

Nonheavy Alcohol Use Associates With Liver Fibrosis and Nonalcoholic Steatohepatitis in the Framingham Heart Study

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BACKGROUND AND AIMS:

While heavy alcohol use consistently associates with liver disease, the effects of nonheavy alcohol consumption are less understood. We aimed to investigate the relationship between nonheavy alcohol use and chronic liver disease.

METHODS:

This cross-sectional study included 2629 current drinkers in the Framingham Heart Study who completed alcohol use questionnaires and transient elastography. We defined fibrosis as liver stiffness measurement (LSM) ≥ 8.2 kPa. We defined at-risk nonalcoholic steatohepatitis (NASH) as FibroScan-aspartate aminotransferase (FAST) score >0.35 (90% sensitivity) or ≥ 0.67 (90% specificity). We performed logistic regression to investigate associations of alcohol use measures with fibrosis and NASH, adjusting for sociodemographic and metabolic factors. Subgroup analysis excluded heavy drinkers (>14 drinks per week for women or >21 for men).

RESULTS:

In this sample (mean age 54.4 ± 8.9 years, 53.3% women), mean LSM was 5.6 ± 3.4 kPa, 8.2% had fibrosis, 1.9% had NASH by FAST ≥ 0.67 , and 12.4% had NASH by FAST >0.35 . Participants drank 6.2 ± 7.4 drinks per week. Total drinks per week and frequency of drinking associated with increased odds of fibrosis (adjusted odds ratio [aOR], 1.18; 95% confidence interval [CI], 1.04–1.33; and aOR, 1.08; 95% CI, 1.01–1.16, respectively). Risky weekly drinking, present in 17.4%, also associated with fibrosis (aOR, 1.49; 95% CI, 1.03–2.14). After excluding 158 heavy drinkers, total drinks per week remained associated with fibrosis (aOR, 1.16; 95% CI, 1.001–1.35). Multiple alcohol use measures positively associated with FAST >0.35 .

CONCLUSIONS:

In this community cohort, we demonstrate that nonheavy alcohol use associates with fibrosis and NASH, after adjustment for metabolic factors. Longitudinal studies are needed to determine the benefits of moderating alcohol use to reduce liver-related morbidity and mortality.

Keywords: Moderate Alcohol Use; Alcohol-Related Liver Disease; Nonalcoholic Fatty Liver Disease.

Nonalcoholic fatty liver disease (NAFLD) and alcohol-related liver disease, the most common causes of chronic liver disease worldwide, are histologically identical and distinguished only by the presence of significant alcohol use.¹ Heavy alcohol use is defined by consensus guidelines of the American Association for the Study of Liver Diseases (AASLD) as >14 alcoholic drinks per week for women or >21 drinks per week for men² and consistently associates with steatohepatitis and cirrhosis.³ In contrast, studies of nonheavy alcohol use on liver health are conflicting, both within the general population^{4–7} and among individuals at risk for NAFLD^{8–10} or with known NAFLD.^{11–13} Additionally, evidence suggests that the pattern of alcohol consumption may be an important predictor of the health effects of alcohol.¹⁴ However, alcohol research frequently focuses on average daily or weekly alcohol consumption, possibly obscuring differences in drinking patterns

such as drinking frequency, the usual quantity of alcohol consumed, and binge drinking behavior.

Recently, we observed an association of different alcohol use patterns, particularly increased weekly drinking and binge drinking, with hepatic steatosis in a sample of nonheavy alcohol users.¹⁵ Whereas it is difficult to predict which individuals with steatosis will progress to more significant liver disease, fibrosis

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Diseases; aOR, adjusted odds ratio; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; FAST, FibroScan-aspartate aminotransferase; HDL, high-density lipoprotein; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; VCTE, vibration-controlled transient elastography.

demonstrated by vibration-controlled transient elastography (VCTE) has been shown to independently associate with important liver outcomes including hepatic decompensation, hepatocellular carcinoma, and liver-related death in populations with NAFLD and alcohol-related liver disease.^{16,17} With a paucity of available NAFLD treatments, understanding factors associated with fibrosis is critical for counseling patients on preventative and mitigation strategies.

Many confounding factors in the relationship between alcohol use and liver disease have not been adequately addressed in prior research. For example, studies comparing current drinkers with nondrinkers may underestimate alcohol-related risk, as nondrinkers are a heterogeneous group of never and former drinkers who may have stopped drinking due to prior heavy use or other confounding factors such as chronic disease. Moreover, we do not know if nonheavy alcohol use impacts tools used to identify those with active nonalcoholic steatohepatitis (NASH) who are most in need of therapy, such as the FibroScan-aspartate aminotransferase (FAST) score.¹⁸

We therefore aimed to investigate the association between various alcohol use measures (including total consumption and several drinking patterns) and VCTE-defined fibrosis among a cohort of community dwellers, and specifically among nonheavy alcohol users whose liver disease, based on current nomenclature, would be presumed nonalcoholic. We also aimed to examine relationships between the FAST scores and these same alcohol use measures.

