0.005**	0.70 (0.43–1.14)	0.154
Total bilirubin > 1.2 mg/dL	0.45 (0.26–0.76)	**0.003**	0.47 (0.24–0.94)	**0.033**
GGT > 55 U/L	0.51 (0.37–0.70)	**< 0.001**	0.54 (0.33–0.88)	**0.014**

AUD = alcohol use disorder; BMI = body mass index; CI = confidence interval; ESR = erythrocyte sedimentation rate; GGT = gamma-glutamyl transferase; MDD = major depression disorder

The global medical comorbidity according to CIRS-SA is mild or moderate for both men and women; however, a high prevalence of hepatic, respiratory, vascular and neurological affectation is shown at the beginning of treatment, which suggests the need for treatment as secondary prevention to the progression of the comorbidity. The literature includes liver diseases as the most frequent complication and the first cause of death in these patients (Timko et al., 2006). Further, preclinical and clinical studies show that women are more susceptible to liver damage caused by alcohol (Alharshawi et al., 2021; Fulham & Mandrekar, 2016).

Our results also show sex differences in laboratory parameters. Specifically, elevated levels of ESR and total cholesterol are more prevalent in women with AUD. The ESR rate is a marker of systemic inflammation that tends to be more frequently altered in women and to increase with age (Alende-Castro et al., 2019; Ernst et al., 2010). Although we have

not found any studies that show sex differences in total cholesterol levels associated with AUD, there is evidence that chronic alcohol consumption alters the synthesis of hepatic cholesterol (Charlet & Heinz, 2017; Rosoff et al., 2020).

On the other hand, this study shows that men are more likely to have elevated levels of GGT and total bilirubin. GGT, in addition to being an indicator of alcohol consumption, is a marker associated with diabetes mellitus, metabolic syndrome, arteriosclerosis and cardiovascular diseases (Hernández-Rubio et al., 2022; Lu et al., 2020; Ndrepepa et al., 2018). According to our results, the literature shows differences between the sexes in the study of GGT as a biomarker of hepatic steatosis with high GGT activity as a predictor of an increase in mortality among men (Haring et al., 2009).

It is noteworthy that when starting the first treatment for AUD, men are more likely to be overweight/obese than women. In contrast, a study published in 2011 showed that women were almost five times more likely to be obese grade II (BMI > 30 kg/m^2) than men (Sanvisens et al., 2011). It is possible that differences in study design and patient selection may have influenced the findings. In any case, BMI has been poorly described in patients requesting treatment for AUD and suggests the need to analyze the impact of alcohol consumption on overweight and obesity.

Another interesting piece of information from the results of this study is that almost 70% of the women had a family history of AUD, which was more frequent than in men. There is literature that relates a family history of alcohol dependence with an increased risk of developing an AUD, as well as developing depressive and anxiety disorders (Hill et al., 2001; Sjoerds et al., 2013).

Men in our study showed a higher prevalence of cocaine use than women. Epidemiological studies have described that substance use disorders are between 3 and 5 times more common in men than in women, although the sex difference in the consumption of alcohol, cannabis and cocaine has been narrowing in recent years (Hecksher & Hesse, 2009).

With regard to psychiatric comorbidity, MDD was the most prevalent diagnosis in patients with AUD, being more frequent in women. This result is consistent with previous studies suggesting that emotional states have a gender-specific impact, based on the evidence of high rates of depressive comorbidity and anxiety disorders among patients in treatment for AUD, especially women (Hasin et al., 2007). There are studies that indicate that women experience complex negative emotional states and psychological stress (Brady & Sinha, 2005; Fox & Sinha, 2009), while men show more substance-induced depression (Karpyak et al., 2016).

Finally, this study has several limitations that should be mentioned. First, it is a cross-sectional design that prevents conclusions about the causality of the findings. The lack of information in relation to specific hormonal situations of women (e.g., menopause, treatment with oral contraceptives) could have caused an overestimation of the frequency of certain alterations. However, the main strength of this study is that, to our knowledge, it is the largest patient cohort on the topic in which sex differences were analyzed comprehensively.

In conclusion, the present findings support the differences between the sexes as a result of the study of the clinical variables collected for the treatment of AUD. The main differences between men and women with AUD are that men present high dysregulation in liver markers (GGT and total bilirubin) and higher risk consumption patterns, while women present high prevalence of psychiatric comorbidity, inflammatory markers (ESR) and elevated cholesterol. These results provide valuable clinical information to establish improvements in therapeutic and preventive measures based on sex in a population especially vulnerable to chronicity, such as patients with AUD.

