Cannabis and Cannabinoid Research
Volume 00, Number 00, 2024

DOI: 10.1089/can.2024.0027

ORIGINAL RESEARCH

Associations of Cannabis Use, Metabolic Dysfunction-Associated Steatotic Liver Disease, and Liver Fibrosis in U.S. Adults

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Abstract

Introduction: Following the introduction of metabolic dysfunction-associated steatotic liver disease (MASLD) as a replacement term for nonalcoholic fatty liver disease, the relationship between MASLD and cannabis use has yet to be established. With the global rise in cannabis consumption, understanding its impact on MASLD is critical for clinical guidance. Our study investigated the association between cannabis use, MASLD, and clinically significant fibrosis (CSF) among U.S. adults.

Methods: Data were collected from the National Health and Nutrition Examination Survey for the period 2017 to 2018 to conduct a cross-sectional analysis. The diagnosis of hepatic steatosis and CSF was based on median values of the controlled attenuation parameter and liver stiffness measurement, with thresholds of 285 dB/m and 8.6 kPa, respectively. Information on cannabis use was obtained through self-report questionnaires. Multinomial logistic regression models and subgroup analyses were used to investigate the association between cannabis use and MASLD with CSF.

Results: Our study assessed data from 2,756 U.S. adults (51.1% female; 32.2% white; mean age 39.41 ± 11.83 years), who had complete information on liver stiffness measurements through transient elastography alongside reported cannabis use. Results indicated that cannabis use overall was not associated with liver stiffness in patients with MASLD. However, among females, cannabis use was associated with MASLD accompanied by CSF, with an adjusted odds ratio (OR) of 0.47 (95% confidence interval [CI]: 0.24–0.91). Heavy cannabis use (9 to 30 times per month) was associated with MASLD accompanied by CSF among female participants, with an adjusted OR of 0.12 (95% CI: 0.02–0.88).

Conclusion: In our study, cannabis use did not show a significant association with liver stiffness in patients diagnosed with MASLD. However, heavy cannabis consumption in women was associated with MASLD accompanied by CSF. These findings suggest that the effects of cannabis on liver health may differ based on gender and frequency of cannabis use, emphasizing the need for further research in this area.

Keywords: metabolic dysfunction-associated steatotic liver disease; clinically significant liver fibrosis; cannabis use; frequency of cannabis use

Introduction

Cannabis, widely recognized as the most popular recreational drug globally, also boasts a significant history in medicinal applications.[1] Over the past decade, both medical and recreational usage of cannabis has surged in the United States.[2] Since 2012, when legalization for recreational use began, 38 states have sanctioned medical cannabis, and 24 have approved it for recreational purposes.[3] The impact of cannabis on human health has been contentious, with only a limited number of studies suggesting potential health risks.[4] The role of cannabis in human health has become clearer with the

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identification of endocannabinoids and their receptors, CB1 and CB2, indicating its broad implications in various health conditions and diseases. Recent research has particularly focused on the association between cannabis use and nonalcoholic fatty liver disease (NAFLD).[5–7] Studies suggested that blocking CB1 receptors can mitigate liver steatosis even in the context of high-energy intake, as these receptors are known to promote fat accumulation in the liver in experimental models of NAFLD.[8,9] Moreover, steatosis is increasingly recognized as accelerating the progression of liver fibrosis.[10] Currently, the dominant causes of hepatocellular carcinoma (HCC) are shifting from viral and alcohol-related liver diseases to obesity, type 2 diabetes, and NAFLD.[11]

The term NAFLD has been deemed insufficient as it relies on exclusionary criteria and fails to adequately describe the underlying pathology. Consequently, metabolic dysfunction-associated steatotic liver disease (MASLD) has been adopted as a more accurate descriptor. This change was ratified after a Delphi consensus process involving global experts and culminated in the publication of a multi-society consensus declaration in June 2023.[12,13]

The prevalence of MASLD rose from 22% to 37% between 1991 and 2019, reflecting a global trend where approximately 30% of adults are now affected.[14] This increase aligns with rising obesity rates and related health issues, making MASLD more prevalent. A more severe form of MASLD, metabolic dysfunction-associated steatohepatitis (MASH), is marked by lobular inflammation and hepatocyte ballooning, factors that significantly raise the risk of progressing to fibrosis.[15] In the United States, MASH has emerged as a primary cause of liver transplantation in adults with HCC.[16,17] Given these trends, both MASLD and its severe complications, including HCC, are expected to continue to rise significantly in the coming years.[17,18]