Materials And Methods

Study Sample

Our cross-sectional study sample was drawn from the Framingham Heart Study, a longitudinal multigenerational cohort study of chronic disease.¹⁹ The original cohort was recruited as a random sample of free-living adults 30–59 years of age residing in the town of Framingham, Massachusetts, in 1948, with additional volunteers from the town.²⁰ All persons who agreed to participate underwent an initial exam, and those with definite evidence of cardiovascular disease were excluded. Over time, adult offspring of participants were invited to enroll in additional cohorts, with no additional exclusion criteria.¹⁹ All participants in the Third Generation and Omni 2 cohorts who presented for an exam April 2016 to April 2019 were eligible to participate in our study. All participants were administered a clinician-directed questionnaire regarding alcohol use and were offered a VCTE to assess hepatic fibrosis, except for those who were pregnant, had implanted medical devices, or could not properly position for the examination. Exams with interquartile range-to-median ratio >0.30 when the median liver stiffness measurement (LSM) was ≥ 7.1 kPa

What You Need to Know

Background

The relationship between alcohol use and chronic liver disease is incompletely understood, particularly in the consumption range that qualifies as nonalcoholic liver disease.

Findings

In a community cohort with few heavy drinkers, multiple alcohol use measures significantly associated with fibrosis on transient elastography and high-risk nonalcoholic steatohepatitis (measured by FibroScan-aspartate aminotransferase score).

Implications for patient care

Nonheavy alcohol use may contribute to fibrosis and nonalcoholic steatohepatitis, both of which predict negative liver-related outcomes and mortality. Nonheavy alcohol use should be considered as a factor contributing to more advanced nonalcoholic fatty liver disease phenotypes.

were considered invalid due to low reliability. Covariate data were collected during the exam visit with the exception of race or ethnicity, income, and education level which were collected at Framingham Heart Study enrollment 2002–2005. As detailed in [Figure 1](#), participants were excluded if they did not undergo VCTE, if VCTE data were invalid ($n = 76$), if data on alcohol use or covariates were missing ($n = 181$), or if they were nondrinkers at the time of the exam ($n = 521$). All participants provided written informed consent and our study was approved by the Boston University Institutional Review Board.

Alcohol Use Measures

We asked participants to estimate the frequency of alcohol use (average number of drinking days per week over the past year) and the usual quantity of alcohol consumed (average number of drinks on a typical drinking day over the past year), and we multiplied these 2 values together to estimate the average total number of drinks per week. Based on the 2020 U.S. Dietary Guidelines for Americans, which recommend limiting alcohol use to 1 drink for women or 2 drinks for men during days when alcohol is consumed, we defined consumption in excess of dietary guidelines as ≥ 2 drinks per typical drinking day for women or ≥ 3 drinks per drinking day for men. We defined risky weekly drinking as >7 drinks per week for women or >14 for men.²¹ We defined heavy drinking as >14 drinks per week for women or >21 for men, based on AASLD consensus guidelines.² Participants also reported the maximum number of drinks in a 24-hour period over the past month. The Centers for Disease Control and Prevention and the

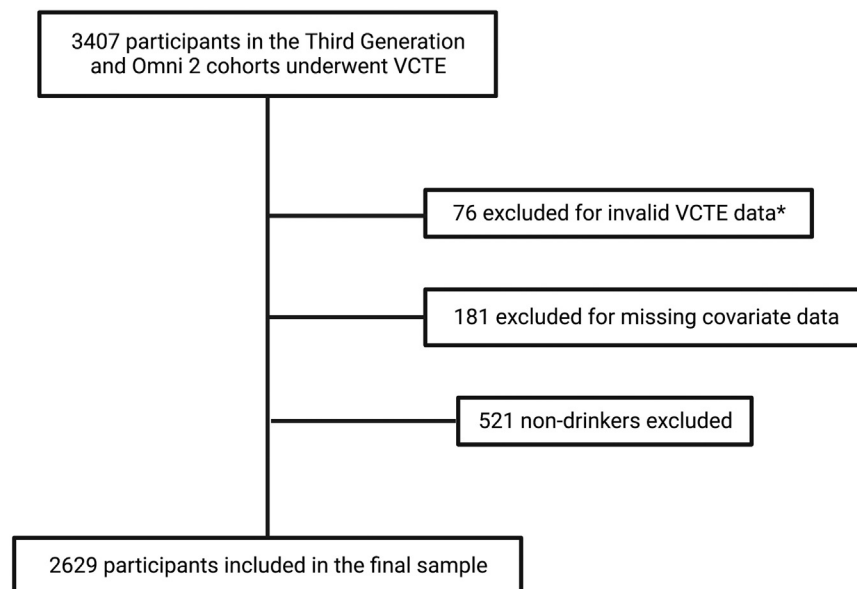


Figure 1. Flowchart of inclusion and exclusion criteria. *VCTE data were considered invalid if the interquartile range-to-median ratio was >0.30 with a median liver stiffness measurement ≥ 7.1 kPa.

National Institute on Alcohol Abuse and Alcoholism define binge drinking as ≥ 4 drinks for women or ≥ 5 drinks for men on a drinking occasion.^{22,23} Based on these guidelines, we defined binge drinking as ≥ 4 drinks within a 24-hour period over the last month for women or ≥ 5 for men, or answering yes to the question, “Since your last exam, has there been a time when you drank 5 or more alcoholic drinks of any kind almost daily?”

