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Effects of Age, Sex, Body Weight, and Quantity of Alcohol Consumption on Occurrence and Severity of Alcoholic Hepatitis

Suthat Liangpunsakul, MD, MPH^{1,2}, Puneet Puri, MD³, Vijay Shah, MD⁴, Patrick Kamath, MD⁴, Arun Sanyal, MD³, Thomas Urban, Ph.D⁵, Xiaowei Ren, Ph.D⁶, Barry Katz, Ph.D⁶, Svetlana Radaeva, Ph.D⁷, Naga Chalasani, MD¹, and David W. Crabb, MD^{1,8} for the TREAT Consortium

¹Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

²Roudebush Veterans Administration Medical Center, Indianapolis, IN

³Division of Gastroenterology and Hepatology, Department of Medicine, Virginia Commonwealth University, Richmond, VA

⁴Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

⁵Division of Pharmacotherapy and Experimental Therapeutics, Center for Pharmacogenomics and Individualized Therapy, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC

⁶Department of Biostatistics, Indiana University School of Medicine and Richard M. Fairbanks School of Public Health

⁷National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD

⁸Eskenazi Health, Indianapolis, IN

Abstract

Background & Aims—Only a minority of heavy drinking individuals develop alcoholic hepatitis (AH), for unclear reasons. We analyzed data from the Translational Research and Evolving Alcoholic Hepatitis Treatment cohort: subjects who drink heavily with normal results from liver tests (controls) and patients with AH. We examined risk factors for the development of AH including body mass index (BMI), drinking pattern and quantity, and sex.

CORRESPONDENCE: Suthat Liangpunsakul, MD MPH, Associate Professor of Medicine, Biochemistry and Molecular Biology, Division of Gastroenterology and Hepatology, 550 N. University Blvd, UH 4100, Indianapolis, IN 46202, Phone: (317) 278-1630, Fax: (317) 988-3180, sliangpu@iupui.edu.

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Roles of authors

All authors have read and approved the manuscript for submission. All have made a substantial contribution to the conception, design, gathering, analysis and/or interpretation of data and a contribution to the writing and intellectual content of the article; and acknowledge that they have exercised due care in ensuring the integrity of the work

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Methods—We compared data from 145 patients with AH cases and 124 controls, based on BMI when they joined the cohort; groups were matched for sex and race. Drinking patterns were assessed using the time line follow back method, the Alcohol Use Disorders Identification Test, and National Institute of Alcohol Abuse and Alcoholism 6-question survey. We performed univariable and multivariable analyses to assess effects of these factors and their interaction in increasing the risk for AH. We also explored the association between *PNPLA3* variants and AH.

Results—Cases with AH were older (47 vs 44 years; $P=.03$). For nearly all measures of quantity of alcohol consumed or frequency of binge drinking, controls drank more heavily than cases with AH. We did not find an association between BMI, sex, drinking patterns, and the presence of AH. Age and BMI were independent predictors for severity of AH. When we analyzed cases and controls of European ancestry, the *PNPLA3* single nucleotide polymorphism rs738409 was associated with risk for AH (odds ratio, 1.89; $P=.007$).

Conclusion—Compared with heavy drinkers without liver disease, subjects with AH consumed lower levels of alcohol and had less binge drinking, suggesting an increased sensitivity to the toxic effects of alcohol. The risk for AH may be associated with the *PNPLA3* rs738409 polymorphism.

Keywords

TREAT; alcohol intake; gender; TLFB

INTRODUCTION

Alcoholic liver disease (ALD) represents a spectrum of clinical illness and pathological change in individuals with acute and chronic alcohol consumption. Patients may have minimal abnormalities ranging from steatosis to more severe signs and symptoms of liver disease associated with inflammation and fibrosis seen in alcoholic hepatitis or cirrhosis¹. Despite the fact that the relationship between alcohol consumption and liver disease is well established, severe alcohol-related morbidity and ALD only develop in a small minority of excessive drinkers¹. This observation suggests that there are other factors that alter the risk of AH from excessive alcohol use. Delineation of such factors could lead to screening for ALD and institution of more intensive treatment for heavy drinking.