Recent studies have demonstrated that cannabidiol and Δ9-tetrahydrocannabinolic acid, a prevalent cannabinoid, mitigate liver fibrosis and inflammation in animal models.[19] However, research on the effects of cannabis on fibrosis in these models has yielded inconsistent results, with some studies suggesting that cannabis may protect against fibrosis progression at the population level.[20] This potential protective association remains a topic of debate.[21] Given the reclassification of NAFLD to MASLD, a new dimension in the study of cannabis interactions with liver conditions has emerged. Current literature on the effects of cannabis on liver fibrosis, specifically related to MASLD, is limited. Our research aims to bridge this gap by investigating the relationship between cannabis use and MASLD through the National Health and Nutrition Examination Survey.

Methods

Data and sample sources

Data on the nutritional status and potential health risk factors of non-institutionalized civilians in the United States were gathered by the National Center for Health Statistics (NCHS) through a cross-sectional survey based on the national population known as the National Health and Nutrition Examination Survey (NHANES). A sophisticated stratified multiple-phase probability cluster sampling design was created to select a representative sample of the entire U.S. population.[22]

Data on the nutritional status and potential health risk factors for non-institutionalized civilians in the United States were collected through a cross-sectional survey by the NCHS. This survey, known as the NHANES, uses a complex stratified multiphase probability cluster sampling design to ensure a representative sample of the entire U.S. population.[22]

This study analyzed data from the 2017–2018 cycle of the NHANES, conducted by the NCHS. NHANES is designed to assess the health and nutritional status of adults and children in the United States through both physical examinations and interviews. It uses a complex, multistage, probability sampling method to ensure the data accurately represents the U.S. population biennially. For this specific analysis, the study excluded individuals who did not have vibration-controlled transient elastography (VCTE) evaluations (n = 3306), those under 20 years of age (n = 1079), participants who tested positive for HBV or HCV infections (n = 127), and those with incomplete data on cannabis use (n = 1986). After these exclusions, the final sample comprised 2756 participants. The 2017–2018 survey cycle was particularly relevant for this study as it was the first to include data on both cannabis use and VCTE.

Assessment of cannabis use

The 2017–2018 cycle of the NHANES incorporated a comprehensive questionnaire focused on both past and current cannabis use. This questionnaire was administered to participants during their interviews at the mobile examination centers. Participants were first asked if they had ever used cannabis or hashish. Subsequent questions delved into the frequency of their cannabis

use. For the analysis in our study, we further classified participants who reported recent use into two categories based on their self-reported data from the Drug Use Questionnaire: light users (1–8 times per month) and heavy users (9–30 times per month).

Definition of MASLD and clinically significant fibrosis

The diagnosis of MASLD is considered for individuals presenting with steatosis and any one of the after cardiometabolic criteria, or at least one specified metabolic disorder:[12] (a) a body mass index (BMI) of ≥25 kg/m^2 or a waist circumference of ≥80 cm for females and ≥94 cm for males; (b) hemoglobin A1c levels ≥ 5.7%, fasting plasma glucose ≥5.6 mmol/L, glucose levels ≥7.8 mmol/L 2 h post-glucose load, a diagnosis of type 2 diabetes, or ongoing treatment for type 2 diabetes; (c) blood pressure (BP) ≥ 130/85 mmHg or treatment for hypertension; (d) plasma triglycerides (TC) ≥ 150 mg/dL or use of lipid-lowering medication; (e) plasma high-density lipoprotein (HDL)-cholesterol ≤ 40 mg/dL in males and ≤50 mg/dL in females or those on lipid-lowering therapy.

The VCTE data were used to assess the extent of fibrosis and steatosis. Clinically significant fibrosis (CSF) was defined as a liver stiffness measurement of 8.6 kPa or higher, with a sensitivity of 66% and a specificity of 80%. Steatosis, on the contrary, was identified with a controlled attenuation parameter of 285 dB/m or more, featuring a sensitivity of 80% and specificity of 77%.[23] Based on the levels of CSF, phenotypes were categorized as follows: non-MASLD, MASLD without CSF, and MASLD with CSF.