VCTE Measurements

LSM by VCTE and controlled attenuation parameter (CAP) were obtained by a certified operator using FibroScan 502 Touch (Echosens, Paris, France) using the M or the XL probe as recommended by the device automatic probe selection tool, as previously described.²⁴ At least 10 measurements were obtained from each participant and used by the device to calculate median values for CAP and LSM, as well as the interquartile range. A qualified hepatologist (M.T.L.) reviewed data from each exam independently of any participant data. Based on prior studies, we defined clinically significant fibrosis as LSM ≥ 8.2 kPa.^{25,26}

FAST Score

The FAST score was developed and validated by Newsome et al¹⁸ to predict at-risk NASH, defined by a fibrosis stage ≥ 2 and a NAFLD activity score ≥ 4 . It is calculated from the following equation combining LSM, CAP, and aspartate aminotransferase (AST):

$$\text{FAST} = \frac{e^{-1.65+1.07 \times \ln(\text{LSM})+2.66 \times 10^{-8} \times \text{CAP}^3-63.3 \times \text{AST}^{-1}}}{1 + e^{-1.65+1.07 \times \ln(\text{LSM})+2.66 \times 10^{-8} \times \text{CAP}^3-63.3 \times \text{AST}^{-1}}}$$

We used previously published thresholds of FAST >0.35 (90% sensitivity) and FAST ≥ 0.67 (90% specificity) to describe the prevalence of at-risk NASH in our cohort.

Covariates and Baseline Measurements

Physical activity index was calculated from participants' response to a questionnaire about daily number of hours of sedentary, light, moderate, and heavy activity.²⁷ The index ranges from a minimum score of 24, denoting 24 hours of resting state, to a maximum score of 120, denoting 24 hours of heavy activity. Participants were considered current smokers if they reported at least 1 cigarette per day over the prior year. Body mass index (BMI) was calculated using measured height and weight. We defined obesity as BMI ≥ 30 kg/m². Blood pressure was measured twice and averaged after participants sat in the upright position for at least 5 minutes. We defined hypertension as average systolic blood pressure ≥ 130 mm Hg, average diastolic blood pressure ≥ 85 mm Hg, or current use of antihypertensive medications. We defined diabetes as fasting plasma glucose ≥ 126 mg/dL, or the use of insulin or oral hypoglycemic medications. We defined impaired fasting glucose as fasting glucose ≥ 100 mg/dL, high triglycerides as fasting triglyceride level ≥ 150 mg/dL, and low high-density lipoprotein (HDL) as <50 mg/dL for women or <40 mg/dL for men. We classified participants as having the metabolic syndrome if they met 3 or more of the following criteria as defined by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: high waist circumference as >35 inches for women or >40 for men, high triglycerides, low HDL, systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, or fasting glucose ≥ 100 mg/dL.²⁸

Statistical Analysis

Our main outcome of interest was significant fibrosis (LSM ≥ 8.2 kPa), with at-risk NASH (FAST >0.35) as a secondary outcome. As expected, the prevalence of FAST

≥ 0.67 was low in our unselected, community-based cohort, so we limited the analysis to the lower FAST threshold of 0.35 to maximize sensitivity. We used descriptive statistics to summarize characteristics of the study sample with means and percentages. We checked variables for normality and log-transformed skewed distributions. We calculated logistic regression models to determine the association of alcohol use measures (modeled per standard deviation increase) with fibrosis and NASH. Model 1 adjusted for primary covariates (age, sex, cohort, income, education, physical activity, and smoking). Because metabolic factors are important potential confounders yet may also be part of the causal pathway between alcohol use and liver disease, we created a second model adding adjustment for each component of the metabolic syndrome (high waist circumference, high triglycerides, low HDL, hypertension, and impaired fasting glucose). We repeated analyses after excluding heavy alcohol users. An adjusted 2-sided alpha threshold of 0.05 was considered statistically significant. We performed the Benjamini-Hochberg procedure to account for multiple comparisons with a false discovery rate threshold of 0.05. Statistical analysis was done using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Study Sample Characteristics

As shown in [Table 1](#), the 2629 participants in our final sample were mostly women (53.3%) with a mean age of 54.4 ± 8.9 years. Mean BMI was 28.2 ± 5.5 kg/m², 7.2% had diabetes, and 26.9% met criteria for the metabolic syndrome. Participants drank a mean of 2.8 ± 2.2 days per week, with usual consumption of 2.0 ± 1.3 drinks per drinking day and mean total weekly alcohol consumption of 6.2 ± 7.4 drinks. The prevalence of binge drinking, risky weekly drinking, and heavy drinking were 33.1% (n = 871), 17.4% (n = 457), and 6% (n = 158), respectively. Mean LSM was 5.6 ± 3.4 kPa, and 8.2% had significant fibrosis (n = 215). Baseline characteristics after excluding heavy drinkers (n = 158) are shown in [Supplementary Table 1](#); mean LSM was unchanged and the prevalence of fibrosis was 8.0% (n = 197).