Appendix

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Funding Open Access Funding provided by Universitat Autonoma de Barcelona.

Declarations

Informed Consent Yes.

Human Rights Yes.

Conflict of Interest None.

References

Agabio, R., Pisanu, C., Gessa, G. L., & Franconi, F. (2017). Sex Differences in Alcohol Use Disorder. *Current Medicinal Chemistry, 24*(24), 2661–2670. https://doi.org/10.2174/0929867323666161202092908

Alende-Castro, V., Alonso-Sampedro, M., Vazquez-Temprano, N., Tuñez, C., Rey, D., García-Iglesias, C., . . . Gonzalez-Quintela, A. (2019). Factors influencing erythrocyte sedimentation rate in adults: New evidence for an old test. *Medicine (Baltimore), 98*(34), e16816. https://doi.org/10.1097/md.0000000000016816

Alharshawi, K., Fey, H., Vogle, A., Klenk, T., Kim, M., & Aloman, C. (2021). Sex specific effect of alcohol on hepatic plasmacytoid dendritic cells. *Int Immunopharmacol, 90*, 107166. https://doi.org/10.1016/j.intimp.2020.107166

Boykoff, N., Schneekloth, T. D., Hall-Flavin, D., Loukianova, L., Karpyak, V. M., Stevens, S. R., . . . Frye, M. A. (2010). Gender differences in the relationship between depressive symptoms and cravings in alcoholism. *Am J Addict*, *19*(4), 352–356. https://doi.org/10.1111/j.1521-0391.2010.00057.x

Brady, K. T., & Sinha, R. (2005). Co-occurring mental and substance use disorders: The neurobiological effects of chronic stress. *American Journal of Psychiatry, 162*(8), 1483–1493. https://doi.org/10.1176/appi.ajp.162.8.1483

Calvo, E., Medina, J. T., Ornstein, K. A., Staudinger, U. M., Fried, L. P., & Keyes, K. M. (2020). Cross-country and historical variation in alcohol consumption among older men and women: Leveraging recently harmonized survey data in 21 countries. *Drug Alcohol Depend, 215*, 108219. https://doi.org/10.1016/j.drugalcdep.2020.108219

Castillo, C., Bulbena, A., Serras, E., Torrens, M., López-Colomés, J. L., Martínez, M. A., & Politinska, B. (2004). Medical assessment in drug addicts: Reliability and validity of the Cumulative Illness Rating Scale (Substance Abuse version). *European Addiction Research, 10*(3), 112–117. https://doi.org/10.1159/000077699

Charlet, K., & Heinz, A. (2017). Harm reduction-a systematic review on effects of alcohol reduction on physical and mental symptoms. *Addiction Biology, 22*(5), 1119–1159. https://doi.org/10.1111/adb.12414

Compton, W. M., Auriacombe, M., Borges, G. L. G, Bucholz, K. K., Budney, A. J., Grant, B. F., . . . O'Brien, C. P. (2013). Substance-Related and Addictive Disorders. In S. K. Schultz & E. A. Kuhl (Eds.), *Diagnostic and statistical manual of mental disorders* (5th ed., pp. 490–497). American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9780890425596

Ernst, A. A., Weiss, S. J., Tracy, L. A., & Weiss, N. R. (2010). Usefulness of CRP and ESR in predicting septic joints. *Southern Medical Journal, 103*(6), 522–526. https://doi.org/10.1097/SMJ.0b013e3181ddd246

Erol, A., & Karpyak, V. M. (2015). Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug and Alcohol Dependence, 156*, 1–13. https://doi.org/10.1016/j.drugalcdep.2015.08.023

Fox, H. C., & Sinha, R. (2009). Sex differences in drug-related stress-system changes: Implications for treatment in substance-abusing women. *Harvard Review of Psychiatry, 17*(2), 103–119. https://doi.org/10.1080/10673220902899680

Fulham, M. A., & Mandrekar, P. (2016). Sexual Dimorphism in Alcohol Induced Adipose Inflammation Relates to Liver Injury. *PLoS One, 11*(10), e0164225. https://doi.org/10.1371/journal.pone.0164225

Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0IGO

Greenfield, S. F., Brooks, A. J., Gordon, S. M., Green, C. A., Kropp, F., McHugh, R. K., . . . Miele, G. M. (2007). Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug Alcohol Depend*, *86*(1), 1–21. https://doi.org/10.1016/j.drugalcdep.2006.05.012

Grucza, R. A., Sher, K. J., Kerr, W. C., Krauss, M. J., Lui, C. K., McDowell, Y. E., . . . Bierut, L. J. (2018). Trends in Adult Alcohol Use and Binge Drinking in the Early 21st-Century United States: A Meta-Analysis of 6 National Survey Series. *Alcohol Clin Exp Res*, *42*(10), 1939–1950. https://doi.org/10.1111/acer.13859

Guinle, M. I. B., & Sinha, R. (2020). The Role of Stress, Trauma, and Negative Affect in Alcohol Misuse and Alcohol Use Disorder in Women. *Alcohol Res, 40*(2), 05. https://doi.org/10.35946/arcr.v40.2.05

Han, B. H., Moore, A. A., Sherman, S., Keyes, K. M., & Palamar, J. J. (2017). Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005–2014. *Drug and Alcohol Dependence, 170*, 198–207. https://doi.org/10.1016/j.drugalcdep.2016.11.003

Haring, R., Wallaschofski, H., Nauck, M., Dörr, M., Baumeister, S. E., & Völzke, H. (2009). Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. *Hepatology, 50*(5), 1403–1411. https://doi.org/10.1002/hep.23135

Hasin, D. S., Stinson, F. S., Ogburn, E., & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry, 64*(7), 830–842. https://doi.org/10.1001/archpsyc.64.7.830

Hecksher, D., & Hesse, M. (2009). Women and substance use disorders. *Mens Sana Monogr, 7*(1), 50–62. https://doi.org/10.4103/0973-1229.42585

Hernández-Rubio, A., Sanvisens, A., Bolao, F., Cachón-Suárez, I., Garcia-Martín, C., Short, A., . . . Muga, R. (2022). Prevalence and associations of metabolic syndrome in patients with alcohol use disorder. *Sci Rep*, *12*(1), 2625. https://doi.org/10.1038/s41598-022-06010-3

Hill, S. Y., De Bellis, M. D., Keshavan, M. S., Lowers, L., Shen, S., Hall, J., & Pitts, T. (2001). Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. *Biological Psychiatry, 49*(11), 894–905. https://doi.org/10.1016/s0006-3223(01)01088-5

Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2019). Demographic subgroup trends among adolescents in the use of various licit and illicit drugs, 1975–2018 (Monitoring the Future Occasional Paper No. 92). Ann Arbor, MI: Institute for Social Research, The University of Michigan. https://monitoringthefuture.org/wp-content/uploads/2021/02/mtf-occ92.pdf

Karpyak, V. M., Biernacka, J. M., Geske, J. R., Abulseoud, O. A., Brunner, M. D., Chauhan, M., . . . Mrazek, D. A. (2016). Gender-specific effects of comorbid depression and anxiety on the propensity to drink in negative emotional states. *Addiction*, *111*(8), 1366–1375. https://doi.org/10.1111/add.13386

Kendler, K. S., Edwards, A. C., & Gardner, C. O. (2015). Sex differences in the pathways to symptoms of alcohol use disorder: A study of opposite-sex twin pairs. *Alcoholism, Clinical and Experimental Research, 39*(6), 998–1007. https://doi.org/10.1111/acer.12694

Lu, G. H., Gong, S. G., Li, C., Zhao, Q. H., Jiang, R., Luo, C. J., . . . Zhang, R. (2020). Prognostic Value of Gamma-Glutamyltransferase in Male Patients With Idiopathic Pulmonary Arterial Hypertension. *Front Cardiovasc Med*, *7*, 580908. https://doi.org/10.3389/fcvm.2020.580908

McHugh, R. K., & Weiss, R. D. (2019). Alcohol Use Disorder and Depressive Disorders. *Alcohol Res*, *40*(1). https://doi.org/10.35946/arcr.v40.1.01

Mumenthaler, M. S., Taylor, J. L., O'Hara, R., & Yesavage, J. A. (1999). Gender differences in moderate drinking effects. *Alcohol Research & Health, 23*(1), 55–64.