The quantity of alcohol consumed is a major factor placing one at risk for ALD. However, studies have shown that such risk may also depend on the *patterns* of alcohol intake, independently of the absolute levels of consumption. For instance, binge drinking (too much too fast) and chronic excessive drinking (too much too often) have been cited as significant determinants of risk for ALD^{2, 3}. It is important to note that a precise study of the relationship between development of ALD and the quantity of alcohol consumed is almost unachievable, because data collection always involves different definitions and subjective estimates of alcohol consumption. The greater vulnerability of women and lower safe limits for alcohol consumption have long been recognized⁴. At any given level of alcohol intake, women had a significantly higher relative risk of developing ALD than men. However, in the Dionysos study, the risk for ALD for both sexes was comparable when the consumption exceeded 30 gram of alcohol/day³.

Another modifiable risk factor for the development of ALD is body weight. In an epidemiological study from the US, overweight and obesity increased the risk of alcohol-related abnormal alanine aminotransferase activity⁵. Another large study from France showed that the presence of excess weight for at least 10 years is a risk factor for AH and alcohol-associated cirrhosis⁶.

Alcoholic hepatitis (AH) is the most florid manifestation of ALD and is associated with high mortality⁷. The majority of patients with severe AH have fibrosis on biopsy at presentation, and approximately 10% to 20% of patients with AH are likely to progress to clinically obvious cirrhosis annually⁸. While quantity of alcohol consumption, gender, and body weight have been associated with the overall risk for ALD, less is known about the associations of these factors for AH specifically. The DIONYSOS study of patterns and types of beverages consumed combined steatosis and AH in the non-cirrhotic liver disease group without doing subgroup analysis³. Naveau et al., on the other hand, found that female gender and obesity were risk factors for AH; however, in the multivariable analysis, the amount of alcohol consumed did not correlate with the risk of AH⁶. Since the development of AH may be a common pathway to cirrhosis for many patients, confirmation of these results in an American population, and multivariable analysis of interactions between these various risk factors are of interest, particularly given the growing number of Americans who are overweight or obese.

The purpose of the present study was to examine the effect of drinking patterns, gender, body weight and their interactions on the risk for AH in a well-characterized cohort of subjects who were recruited by the **T**ranslational **R**esearch and **E**volving **A**lcoholic hepatitis **T**reatment (TREAT) consortium.

METHODS

See full details in Supplementary material.

RESULTS

Demographic and clinical characteristics of the study cohort

The detailed characteristics of the study cohort are summarized in Table 1. Subjects with AH were older than controls (47 vs. 44 yr, $p=0.03$). Among AH cases, the majority of subjects were men (60%) and White (88%). There were no differences in the mean BMI between the groups; and the percentage of individuals with a BMI>25 was not significantly different (67% of cases vs 63% of the controls ($p = 0.445$)). As expected from the inclusion criteria, the liver tests were worse in the cases than the controls, and the MELD scores higher. The cases had lower hemoglobin and platelet counts, and higher leukocyte counts; serum creatinine was slightly higher in the cases.

Quantity and patterns of alcohol consumption in controls and AH cases

The drinking patterns of the cases with AH and control subjects are shown in Table 2. Total drinks and average drinks per drinking day during the 30 days prior to recruitment and estimated drinks in the past year (assessed from the TLFB survey) were significantly lower

in cases compared to controls. Using a definition of binge drinking as more than 4 drinks/day for men or more than 3 drinks for women, more of the controls were classified as binge drinkers. Using an episodic drinking score, the controls drank more episodically (they were more likely to drink larger amounts on fewer days) than the cases (more likely to drink on more days). Among subjects with AH, the episodic drinking score was higher in men than that in women (28 ± 43 vs. 15 ± 18 , $p = 0.04$). This was confirmed using AUDIT and NIAAA six question results: more control patients reported daily binge drinking, and more also reported weekly binge drinking than did the patients with AH. Total drinks in the past year calculated from the NIAAA questions were significantly higher for the controls than the cases. The results were similar to those calculated from the TLFB. Among subjects with AH, men had a higher estimated number of drinks in the past year based on NIAAA questions compared to women ($3,200 \pm 2,520$ vs. $2,353 \pm 2,273$, $p = 0.04$). One final measure was the maximum number of drinks ever consumed in one day: 50% of the controls and 40% of the cases reported drinking more than 23 drinks in 24 hours (not significant).