As shown in [Figure 2](#), using the 90% specificity threshold of FAST ≥ 0.67 classified 1.9% (n = 50) of participants as likely to have at-risk NASH, with higher prevalence in those with obesity (4.5% [n = 37]) or diabetes (9.5% [n = 18]). At the 90% sensitivity threshold of FAST > 0.35 , the prevalence of at-risk NASH was 12.4% (n = 327) overall; this was again higher in those with obesity (26.3% [n = 215]) or diabetes (34.4% [n = 65]).

Association of Alcohol Use Patterns with Fibrosis

As shown in [Table 2](#), increased total number of drinks per week associated with fibrosis (adjusted odds ratio

[aOR] 1.13; 95% confidence interval [CI], 1.00–1.27) in model 1. After additional adjustment for metabolic factors in model 2, fibrosis associated with increased total number of drinks per week (aOR, 1.18; 95% CI, 1.04–1.33), frequency of drinking days (aOR, 1.08; 95% CI, 1.01–1.16), and risky weekly drinking (aOR, 1.49; 95% CI, 1.03–2.14). Associations remained statistically significant after adjustment for multiple testing. When excluding heavy drinkers, increased total number of drinks per week still significantly associated with fibrosis (aOR, 1.16; 95% CI, 1.00–1.35; $P < .05$). Associations for frequency of drinking days (aOR, 1.06; 95% CI, 0.99–1.15) and risky weekly drinking (aOR, 1.48; 95% CI, 0.95–2.31) were attenuated.

Association of Alcohol Use Patterns With Elevated FAST Score

As shown in [Table 3](#), most alcohol use measures we evaluated were associated with FAST > 0.35 after multivariable adjustment. Results remained significant after adjusting for multiple comparisons, and were similar after excluding heavy alcohol users.

Discussion

In our community-based cohort with few heavy drinkers, we showed that multiple alcohol use measures positively associated with significant fibrosis defined by VCTE and at-risk NASH, both of which predict negative liver-related outcomes and mortality. Results were similar after adjusting for components of the metabolic syndrome and excluding participants with alcohol consumption above levels typically used to define fatty liver disease as nonalcoholic.² Although alcohol use may not be the primary driver of inflammation and fibrosis in persons with NAFLD, our results suggest that nonheavy alcohol use should be considered as a factor contributing to more advanced-NAFLD phenotypes. Current terminology categorizing liver disease as “alcoholic” or “nonalcoholic” is misleading and may hinder efforts to recognize the likely contribution of chronic alcohol use, even at nonheavy levels, to chronic liver disease.

These findings have significant implications for counseling patients with and without pre-existing NAFLD, especially as current AASLD guidelines do not make any recommendations regarding nonheavy alcohol use in NAFLD.² Our results reinforce the importance of encouraging all patients to reduce alcohol intake as much as possible, and to at least adhere to current U.S. dietary guideline–recommended limits.²¹ Almost half of participants in our study consumed in excess of these limits, which strongly associated with at-risk NASH. In addition, our finding that multiple alcohol use patterns associated with increased fibrosis or at-risk NASH merits further investigation into the importance of how patients use alcohol beyond simply quantifying the total amount of

Table 1. Characteristics of Study Sample

	Hepatic Fibrosis (n = 215) ^a	No Fibrosis (n = 2414)	Total Sample (N = 2629)
Age, y	56.3 ± 8.5	54.3 ± 8.9	54.4 ± 8.9
Female	94 (43.7)	1307 (54.1)	1401 (53.3)
Current smoking	23 (10.7)	228 (9.4)	251 (9.6)
Physical activity index	34.7 ± 6.7	33.9 ± 5.4	34 ± 5.6
Race			
White	202 (94)	2230 (92.5)	2432 (92.6)
Asian	3 (1.4)	36 (1.5)	39 (1.5)
Black	4 (1.9)	33 (1.4)	37 (1.4)
Hispanic	2 (0.9)	57 (2.4)	59 (2.3)
Other/mixed race	4 (1.9)	56 (2.3)	60 (2.3)
Education			
Some high school	1 (0.5)	18 (0.8)	19 (0.7)
High school graduate	38 (17.7)	267 (11.1)	305 (11.6)
Some college	60 (27.9)	705 (29.2)	765 (29.1)
College graduate	82 (38.1)	950 (39.4)	1032 (39.3)
Graduate degree	34 (15.8)	474 (19.6)	508 (19.3)
Income			
<\$12,000/y	1 (0.5)	41 (1.7)	42 (1.6)
\$12,000–\$24,999/y	10 (4.7)	91 (3.8)	101 (3.8)
\$25,000–\$49,999/y	32 (14.9)	422 (17.5)	454 (17.3)
\$50,000–\$74,999/y	53 (24.7)	571 (23.7)	624 (23.7)
\$75,000–\$100,000/y	54 (25.1)	540 (22.4)	594 (22.6)
>\$100,000/y	65 (30.2)	749 (31)	814 (31)
Metabolic and liver parameters			
Body mass index, kg/m ²	31.7 ± 7.1	27.9 ± 5.2	28.2 ± 5.5
Waist circumference, cm	108.2 ± 17.9	98.1 ± 14	98.9 ± 14.6
Diabetes ^b	49 (22.8)	140 (5.8)	189 (7.2)
Impaired fasting glucose ^b	98 (45.6)	800 (33.1)	898 (34.2)
Metabolic syndrome ^b	105 (48.8)	602 (24.9)	707 (26.9)
Hypertension ^b	134 (62.3)	918 (38)	1052 (40)
High triglycerides ^b	64 (29.8)	423 (17.5)	487 (18.5)
Low HDL cholesterol ^b	66 (30.7)	405 (16.8)	471 (17.9)
Liver stiffness measurement, kPa	12.4 ± 8.7	5 ± 1.28	5.6 ± 3.4
Controlled attenuation parameter, dB/m	297.2 ± 62.1	256.6 ± 53.3	259.9 ± 55.2
FibroScan-AST score			
<0.35	108 (50.2)	2194 (90.9)	2302 (87.6)
0.35–<0.67	73 (34)	204 (8.5)	277 (10.5)
≥0.67	34 (15.8)	16 (0.7)	50 (1.9)
FibroScan-AST score >0.35	107 (49.8)	220 (9.1)	327 (12.4)
Alcohol use measures			
Alcohol drinks per week	7.7 ± 10.6	6 ± 7	6.2 ± 7.4
Frequency of drinking days (per week)	3 ± 2.4	2.7 ± 2.2	2.8 ± 2.2
Usual quantity (drinks per drinking day)	2.2 ± 1.5	2 ± 1.3	2 ± 1.3