Ndrepepa, G., Colleran, R., & Kastrati, A. (2018). Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease. *Clinica Chimica Acta, 476*, 130–138. https://doi.org/10.1016/j.cca.2017.11.026

Nolen-Hoeksema, S. (2004). Gender differences in risk factors and consequences for alcohol use and problems. *Clinical Psychology Review, 24*(8), 981–1010. https://doi.org/10.1016/j.cpr.2004.08.003

Randall, C. L., Roberts, J. S., Del Boca, F. K., Carroll, K. M., Connors, G. J., & Mattson, M. E. (1999). Telescoping of landmark events associated with drinking: a gender comparison. *J Stud Alcohol, 60*(2), 252–260. https://doi.org/10.15288/jsa.1999.60.252

Rivas, I., Sanvisens, A., Bolao, F., Fuster, D., Tor, J., Pujol, R., . . . Muga, R. (2013). Impact of medical comorbidity and risk of death in 680 patients with alcohol use disorders. *Alcohol Clin Exp Res*, *37 Suppl 1*, E221–227. https://doi.org/10.1111/j.1530-0277.2012.01861.x

Rosoff, D. B., Charlet, K., Jung, J., Lee, J., Muench, C., Luo, A., . . . Lohoff, F. W. (2020). Lipid profile dysregulation predicts alcohol withdrawal symptom severity in individuals with alcohol use disorder. *Alcohol*, *86*, 93–101. https://doi.org/10.1016/j.alcohol.2020.02.164

Sanvisens, A., Rivas, I., Bolao, F., Tor, J., Rosón, B., Rey-Joly, C., & Muga, R. (2011). Gender and liver, nutritional and metabolic alterations of severe alcoholism: A study of 480 patients. *Medicina Clínica (barcelona), 137*(2), 49–54. https://doi.org/10.1016/j.medcli.2010.11.030. Géneroyalteraci oneshepáticas,nutricionalesymetabólicasdelalcoholismograve:estudiode480pacientes.

Sanvisens, A., Zuluaga, P., Short, A., Rubio, G., Gual, A., Torrens, M., . . . Muga, R. (2021). Sex-specific Associations of Alcohol Withdrawal in Patients Admitted for the Treatment of Alcohol Use Disorder. *J Addict Med*, *15*(1), 68–73. https://doi.org/10.1097/adm.0000000000000704

Schutte, K. K., Hearst, J., & Moos, R. H. (1997). Gender differences in the relations between depressive symptoms and drinking behavior among problem drinkers: A three-wave study. *Journal of Consulting and Clinical Psychology, 65*(3), 392–404. https://doi.org/10.1037//0022-006x.65.3.392

Sjoerds, Z., van Tol, M. J., van den Brink, W., van der Wee, N. J., Aleman, A., Beekman, A. T., . . . Veltman, D. J. (2013). Family history of alcohol dependence modulates functional neurophysiology in mood/anxiety disorders. *Psychol Med*, *43*(7), 1487–1497. https://doi.org/10.1017/s003329171200222x

Slade, T., Chapman, C., Swift, W., Keyes, K., Tonks, Z., & Teesson, M. (2016). Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. *BMJ Open, 6*(10), e011827. https://doi.org/10.1136/bmjopen-2016-011827

Timko, C., Debenedetti, A., Moos, B. S., & Moos, R. H. (2006). Predictors of 16-year mortality among individuals initiating help-seeking for an alcoholic use disorder. *Alcoholism, Clinical and Experimental Research, 30*(10), 1711–1720. https://doi.org/10.1111/j.1530-0277.2006.00206.x

White, A. M. (2020). Gender Differences in the Epidemiology of Alcohol Use and Related Harms in the United States. *Alcohol Res, 40*(2), 01. https://doi.org/10.35946/arcr.v40.2.01

White, A. M., Castle, I. P., Hingson, R. W., & Powell, P. A. (2020). Using Death Certificates to Explore Changes in Alcohol-Related Mortality in the United States, 1999 to 2017. *Alcoholism, Clinical and Experimental Research, 44*(1), 178–187. https://doi.org/10.1111/acer.14239

White, A. M., Slater, M. E., Ng, G., Hingson, R., & Breslow, R. (2018). Trends in Alcohol-Related Emergency Department Visits in the United States: Results from the Nationwide Emergency Department Sample, 2006 to 2014. *Alcoholism, Clinical and Experimental Research, 42*(2), 352–359. https://doi.org/10.1111/acer.13559

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