When we stratified the alcohol consumption data by gender for the cases vs controls; we observed that the total alcohol consumption in the past 30 days (total drinks and average drinks per drinking day) was similar between men and women within the control and case groups. The episodic drinking score was higher in the women than the men in the case, but not control, group. There were no differences in the binge drinking measures between men or women within the control or case groups (Table 2). Men reported higher maximum drinks on a single occasion than women in both the controls and cases.

We also examined the differences in alcohol drinking quantity and pattern between men with and without AH, and women with and without AH (Table 2). For the men, the controls had higher total drinks and average drinks per drinking day, and a higher percentage of binge drinking daily than the men with AH. For women, the controls had higher total drinks and average drinks per day, higher episodic drinking scores, and higher binge drinking daily or weekly (NIAAA questions) than did the women with AH. There were no differences in maximum drinks on one occasion between men and women with and without AH.

Taken together, these data show that the patients with AH had less exposure to alcohol (quantity consumed), and were less likely to binge drink than the control patients, suggesting that the subjects with AH were more susceptible to the toxic effects of alcohol.

The association between the quantity and pattern of alcohol consumption and the effect of gender and BMI on AH

Previous studies have suggested that overweight or obese patients, and women, are at greater risk of developing AH⁶. We therefore examined the interactions between BMI and gender and either total alcohol consumption in the last 30 days (Table 3) or a history of binge drinking (Table 4) and the diagnosis of AH.

There was no association between total alcohol consumption in the past 30 days, BMI, and gender and increased risk for AH (Table 3), nor an interaction between these factors. The same results were found when we analyzed the association between pattern of drinking (using the NIAAA questionnaire reflecting daily binge drinking) and increased risk for AH

(Table 4). When compared to controls, heavier alcohol use and binge drinking were inversely associated with the presence of AH because of the higher levels of drinking observed in the control group than in the cases (Table 2). We did not find any interaction between BMI, gender, and binge drinking and the presence of AH.

The effect of age, gender, and BMI on the severity of AH

We next assessed interactions between age, gender, and BMI on the severity of AH, as indicated by MELD scores (Table 5). In the unadjusted linear regression model, we found that age was inversely associated with the MELD scores (β estimate -0.09 , $p = 0.0004$). Women and subjects with higher BMI were likely to have more severe AH. However, in the adjusted model, only age (β estimate -0.18 , $p = 0.0005$) and BMI (β estimate 0.31 , $p < 0.001$) were independent predictors for severity of AH. The interaction of gender and BMI was not statistically significant ($p = 0.06$).

The association between PNPLA3 polymorphism and AH

Our data indicated that when compared to heavy drinkers without liver disease, the cases developed AH despite consuming less alcohol, suggesting they are more susceptible to the hepatotoxicity of alcohol, which could reflect a genetic susceptibility. A recent meta-analysis showed that the rs738409 variant of *PNPLA3* was associated with alcoholic liver cirrhosis¹³; however, the association between this *PNPLA3* variant and AH has not been studied.

We focused our analyses on *PNPLA3* polymorphism on those of European ancestry among 124 controls and 145 cases with AH. Ninety cases with AH and 93 controls met this criterion. The quantity and patterns of alcohol consumption among these subjects are shown in Supplementary material, Table S1. The overall *Minor allele frequency* (MAF) of *PNPLA3* rs738409 was 0.34 in cases, and 0.22 in controls ($p = 0.007$, OR 1.89 (95% CI 1.171 – 3.056), Supplementary material, Table S2). The relationship between rs738409 genotype and age, gender and BMI was assessed, but none of the statistical tests (both parametric and non-parametric) reached significance (Supplementary material, Table S3), suggesting that age, gender and BMI are not associated with rs738409 genotype.