Table 1. Continued

	Hepatic Fibrosis (n = 215) ^a	No Fibrosis (n = 2414)	Total Sample (N = 2629)
Usual consumption in excess of dietary guidelines ^c	96 (44.7)	1037 (43)	1133 (43.1)
Risky weekly drinking ^c	46 (21.4)	411 (17)	457 (17.4)
Binge drinking ^c	71 (33)	800 (33.1)	871 (33.1)
Maximum drinks in 24 h in last month	3.7 ± 3.4	3.5 ± 2.7	3.5 ± 2.8
Heavy drinking ^c	18 (8.4)	140 (5.8)	158 (6)

Values are mean ± SD or n (%).

AST, aspartate aminotransferase; HDL, high-density lipoprotein.

^aDefined as liver stiffness measurement ≥8.2 kPa.

^bDiabetes was defined as fasting plasma glucose ≥126 mg/dL or the use of insulin or oral hypoglycemic medications. Impaired fasting glucose was defined as fasting glucose ≥100 mg/dL. Metabolic syndrome was defined as 3 or more of the following criteria: high waist circumference as >35 inches for women or >40 inches for men, high triglycerides, low HDL, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, or fasting glucose ≥100 mg/dL. Hypertension was defined as average systolic blood pressure ≥130 mm Hg, average diastolic blood pressure ≥85 mm Hg, or current use of antihypertensive medications. High triglycerides were defined as fasting triglyceride level ≥150 mg/dL. Low HDL cholesterol was defined as HDL <50 mg/dL for women or <40 mg/dL for men.

^cUsual consumption above U.S. dietary guidelines was defined as ≥2 drinks per drinking day for women or ≥3 drinks per drinking day for men. Risky weekly drinking was defined as >7 drinks per week for women and >14 drinks per week for men. Binge drinking was defined as ≥4 drinks for women or ≥5 drinks for men in 24 hours, or drinking ≥5 drinks almost daily. Heavy drinking was defined as >14 drinks per week for women or >21 drinks per week for men.

consumption. Further longitudinal studies are needed to understand the temporal relationship of nonheavy alcohol use and specific alcohol use patterns with liver disease, and to investigate potential benefits of reducing alcohol consumption among persons with NAFLD or NASH.

Our results also highlight the importance of understanding how alcohol use may affect tools used in NAFLD clinical trials to select candidates and assess outcomes, including the FAST score. Our finding that multiple alcohol use patterns significantly associated with NASH, at alcohol levels typically allowed in NAFLD clinical trials, suggests that clinicians should consider alcohol use when interpreting markers of NASH and raises concern that changes in drinking behaviors during the trial period may contribute to changes in indirect trial outcomes. As patients frequently change lifestyle and diet choices when enrolled in trials,²⁹ evaluating alcohol use both at trial entry and throughout the trial period may be necessary to account for alcohol use as a possibly significant confounding factor³⁰ when using the FAST score or other indirect measures.

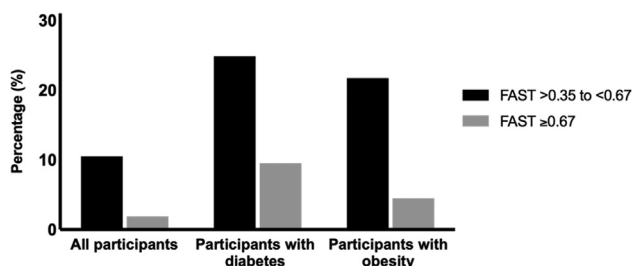


Figure 2. Prevalence of elevated FAST score among all participants and stratified by diabetes and obesity status.