Other definitions

We extracted demographic characteristics of participants with MASLD from the NHANES database, focusing on socioeconomic factors such as gender, age, race (non-Hispanic White, non-Hispanic Black, Hispanic, and Other or Multiracial), educational level (less than high school, high school graduate, and college graduate or above), marital status (married or living with partner, divorced or living without partner), and family income-to-poverty ratio. In addition, we collected data on lifestyle habits and medical histories. Smoking history was defined as individuals who had smoked 100 cigarettes or more in their lifetime. Alcohol consumption was categorized as never/light (less than two drinks per day for females and less than three drinks per day for males) or heavy (two or more drinks per day for females and three or more drinks per day for males). Hypertension was defined as BP ≥ 140/90 mmHg or the use of medication to manage BP. Diabetes mellitus was defined by a fasting plasma glucose level of 126 mg/dL, a glycosylated hemoglobin A1c level of ≥6.5%, or a prior diagnosis reported by the participant. Further, physical and laboratory examinations included waist circumference, BMI, TG, fasting blood glucose, total cholesterol, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, fasting glucose, insulin, high-sensitive-reactive protein, glycosylated hemoglobin, HDL, and cotinine. Detailed protocols for laboratory procedures, examination components, and questionnaires can be found in the report and reference guides for the NHANES, which are publicly available at: https://wwwn.cdc.gov/nchs/nhanes/.

Statistical analysis

All statistical analyses were conducted using R version 4.4.1 in RStudio. Categorical variables were expressed as counts and percentages, although continuous variables were presented as means ± standard deviation (SD). To compare baseline characteristics across different exposure groups, we first applied the Shapiro–Wilk test to assess the normality of continuous variables within groups categorized by MASLD phenotypes. Results indicated that the variables were not normally distributed. Consequently, we used the Kruskal–Wallis test to evaluate differences among the three groups. Liver stiffness was categorized based on the CSF value of 8.6 kPa, converting it from a continuous to a categorical variable. The relationship between cannabis use and MASLD, with or without CSF, was analyzed using multinomial logistic regression. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics based on MASLD phenotypes

This study encompassed 2,756 participants, all 20 years or older, who had completed both an interview and an examination. Table 1 outlines the overall characteristics of the participants categorized by their MASLD phenotype. The average age was 39 years (SD = 12 years), with women constituting 51.1% (1,409 participants) of the sample. Among the participants, 31.2% (860) were non-Hispanic white, 23% (634) were non-Hispanic Black, and 24.78% (683) were Hispanic adults. Based on definitions of MASLD and CSF, 164 participants (5.95%) were identified as having MASLD with CSF, 826 participants (29.97%) as having MASLD without CSF, and 1,766 participants (64.08%) as not having MASLD.

Table 1. Demographic and Clinical Characteristics of Adults Aged 20 Years or Older at Baseline Across the MASLD Phenotypes in the NHANES 2017–2018