DISCUSSION

The major findings in our study are the following: 1) the total amount of alcohol consumption in the last 30 days, and rates of binge drinking were significantly lower in cases with AH when compared to controls, 2) age was inversely associated with the severity of AH, 3) subjects with higher BMI had higher risk for severe AH, and 4) the rs738409 variant of *PNPLA3* may be associated with risk for AH, independently from age, gender, and BMI.

Information is limited on the effect of age, gender, body weight, and the quantity and frequency of alcohol consumption and the risk of AH, as several previous studies focused mainly on alcoholic cirrhosis^{14, 15}. The risk for alcoholic cirrhosis in general is related to the quantity of alcohol consumed^{14, 15}. A meta-analysis found that consumption of more than 25 g/day increased the relative risk of cirrhosis¹⁶; and that the threshold for harm is lower

for women^{17, 18}. In addition to drinking frequency, episodic or binge drinking has been associated with an increased risk of alcoholic cirrhosis^{19, 20}. Although alcohol itself is an important risk factor for ALD, as previously observed by numerous groups, and conclusively proven by Lieber in his baboon feeding experiments²¹, only a subset of subjects who consume alcohol excessively develop liver disease; suggesting that other risk factors besides the amount of alcohol must be important for alcohol-associated liver disease¹.

Our study is perhaps the first to examine the various measures of alcohol use (quantity, frequency of binge drinking) between heavy drinking patients with normal liver tests and heavy drinking patients with alcoholic hepatitis, using validated questionnaires to quantify these measures. All of the patients in our cohorts drank more than the thresholds for alcoholic liver disease cited above, and most were drinking at a level which confounds the determination of binge drinking. The notion of binge drinking as a risk for alcoholism and liver injury is based on the definition of more than 3 or 4 drinks within a two hour period, a level of drinking expected to raise the blood alcohol level to 80 mg/dL or more. This is the measure assessed in the NIAAA six question survey. Since nearly all of the control patients reported binge drinking nearly daily or weekly, as did 75% of the cases, this formal definition of binge drinking does not discriminate between those with and without liver injury, nor did it appear to contribute to severity of the AH. This may simply be a reflection of the very high levels of drinking we observed in both groups: the average drinks per drinking day exceeded the threshold for binge drinking by about two-fold. In a similar vein, measures of total alcohol consumption in the last month or year did not predict the occurrence of AH. While we did not collect information about the age of onset of heavy drinking, the fact that the AH cases were only slightly older than the controls suggests that total duration of drinking is not a strong determinant of the development of AH. Further, our data suggest that beyond a threshold of heavy drinking, there is not a direct relationship between amount or pattern of drinking and the occurrence of AH. This is consistent with the data reported by Naveau et al. when they compared alcohol consumption between heavy drinkers with normal liver biopsies and those with pure (i.e., not cirrhotic) AH⁶. We note that our control patients reported drinking approximately 50% more alcohol (converting the drinks per month to grams of absolute alcohol per day) than the French patients with normal histology, while our patients with AH drank at nearly the same level. The fact that the subjects with AH were drinking less than the controls points to some other factors in addition to alcohol per se that predisposed them to liver injury.

We examined three other potential risk factors which had previously been suggested to contribute to AH risk, age, gender, and BMI, and looked for interactions with measures of alcohol consumption. We found that age at presentation is inversely associated with the severity of AH, as measured by MELD scores, i.e. that older patients are likely to present with less severe AH. Our findings are consistent with a previous report which showed that younger people are at higher risk to develop AH^{22, 23}. The reason behind this observation is unclear, but might be consistent with the development of AH in patients with a genetic predisposition (however, we did not see an association of the *PNPLA3* risk allele and age of diagnosis). On the other hand, a recent study reported that older age at onset of heavy drinking (after age 24), was associated with increased risk of developing cirrhosis (alcoholic hepatitis was not studied), with shorter duration of heavy drinking, lower daily alcohol