Few other studies have investigated the relationship between nonheavy alcohol use and fibrosis in an unselected population. Our results support those of a recent large prospective study observing an association between moderate alcohol use and increased incidence of hepatic steatosis and elevated Fibrosis-4 index, another surrogate marker of fibrosis.³¹ While several cross-sectional analyses did not observe an association between moderate alcohol use and VCTE-defined fibrosis, they may not have adequately addressed confounding variables as they used nondrinkers as their reference group^{5,6,32} or did not exclude nondrinkers in the analysis.³³ This may bias results in favor of moderate drinkers for several reasons.^{14,34,35} Self-reported never-drinkers are often actually former drinkers, including people who stopped drinking due to poor health or former heavy alcohol use.^{36–38} Additionally, studies have shown significant differences in social and behavioral factors, health access, and health conditions between nondrinkers and moderate drinkers, with nondrinkers having higher BMI and lower levels of income, education, physical activity, and overall health status.^{39,40} In observational studies, the challenges of adequately accounting for all these differences may lead to residual confounding and underestimation of alcohol-related risk.

Our finding that nonheavy alcohol use may contribute to fibrosis and at-risk NASH is consistent with multiple population-based studies investigating alcohol and clinical liver-related outcomes.^{4,7,41–43} For example, the Finnish Health 2000 study demonstrated that among nonheavy alcohol users (<140 g/wk for women or <210 g/wk for men), drinking more alcohol per week associated with increased hospitalization for liver disease, hepatocellular carcinoma, and liver-related death.⁴

Table 2. Multivariable-Adjusted Logistic Regression Models for the Association Between Various Drinking Measures and Liver Fibrosis (LSM ≥ 8.2 kPa) in the Full Cohort, and in an Analysis Restricted to Nonheavy Drinkers

Alcohol Use Measure	Model 1 ^a		Model 2 ^a	
	aOR (95% CI)	P Value	aOR (95% CI)	P Value
Full cohort (N = 2629)				
Alcohol drinks per week	1.13 (1.00–1.27)	.047	1.18 (1.04–1.33)	.01
Frequency of drinking days (per week)	1.02 (0.96–1.10)	.52	1.08 (1.01–1.16)	.02
Usual quantity (drinks per drinking day)	1.06 (0.96–1.17)	.26	1.04 (0.93–1.15)	.51
Risky weekly drinking ^b	1.30 (0.92–1.85)	.01	1.49 (1.03–2.14)	.03
Usual consumption in excess of dietary guidelines ^b	1.16 (0.87–1.56)	.32	1.14 (0.84–1.55)	.39
Maximum drinks in 24 h in last month	1.02 (0.97–1.07)	.52	1.02 (0.97–1.08)	.38
Binge drinking ^b	0.97 (0.71–1.33)	.86	0.98 (0.71–1.36)	.91
Restricted to nonheavy drinkers (n = 2471)				
Alcohol drinks per week	1.08 (0.93–1.24)	.33	1.16 (1.001–1.35)	.049
Frequency of drinking days (per week)	1.00 (0.93–1.07)	.93	1.06 (0.99–1.15)	.10
Usual quantity (drinks per drinking day)	1.06 (0.93–1.20)	.38	1.02 (0.9–1.16)	.71
Risky weekly drinking ^b	1.26 (0.82–1.93)	.28	1.48 (0.95–2.31)	.08
Usual consumption in excess of dietary guidelines ^b	1.10 (0.80–1.50)	.57	1.07 (0.78–1.48)	.67
Maximum drinks in 24 h in last month	1.01 (0.95–1.08)	.74	1.02 (0.96–1.09)	.57
Binge drinking ^b	0.96 (0.68–1.34)	.79	0.96 (0.68–1.36)	.82

aOR, adjusted odds ratio; CI, confidence interval; LSM, liver stiffness measurement.

^aModel 1 is adjusted for age, sex, cohort, smoking, physical activity, income and education. Model 2 is adjusted for model 1 and each component of the metabolic syndrome (high waist circumference, high triglycerides, low high-density lipoprotein cholesterol, hypertension, and impaired fasting glucose).

^bRisky weekly drinking was defined as >7 drinks per week for women and >14 drinks per week for men. Usual consumption above U.S. dietary guidelines was defined as ≥ 2 drinks per drinking day for women or ≥ 3 drinks per drinking day for men. Binge drinking was defined as ≥ 4 drinks for women or ≥ 5 drinks for men in 24 hours, or drinking ≥ 5 drinks almost daily.

Similarly, the UK Million Women Study followed current drinkers for 15 years and observed that consuming 7–14 drinks weekly associated with increased cirrhosis risk compared with 1–2 drinks weekly.⁷

Our study has multiple important strengths. Our assessment of fibrosis in a community cohort of unselected patients is unique, as much research on fibrosis has been conducted in patients who are suspected of or

Table 3. Multivariable-Adjusted Logistic Regression Models for the Association Between Various Drinking Measures and Elevated FAST Score (FAST >0.35) in the Full Cohort, and in an Analysis Restricted to Nonheavy Drinkers