	Non-MASLD $n = 1766$	MASLD without CSF $n = 826$	MASLD with CSF $n = 164$	p value
Demographics				
Age, years	37.90 ± 11.78	42.04 ± 11.61	43.47 ± 10.19	<0.0001
Gender				0.0369
Male, $n = 1347$	891 (50.46%)	371 (44.96%)	81 (49.24%)	
Female, $n = 1409$	875 (49.54%)	455 (55.04%)	33 (50.76%)	
Race/ethnicity				<0.0001
Non-Hispanic White, $n = 860$	1041 (58.95%)	465 (56.29%)	105 (64.31%)	
Non-Hispanic Black, $n = 634$	236 (13.37%)	79 (9.56%)	15 (9.38%)	
Hispanic, $n = 683$	287 (16.27%)	197 (23.87%)	30 (18.12%)	
Other or multiracial, $n = 579$	202 (11.41%)	85 (10.28%)	13 (8.20%)	
Education level				<0.0001
Less than high school graduate, $n = 426$	159 (9.00%)	89 (10.79%)	14 (8.44%)	
High school graduate or GED, $n = 659$	424 (24.03%)	243 (29.39%)	68 (41.65%)	
Some college or above, $n = 1670$	1183 (66.97%)	494 (59.82%)	82 (49.90%)	
Marital status				<0.001
Married or living with partner	981 (55.6%)	537 (65.0%)	101 (61.6%)	
Divorced or living without partner	784 (44.4%)	289 (35.0%)	63 (38.4%)	
Family income-to-poverty ratio	3.10 ± 1.68	3.00 ± 1.64	3.12 ± 1.54	0.755
Lab panel				
ALT (U/L)	20.23 ± 13.22	29.52 ± 19.98	38.68 ± 29.69	<0.0001
AST (U/L)	21.01 ± 11.61	23.16 ± 12.41	29.09 ± 22.56	<0.0001
GGT (U/L)	24.69 ± 38.29	37.36 ± 39.66	54.76 ± 64.08	<0.0001
Triglycerides (mg/dL)	115.67 ± 89.45	185.36 ± 143.19	206.47 ± 150.74	<0.0001
Fasting glucose (mmol/L)	5.60 ± 1.02	6.49 ± 2.40	7.47 ± 2.57	<0.0001
Insulin (uU/mL)	9.16 ± 7.45	18.65 ± 16.88	27.58 ± 35.08	<0.0001
HS-CRP (mg/L)	2.92 ± 5.91	4.92 ± 7.64	6.46 ± 8.28	<0.0001
Glycosylated hemoglobin (%)	5.36 ± 0.57	5.82 ± 1.12	6.22 ± 1.32	<0.0001
HDL (mg/dL)	56.35 ± 15.17	47.02 ± 12.07	43.59 ± 12.55	<0.0001
Cotinine (ng/mL)	64.1 ± 134.3	61.4 ± 134.0	57.3 ± 126.7	0.369
VCTE measurements				
LSM (kPa)	4.79 ± 2.28	5.36 ± 1.32	17.48 ± 14.38	<0.0001
CAP (dB/m)	223.25 ± 38.68	327.32 ± 32.31	356.04 ± 38.27	<0.0001
Comorbidities				
BMI (kg/m^2)	27.06 ± 6.08	33.95 ± 6.52	41.46 ± 8.23	<0.0001
WC (cm)	92.48 ± 14.74	110.50 ± 13.88	128.62 ± 16.48	<0.0001
Hypertension				<0.0001
Yes, $n = 668$	271 (15.37%)	283 (34.25%)	69 (41.96%)	
No, $n = 2088$	1495 (84.63%)	543 (65.75%)	95 (58.04%)	
Diabetes mellitus				<0.0001
Yes, $n = 205$	45 (2.52%)	87 (10.59%)	38 (23.29%)	
No, $n = 2551$	1721 (97.48%)	739 (89.41%)	126 (76.71%)	
Smoked at least 100 cigarettes in life				<0.001
Yes, $n = 1047$	671 (37.97%)	365 (44.13%)	76 (46.47%)	
No, $n = 1709$	1095 (62.03%)	461 (55.87%)	88 (53.53%)	
Alcohol use				0.0230
Never/light drinkers, $n = 999$	850 (48.12%)	344 (41.64%)	77 (47.17%)	
Heavy drinkers, $n = 1135$	916 (51.88%)	482 (58.36%)	87 (52.83%)	
Marijuana use				0.1281
Yes, $n = 1496$	1102 (62.42%)	488 (59.06%)	93 (56.63%)	
No, $n = 1260$	664 (37.58%)	338 (40.94%)	71 (43.37%)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CSF, clinically significant fibrosis; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HS-CRP, high-sensitive-reactive protein; LSM, liver stiffness measure; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography; and WC, waist circumference.

Participants diagnosed with MASLD with CSF were typically older, with a mean age of 43.47 years (SD = 10.19), compared with those without CSF (mean age = 42.04 years, SD = 11.61) and those without MASLD (mean age = 37.90 years, SD = 11.78). Significant differences were observed across the groups in terms of demographic characteristics, biochemical indexes, and anthropometric measurements. Specifically, variables such as gender, age, race/ethnicity, education level, marital status, and levels of HDL and TG showed significant

disparities among the groups ($p < 0.01$). However, the family income-to-poverty ratio and history of cannabis use did not differ significantly between the MASLD phenotypes (all $p > 0.05$).

Multinomial logistic regression analyses between cannabis use and MASLD phenotypes, stratified by gender

Due to significant gender differences, we conducted gender-stratified multinomial regression analyses. After adjusting for covariates, we found that the prevalence of MASLD with CSF in females who used cannabis was lower compared with females who did not use cannabis (Model II, adjusted odds ratio [OR]: 0.47, 95% confidence interval [CI]: 0.24–0.94) (Table 2). No significant differences were found in male participants. Further analysis stratified by the frequency of cannabis use showed that heavy cannabis consumption was associated with MASLD accompanied by CSF in females (Model II, adjusted OR: 0.12, 95% CI: 0.02–0.88) (Table 3).