consumption, and worse Child-Pugh score at diagnosis²⁴. A possible explanation is that there is a greater risk of developing AH as well as cirrhosis in those who begin drinking heavily after age 24, with more rapid progression and presentation with more severe disease; this would have been observed in our cohort as less severity in those presenting at an older age. Women tend to develop higher blood alcohol concentrations per unit of alcohol consumed due to their lower volume of distribution for alcohol⁴. High levels of estrogen in women may cause alterations in gut permeability to endotoxin and accordingly up-regulate endotoxin receptors on Kupffer cells, leading to an increased production of tumor necrosis factor in response to endotoxin and the risk of ALD²⁵, and higher BMI in women is expected to be associated with elevated levels of estradiol (generated, particularly after menopause from the conversion of androgens to estrogen in the adipose tissue)²⁶. In our study, we found that women are at greater risk for severe AH; however, the association disappeared after controlling for other covariates. Naveau et al.⁶ reported that obesity increased the risk of AH without cirrhosis. We found that BMI is an independent predictor for severe AH (and our inclusion criteria included patients with AH superimposed on cirrhosis). Increasing body weight may predispose patients to hepatotoxicity of alcohol because of the inflammatory nature of obesity, a greater degree of steatosis, or other factors.

PNPLA3 gene is located on the long arm of chromosome 22 and codes for the protein adiponutrin²⁷. Tian et al. found a significant association between *PNPLA3* rs738409 and alcoholic cirrhosis and the results were confirmed in a German cohort²⁸ and the study by Buch et al.²⁹. *PNPLA3* rs738409 (G/G) carriers represent a genetically defined subpopulation of high-risk patients susceptible to progression from clinically-silent to overt ALD. Interestingly, our preliminary results also show the association between this variant and the risk for AH. We are currently investigating this finding, and other possible leads to genetic predisposition to AH, in more detail.

The strengths of this study are the prospective design, inclusion of well characterized heavy drinking control group, the extensive assessment of drinking behavior, and its large sample size. A limitation common to all studies of long term alcohol consumption is the validity of self-reported drinking. We attempted to overcome this by using three different questionnaires to assess the quantity as well as pattern of drinking. We also considered the quantity of drinking over the past year, based on the fact that many patients with AH may have reduced or stopped alcohol within the weeks preceding the episode of AH. Regardless of the methods to determine the levels as well as drinking pattern, we found that subjects with AH were drinking less than the controls. The important conclusion is that beyond a certain level of heavy drinking, the amount of alcohol consumed does not appear to be a specific risk factor for development of AH. Further, our alcohol consumption data are cross sectional and we have no way of knowing what the total exposure to alcohol was in either group. Other limitations include the impracticality of performing a liver biopsy on all patients, and the ethical impossibility to perform biopsy in controls, to be certain of the diagnosis. It is possible that our subjects could have any degree of liver disease from no fibrosis to cirrhosis. The use of non-invasive tool such as ultrasound has high specificity for cirrhosis; however, its low sensitivity prohibits its use as a screening modality³⁰. In future studies, Fibroscan might be useful in further characterizing the controls and cases, recognizing the effect of heavy drinking per se on the liver stiffness measurement. It is worth

noting that none of the control patients developed clinical liver disease in the year of follow up. Understanding the baseline hepatic pathology is of importance, as it is possible that development of fibrosis or cirrhosis indeed predisposes the patient to the development of AH. Alternatively, sub-clinical AH may be a precursor to fibrosis and cirrhosis. These hypotheses cannot be directly tested due to the cross sectional study design of our study.

In conclusion, we found that when compared to heavy drinkers without liver disease, subjects with AH had lower levels of alcohol consumption and less binge drinking. Younger subjects, and those with high BMI are at risk for more severe AH at presentation. The risk for AH appears to be associated with the presence of *PNPLA3* polymorphism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AH	Alcoholic hepatitis
ALD	Alcoholic liver disease
BMI	Body mass index
MELD	Model for end stage liver disease
TLFB	Timeline Follow Back

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Members of the TREAT Consortium

TREAT Consortium: The consortium was established with the funding from the NIH/NIAAA to study the pathogenesis and new treatments for AH. It consists of 3 academic centers in the US: Indiana University (Indianapolis, IN), Mayo Clinic (Rochester, MN), and Virginia Commonwealth University (Richmond, VA).