Alcohol Use Measure	Model 1 ^a		Model 2 ^a	
	aOR (95% CI)	P Value	aOR (95% CI)	P Value
Full sample (N = 2629)				
Alcohol drinks per week	1.18 (1.07–1.30)	.001	1.27 (1.14–1.42)	<.0001
Frequency of drinking days (per week)	1.01 (0.96–1.07)	.63	1.11 (1.04–1.18)	.001
Usual quantity (drinks per drinking day)	1.15 (1.06–1.24)	.0007	1.12 (1.03–1.22)	.01
Risky weekly drinking ^b	1.40 (1.03–1.90)	.03	1.75 (1.24–2.47)	.002
Usual consumption in excess of dietary guidelines ^b	1.52 (1.18–1.96)	.001	1.50 (1.14–1.98)	.004
Maximum drinks in 24 h in last month	1.07 (1.03–1.12)	.0003	1.09 (1.05–1.14)	<.0001
Binge drinking ^b	1.36 (1.06–1.76)	.02	1.43 (1.07–1.90)	.01
Restricted to nonheavy drinkers (n = 2471)				
Alcohol drinks per week	1.07 (0.95–1.2)	.30	1.20 (1.05–1.36)	.01
Frequency of drinking days (per week)	0.99 (0.93–1.05)	.74	1.09 (1.02–1.17)	.02
Usual quantity (drinks per drinking day)	1.11 (1.01–1.23)	.04	1.06 (0.96–1.18)	.26
Risky weekly drinking ^b	1.14 (0.77–1.69)	.50	1.46 (0.95–2.26)	.09
Usual consumption in excess of dietary guidelines ^b	1.37 (1.05–1.8)	.02	1.33 (0.99–1.79)	.05
Maximum drinks in 24 h in last month	1.05 (0.999–1.10)	.05	1.06 (1.01–1.12)	.02
Binge drinking ^b	1.33 (1.01–1.74)	.04	1.37 (1.01–1.85)	.04

aOR, adjusted odds ratio; CI, confidence interval; FAST, FibroScan-aspartate aminotransferase.

^aModel 1 is adjusted for age, sex, cohort, smoking, physical activity, income and education. Model 2 is adjusted for model 1 and the components of the metabolic syndrome (waist circumference, low high-density lipoprotein cholesterol, high triglycerides, increased blood pressure, and impaired fasting glucose).

^bRisky weekly drinking was defined as >7 drinks per week for women and >14 drinks per week for men. Usual consumption above U.S. dietary guidelines was defined as ≥ 2 drinks per drinking day for women or ≥ 3 drinks per drinking day for men. Binge drinking was defined as ≥ 4 drinks for women or ≥ 5 drinks for men in 24 hours, or drinking ≥ 5 drinks almost daily.

known to have liver disease, and other studies investigating alcohol use in the general population have not evaluated fibrosis. Because fibrosis predicts liver-related outcomes and mortality, evaluating the relationship of alcohol use with fibrosis is important to provide clinically meaningful findings. Further, we designed our study to account for confounding factors, including metabolic disease and the heterogeneous nondrinker group in order to reduce bias. Additionally, our detailed alcohol use questionnaires allowed us to investigate multiple patterns of alcohol use that may be obscured by evaluating only total daily or weekly alcohol consumption. We are unable to find any other published research to date that examines the relationship between alcohol use and the FAST score.

There are several limitations to consider. Our cross-sectional design did not allow us to investigate any temporal relationship between alcohol use patterns and fibrosis, and further prospective studies are needed to understand the causality of these relationships. Furthermore, we measured alcohol exposure at one point in time, which may differ from that over one's lifetime. Additionally, alcohol use data collected via questionnaire is at risk of recall and underreporting biases. Our results may be less generalizable to non-White populations, as most of the participants in our cohort were of White race, though we would not expect biological differences in the association between alcohol use and liver disease between races. Additionally, we did not have data on the presence of other chronic liver diseases that could have contributed to fibrosis. However, the prevalence of chronic viral hepatitis is low in the state of Massachusetts overall,⁴³ and we would expect a similarly low prevalence of other less common etiologies of liver disease.⁴⁴ As the prevalence of fibrosis was modest in our unselected cohort, we had limited power to investigate the association of specific types of alcohol with fibrosis, or to detect small contributions of alcohol use patterns on fibrosis. Additionally, we acknowledge that the FAST score is an indirect indicator of at-risk NASH. Recent alcohol use may affect the FAST score by transiently increasing the AST level, and binge drinking in the last month was associated with higher FAST score. VCTE is also a surrogate marker of fibrosis, and recent alcohol use may transiently increase liver stiffness by increasing inflammation. However, we did not observe an association between binge drinking in the last month and liver stiffness, suggesting that our VCTE results were not measuring only acute effects of alcohol. Further, because VCTE is commonly used to identify and monitor fibrosis in patients with NAFLD, our findings still have important clinical implications.

In conclusion, we showed that several alcohol use measures, including total weekly alcohol consumption, were associated with clinically significant fibrosis and at-risk NASH among nonheavy alcohol users in a community

cohort after multivariable adjustment for sociodemographic and metabolic factors. Additional studies are needed to determine the benefits of modifying alcohol use behavior for reducing liver-related morbidity and mortality.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2022.10.039>.

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Conflicts of Interest

The authors have no conflicts to disclose.