Multinomial logistic regression analyses between cannabis use and liver stiffness, stratified by MASLD phenotype

The association between cannabis use and liver stiffness in participants with MASLD was assessed using multinomial logistic regression analyses. After adjusting for covariates, no significant association was found between cannabis use and liver stiffness in participants with MASLD, whether with CSF (Model II, adjusted OR: 0.61, 95% CI: 0.33–1.13) or without CSF (Model II, adjusted OR: 0.91, 95% CI: 0.55–1.52) (Table 4). Similarly, the frequency of cannabis use did not show a significant association with liver stiffness. Specifically, those with heavy cannabis use did not exhibit significant differences in liver stiffness compared with those with light use in participants with MASLD (adjusted OR: 0.73, 95% CI: 0.20–2.66) (Table 5).

Discussion

Our gender-stratified analyses suggest that cannabis use may be associated with MASLD with CSF in females, indicating a potential gender-specific protective effect. This association was not found in males. In addition, although heavy cannabis use in females showed a significant reduction in MASLD with CSF, no significant relationship was found between cannabis use and liver stiffness in MASLD patients overall. Our findings are similar to a previous study, which used NHANES data to assess the association between cannabis use and liver

Table 2. Multinomial Logistic Regression Analyses Between Cannabis Use and MASLD Phenotypes, Stratified by Gender

Gender									
				Male					
		Non-adjusted			Model I			Model II	
MASLD phenotype	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF
aOR (95% CI) Cannabis use									
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	Reference	0.96 (0.76–1.22) 0.76	1.34 (0.83–2.16)0.23	Reference	1.24 (0.95–1.61) 0.47	1.36 (0.81–2.27) 0.08	Reference	0.98 (0.68–1.42)0.93	1.41 (0.65–3.08) 0.39
Gender					Female				
Yes	Reference	0.81 (0.65–1.03) 0.08	0.72 (0.46–1.12) 0.14	Reference	0.92 (0.72–1.19) 0.54	0.87 (0.54–1.40) 0.57	Reference	0.87 (0.62–1.22) 0.41	0.47 (0.24–0.94) 0.033

Model I was adjusted for age and race.
Model II was further adjusted for age, gender, race, education level, marital status, family income-to-poverty ratio, body mass index, waist circumference, triglycerides, cotinine, smoking history, and alcohol use.
All analyses were conducted with multinomial logistic regression models.
aOR, adjusted odds ratio; CI, confidence interval; CSF, clinically significant fibrosis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 3. Multinomial Logistic Regression Analyses Between Frequency of Cannabis Use and MASLD, Stratified by Gender

Gender	Male								
	Non-adjusted			Model I			Model II		
MASLD phenotype	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF
aOR (95% CI) Cannabis use frequency									
Light (1–8 times per month)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Heavy (9–30 times per month)	Reference	0.83 (0.54–1.31) 0.44	1.84 (0.65–5.22) 0.25	Reference	0.92 (0.58–1.46) 0.73	2.02 (0.71–5.82) 0.19	Reference	0.78 (0.38–1.61) 0.51	2.35 (0.35–15.93) 0.38
Heavy (9–30 times per month)	Reference	1.52 (0.93–2.48) 0.10	1.09 (0.38–3.15) 0.88	Reference	1.63 (0.99–2.68) 0.06	1.21 (0.41–3.56) 0.73	Reference	1.09 (0.51–2.32) 0.82	0.12 (0.02–0.88) 0.04

Model I was adjusted for age and race.
Model II was further adjusted for age, gender, race, education level, marital status, family income-to-poverty ratio, body mass index, waist circumference, triglycerides, cotinine, smoking history, and alcohol use.
All analyses were conducted with multinomial logistic regression models.
aOR, adjusted odds ratio; CSF, clinically significant fibrosis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 4. Multinomial Logistic Regression Analyses Between Cannabis Use and Liver Stiffness Stratified by MASLD Phenotype

Liver stiffness	LSM								
	Non-adjusted			Model I			Model II		
MASLD phenotype	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF
aOR (95% CI) Cannabis use									
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	Reference	1.11 (0.76–1.62) 0.58	0.86 (0.568–1.31) 0.49	Reference	1.15 (0.77–1.71) 0.50	0.95 (0.60–1.49) 0.82	Reference	0.91 (0.55–1.52) 0.72	0.61 (0.33–1.13) 0.12