Indiana University, Indianapolis, IN:

David Crabb, MD, Naga Chalasani, MD, Suthat Liangpunsakul, MD, Barry Katz, PhD, Spencer Lourens, PhD, Andy Borst, BS, Ryan Cook, MPH, Andy Qigui Yu, PhD, David Nelson, PhD, Romil Saxena, MD, Sherrie Cummings, RN, Megan Comerford, BS, Lakye Edwards, BS

Mayo Clinic, Rochester, MN:

Vijay Shah, MD, Gregory Gores, MD, Patrick Kamath, MD, Vikas Verma, PhD, Sarah Wilder, RN, BSN, Amy Olofson, RN, Amanda Schimek

Virginia Commonwealth University, Richmond, VA:

Arun Sanyal, MD, Puneet Puri, MD, Susan Walker, RN, MSN

The National Institute of Alcohol Abuse and Alcoholism (NIAAA)

Scientific/Program Collaborator: Svetlana Raedeva, PhD.

Table 1

Baseline demographic and clinical characteristics of the study cohort

Variables	Controls (N=124)	AH cases (N=145)	p-value
Age (years)	44 ± 12	47 ± 11	0.03
Men, n (%)	78 (63)	87 (60)	0.62
Race, White, n (%)	103 (83%)	128 (88%)	0.22
BMI (kg/m ²)	28.7±7.1	29.4±7.6	0.44
WBC (cells/mm ³)	7.1 ±2.8	11.6±8.2	<0.0001
Hemoglobin (g/dl)	13.0±2.1	10.0±1.9	<0.0001
Platelet counts (cells/mm ³)	245±72	145±87	<0.0001
T. Bilirubin (mg/dL)	0.5±0.3	13.7±11.6	<0.0001
INR	1.0±0.3	1.8 ±0.5	<0.0001
AST (U/L)	27±9	140±87	0.0001
ALT (U/L)	26±10	64±7	0.0001
Albumin (g/dL)	3.8±0.6	2.8±0.6	<0.0001
Creatinine (mg/dL)	0.8±0.3	1.0±0.8	0.05
MELD Scores	7.2±2.2	22.1±7.1	<0.0001

Table 2
The quantity and patterns of alcohol consumption in controls and AH cases and analyses stratified by gender