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Supplementary Table 1. Characteristics of Study Sample, After Excluding Heavy Drinkers

	Hepatic Fibrosis (n = 197) ^a	No Fibrosis (n = 2274)	Total Sample (n = 2471)
Age, y	56.2 ± 8.1	54.2 ± 8.9	54.4 ± 8.8
Female	108 (54.8)	1239 (54.5)	1328 (53.7)
Current smoking	18 (9.1)	195 (8.6)	213 (8.6)
Physical activity index	34.6 ± 6.6	33.9 ± 5.4	33.9 ± 5.5
Race			
White	184 (93.4)	2098 (92.3)	2282 (92.4)
Asian	3 (1.5)	36 (1.6)	39 (1.6)
Black	4 (2)	31 (1.4)	35 (1.4)
Hispanic	2 (1)	53 (2.3)	55 (2.2)
Other/mixed race	4 (2)	54 (2.3)	58 (2.3)
Education			
Some high school	1 (0.5)	15 (0.7)	16 (0.7)
High school graduate	33 (16.8)	241 (10.6)	274 (11.1)
Some college	53 (26.9)	668 (29.4)	721 (29.2)
College graduate	77 (39.1)	903 (39.7)	980 (39.7)
Graduate degree	33 (16.8)	447 (19.7)	480 (19.4)
Income			
<\$12,000/y	1 (0.5)	37 (1.6)	38 (1.5)
\$12,000–\$24,999/y	10 (5.1)	86 (3.8)	96 (3.9)
\$25,000–\$49,999/y	27 (13.7)	403 (17.7)	430 (17.4)
\$50,000–\$74,999/y	48 (24.4)	537 (23.6)	585 (23.7)
\$75,000–\$100,000/y	52 (26.4)	512 (22.5)	564 (22.8)
>\$100,000/y	59 (30)	699 (30.7)	758 (30.7)
Metabolic and liver parameters			
Body mass index, kg/m ²	31.9 ± 7.1	27.9 ± 5.3	28.2 ± 5.5
Waist circumference, cm	108.3 ± 18	98.1 ± 14.1	98.9 ± 14.7
Diabetes ^b	45 (22.8)	132 (5.8)	177 (7.2)
Impaired fasting glucose ^b	88 (44.7)	748 (32.9)	836 (33.8)
Metabolic syndrome ^b	95 (48.2)	567 (24.9)	662 (26.8)
Hypertension ^b	119 (60.4)	844 (37.1)	963 (39)
High triglycerides ^b	58 (29.4)	394 (17.3)	452 (18.3)
Low HDL cholesterol ^b	63 (32)	394 (17.3)	457 (18.5)
Liver stiffness measurement, kPa	12.3 ± 8.7	5.1 ± 1.28	5.6 ± 3.4
Controlled attenuation parameter, dB/m	296.7 ± 62	255.8 ± 53.3	249.1 ± 55.1
FibroScan-AST score			
<0.35	101 (51.3)	2076 (91.3)	2177 (88.1)
0.35–<0.67	66 (33.5)	186 (8.2)	252 (10.2)
≥0.67	30 (15.2)	12 (0.5)	42 (1.7)
FibroScan-AST score >0.35	96 (48.7)	198 (8.7)	294 (11.9)
Alcohol use patterns			
Alcohol drinks per week	5.5 ± 5.3	4.9 ± 4.5	4.9 ± 4.6
Frequency of drinking days (per week)	2.6 ± 2.2	2.5 ± 2.1	2.5 ± 2.1
Usual quantity (drinks per drinking day)	2 ± 1.2	1.9 ± 1.1	1.87 ± 1.1
Usual consumption in excess of dietary guidelines ^c	78 (39.6)	907 (39.9)	985 (39.9)
Risky weekly drinking ^c	28 (14.2)	271 (11.9)	299 (12.1)

Supplementary Table 1. Continued

	Hepatic Fibrosis (n = 197) ^a	No Fibrosis (n = 2274)	Total Sample (n = 2471)
Binge drinking ^c	57 (29)	684 (30)	741 (30)
Maximum drinks in 24 h in last month	3.4 ± 3	3.3 ± 2.4	3.3 ± 2.5

Values are mean ± SD or n (%).

AST, aspartate aminotransferase; HDL, high-density lipoprotein.

^aDefined as liver stiffness measurement ≥8.2 kPa.

^bDiabetes was defined as fasting plasma glucose ≥126 mg/dL or the use of insulin or oral hypoglycemic medications. Impaired fasting glucose was defined as fasting glucose ≥100 mg/dL. Metabolic syndrome was defined as three or more of the following criteria: high waist circumference as >35 inches for women or >40 inches for men, high triglycerides, low HDL, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, or fasting glucose ≥100 mg/dL. Hypertension was defined as average systolic blood pressure ≥130 mm Hg, average diastolic blood pressure ≥85 mm Hg, or current use of antihypertensive medications. High triglycerides were defined as fasting triglyceride level ≥150 mg/dL. Low HDL cholesterol was defined as HDL <50 mg/dL for women or <40 mg/dL for men.

^cHeavy drinking was defined as >14 drinks per week for women or >21 drinks per week for men. Usual consumption above United States Dietary Guidelines was defined as ≥2 drinks per drinking day for women or ≥3 drinks per drinking day for men. Risky weekly drinking was defined as >7 drinks per week for women and >14 drinks per week for men. Binge drinking was defined as ≥4 drinks for women or ≥5 drinks for men in 24 hours, or drinking ≥5 drinks almost daily.