Model I was adjusted for age, gender, and race.
Model II was further adjusted for age, gender, race, education level, marital status, family income-to-poverty ratio, body mass index, waist circumference, triglycerides, cotinine, smoking history, and alcohol use.
Liver stiffness was categorized based on the CSF value of 8.6 kPa.
All analyses were conducted with multinomial logistic regression models. No estimates were statistically significant at $p < 0.05$.
aOR, adjusted odds ratio; CI, confidence interval; CSF, clinically significant fibrosis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 5. Multinomial Logistic Regression Analyses Between the Frequency of Cannabis Use and Liver Stiffness Stratified by MASLD Phenotype

Liver stiffness	LSM									
	Non-adjusted			Model I			Model II			
MASLD phenotype	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF	No MASLD	MASLD without CSF	MASLD with CSF
aOR (95% CI) Cannabis use frequency									
Light (1–8 times per month)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Heavy (9–30 times per month)	Reference	1.06 (0.71–1.59) 0.78	1.05 (0.43–2.57) 0.92	Reference	1.08 (0.72–1.64) 0.69	1.29 (0.51–3.23) 0.59	Reference	0.98 (0.59–1.60) 0.94	0.73 (0.20–2.66) 0.64

Model I was adjusted for age, gender, and race.
Model II was further adjusted for age, gender, race, education level, marital status, family income-to-poverty ratio, body mass index, waist circumference, triglycerides, cotinine, smoking history, and alcohol use.
Liver stiffness was categorized based on the CSF value of 8.6 kPa.
All analyses were conducted with multinomial logistic regression models. No estimates were statistically significant at $p < 0.05$.
aOR, adjusted odds ratio; CSF, clinically significant fibrosis; MASLD, metabolic dysfunction-associated steatotic liver disease.

steatosis, they found that current cannabis use was inversely associated with steatosis, and no significant association was established between cannabis use and liver fibrosis.[6] Our study used gender-stratified analyses to explore differences based on gender between cannabis use and MASLD. Recent studies have also demonstrated gender differences in chronic liver diseases.

Experimental evidence indicates that cannabinoids and their receptors play a role in various liver diseases, including liver fibrosis, metabolic steatosis, and cirrhotic cardiomyopathy.[24] Cannabis contains numerous chemically active compounds, such as cannabinoids, terpenoids, flavonoids, and alkaloids, which can modulate the endocannabinoid system (ECS).[25] The ECS is a network of cannabinoid receptors, such as CB1R and CB2R, and their ligands, regulating the synthesis and degradation of enzymes.[26] Cannabinoids such as Δ9-THC, a CB1R and CB2R agonist, affect lipid metabolism, insulin sensitivity, and the development of hepatic steatosis.[27,28] ECS is upregulated in advanced liver diseases, including cirrhosis, nonalcoholic steatohepatitis, alcoholic liver disease, autoimmune hepatitis, and viral hepatitis,[29,30] and may influence the progression from fibrosis to cirrhosis.[31]

However, the exact effects of cannabis and its derivatives on chronic liver diseases are unclear, with conflicting data from animal models and population studies.[9,29] Although some studies suggest cannabis may protect against fibrosis through anti-inflammatory pathways,[21,32,33] others, particularly in hepatitis C patients, indicate it may exacerbate fibrosis.[24] MASLD is characterized by an excess of TG in hepatocytes, which can progress to steatosis with inflammation or ballooning and further to hepatic fibrosis, cirrhosis, and HCC.[34] Individual differences in MASLD progression are influenced by obesity, insulin resistance, and estrogens.[35] Age and gender are significant risk factors,[11] with a higher prevalence in postmenopausal women suggesting a protective role of estrogens.[36–39] Gender differences in ECS response, such as higher CB1R expression and faster neuroadaptation in females,[40,41] may explain the observed gender-specific effects of cannabis on liver disease.[42]

Although no associations with MASLD were found in subgroup analyses by age and additional subgroup analyses were limited by data volume, future research is needed to investigate the impact of cannabis use across different age groups, particularly in older women, to better understand its effects on MASLD given the increasing prevalence of cannabis use. Due to the limited number of people in our study who used cannabis and