Drinking parameters	Controls (N=124)		AH Cases (N=145)		p-value		Controls (N=124)			AH Cases (N=145)		
	Men (n=78)	Women (n=46)	Men (n=87)	Women (n=58)	Men (n=87)	Women (n=58)	Men (n=87)	Women (n=58)	Men (n=87)	Women (n=58)	Men (n=87)	Women (n=58)
Based on TLFB												
Total drinks in the past 30 days (standard drinks)	379.4 ± 285.7	379.4 ± 285.7	245.3 ± 243.5	0.0001	370.1 ± 263.5*	395.0 ± 322.1 [^]	268.5 ± 257.3*	210.1 ± 218.7 [^]	0.64	0.16		
Average drink per drinking day	15.1 ± 10.8	15.1 ± 10.8	10.1 ± 8.8	0.0000	14.3 ± 9.1*	16.5 ± 13.1 [^]	11.2 ± 9.6*	8.5 ± 7.2 [^]	0.29	0.07		
Estimated drinks in the last year	4553 ± 3429	4553 ± 3429	2944 ± 2922	0.0001	4441 ± 3162*	4740 ± 3865 [^]	3222 ± 3087*	2521 ± 2624 [^]	0.6421	0.1642		
Episodic drinking score	43.2 ± 66.6	43.2 ± 66.6	22.7 ± 35.8	0.0017	35.9 ± 48.7	55.4 ± 88.1 [^]	27.6 ± 43.3	15.2 ± 17.6 [^]	0.1161	0.0444		
Based on AUDIT questionnaire												
% Binge drinking weekly	28 (22.6%)	28 (22.6%)	28 (19.3%)	0.5110	17 (21.8%)	11 (23.9%)	19 (21.8%)	9 (15.5%)	0.7861	0.3464		
% Binge drinking daily	82 (66.1%)	82 (66.1%)	75 (51.7%)	0.0171	53 (67.9%)*	29 (63.0%)	46 (52.9%)*	29 (50.0%)	0.5787	0.7353		
Based on NIAAA questionnaire												
Estimated drinks in the last year	3491.5 ± 2625.0	3491.5 ± 2625.0	2861.4 ± 2452.2	0.0430	3530.7 ± 2482.5	3425.2 ± 2877.8 [^]	3200.1 ± 2520.7	2353.4 ± 2273.0 [^]	0.8299	0.0413		
% Binge drinking weekly	46 (37.1%)	46 (37.1%)	36 (24.8%)	0.0296	27 (34.6%)	19 (41.3%) [^]	24 (27.6%)	12 (20.7%) [^]	0.4582	0.3480		
% Binge drinking daily	66 (53.2%)	66 (53.2%)	57 (39.3%)	0.0226	41 (52.6%)	25 (54.3%) [^]	37 (42.5%)	20 (34.5%) [^]	0.8481	0.3328		
NIAAA Q 6 answer 1 or 2	63 (50.8%)	63 (50.8%)	59 (40.7%)	0.0973	45 (57.7%)	18 (39.1%)	43 (49.4%)	16 (27.6%)	0.0467	0.0090		

* p<0.05, the differences between the variable of interest in men between cases and controls

[^] p<0.05, the differences between the variable of interest in women between cases and controls

Standard deviation shown in parentheses after the mean value.

Table 3

Multivariable analysis of the effect of total alcohol consumption in the past 30 days, gender and BMI on alcoholic hepatitis

Parameters	Odds Ratio (95%CI)	p-value	p-value for total drinks and gender interaction	p-value for total drinks and BMI interaction
Age	1.01 (0.99–1.04)	0.16	-	-
Race (white vs. Non-White)	1.53 (0.74–3.15)	0.24	-	-
Total drinks in the past 30 days (standard drinks)	0.99 (0.99–0.99)	0.003	-	-
Gender (Men vs. Women)	0.89 (0.53–1.50)	0.66	-	-
BMI	1.01 (0.97–1.04)	0.61	-	-
Total drinks in the past 30 days (standard drinks)*Gender	-	-	0.95	-
Total drinks in the past 30 days (standard drinks)*BMI	-	-	-	0.77

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Table 4

Multivariable analysis of the effect of binge drinking, gender and BMI on alcoholic hepatitis

Parameters	Odds Ratio (95%CI)	p-value	p-value for binge drinking and gender interaction	p-value for binge drinking and BMI interaction
Age	1.02 (0.99–1.04)	0.07	-	-
Race (white vs. Non-White)	1.48 (0.70–3.14)	0.30	-	-
Binge drinking	0.13 (0.04–0.39)	0.0003	-	-
Gender (Men vs. Women)	0.97 (0.56–1.65)	0.91	-	-
BMI	1.02 (0.98–1.05)	0.34	-	-
Binge drinking*Gender	-	-	0.95	-
Binge drinking*BMI	-	-	-	0.62

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Table 5

Linear regression analysis on the effect of BMI and gender and severity of AH

Parameters	Beta-estimate Unadjusted	p-value	Beta-estimate Adjusted	p-value	Beta-estimate Interactions between BMI and gender	p-value
Age	-0.19	0.0004	-0.18	0.0005	-	-
Gender (Women vs. Men)	2.58	0.03	1.70	0.1284	-	-
BMI	0.30	<.0001	0.31	<.0001	-	-
Gender*BMI	-	-	-	-	-0.25	0.06