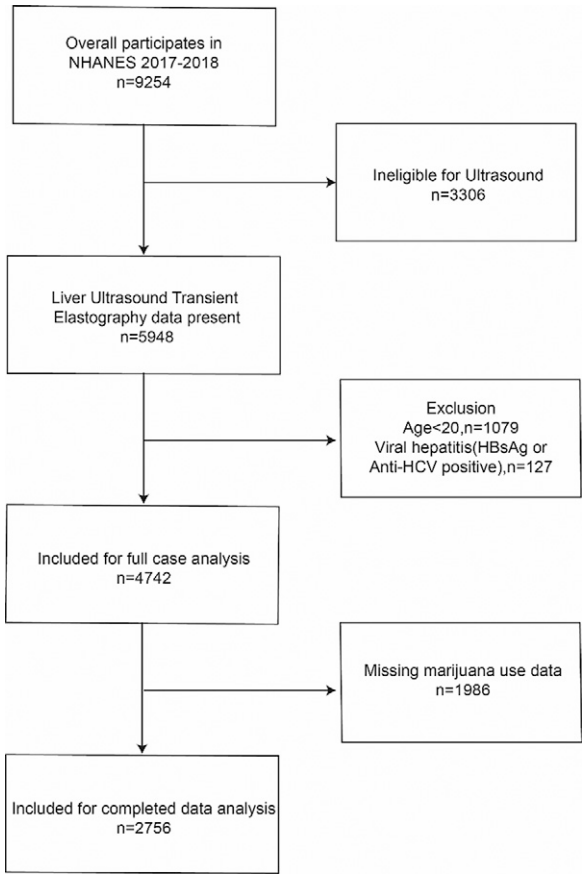

FIG. 1. Flow Diagram of Participant Inclusion and Attrition in the Study.

were diagnosed with MASLD, this conclusion should be regarded cautiously. Additional carefully planned prospective studies are required in this area. Further, research should focus on specific subpopulations, such as individuals with different chronic liver diseases, to assess the broader implications of cannabis use on liver health.

Limitations

The current study has several limitations. First, the cross-sectional design prevents us from establishing causal associations between cannabis use and MASLD, and prospective studies with larger sample sizes are needed to determine causality. Second, although we adjusted for several relevant confounders, unmeasured confounding factors could still influence our results. Third, the secondary analysis of cannabis use frequency was based on self-reported data, which may be prone to misclassification due to the skewed distribution of user numbers. In addition, although MASLD can be diagnosed without ruling out viral hepatitis or other liver diseases, we excluded participants who tested positive for HBV or HCV infection. Because regular cannabis use could exacerbate fibrosis in patients with hepatitis C, potentially impacting the contribution of MASLD in patients with dual or multiple etiologies such as chronic viral hepatitis or autoimmune liver disease. Finally, due to data volume limitations, our findings should be validated using other databases or different NHANES cycles. However, only the 2017–2018 cycle includes complete data on VCTE and cannabis use. Other years either have outdated data that may not accurately reflect current MASLD prevalence and cannabis use or they lack complete VCTE and cannabis use data simultaneously, which may introduce bias. Thus, more research is needed to explore the contribution of MASLD in patients with dual or multiple etiologies and to assess the impact of cannabis use on the risk of liver fibrosis in patients with MASLD.

Conclusions

Our findings suggest that cannabis use in females is associated with a significant reduction in MASLD with CSF. However, no significant association was found between cannabis use and liver stiffness in patients with MASLD overall. Further, large-scale prospective studies are required to validate these findings.

Authors' Contributions

Y.W.: Conceptualization; data curation; formal analysis; and writing—original draft. F.F.: Formal analysis; writing—review and editing; and data curation. X.F.: Formal analysis and writing—review and editing. H.N.: Conceptualization and supervision.

Author Disclosure Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Funding Information

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Cite this article as: Wu Y, Fei F, Fan X, Nie H. (2024) Associations of cannabis use, metabolic dysfunction-associated steatotic liver disease, and liver fibrosis in U.S. adults, *Cannabis and Cannabinoid Research* 00:0, 000–000, DOI: 10.1089/can.2024.0027.

Abbreviations Used

ALT = alanine aminotransferase
aOR = adjusted odds ratio
AST = aspartate aminotransferase
BMI = body mass index
CAP = controlled attenuation parameter
CI = confidence interval
CSF = clinically significant fibrosis
GGT = gamma-glutamyl transferase
HDL = high-density lipoprotein
HS-CRP = high-sensitive-reactive protein
LSM = liver stiffness measure
MASLD = Metabolic dysfunction associated steatotic liver disease
VCTE = vibration-controlled transient elastography
WC = waist circumference