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Association Between Cardiometabolic Index and Liver Fibrosis: Mediation Analysis of Oxidative Stress Factors

ORIGINAL INVESTIGATION

ABSTRACT

Background: Liver fibrosis (LF) is a serious complication of chronic liver disease that may progress to cirrhosis and liver cancer, posing a daunting threat to human health. Cardiometabolic Index (CMI) is closely associated with metabolic disorders related to obesity, which may be implicated in the pathological process of liver disease by inducing oxidative stress. However, previous observational studies have reached inconsistent conclusions on the association between CMI and hepatic fibrosis. This study aimed to assess the association of CMI and LF with oxidative stress by utilizing a population-based study.

Methods: A total of 3170 participants from the National Health and Nutrition Examination Survey (2017-2020) were included. A weighted logistics regression model was generated to analyze the correlation between CMI and LF, followed by the construction of the restricted cubic spline (RCS) model to explore the potential nonlinear relationship between the 2. In addition, the potential mediating role of oxidative stress factors (serum albumin, uric acid, γ-glutamyl transferase [GGT]) in the association of CMI with hepatic fibrosis was further investigated by regression analysis.

Results: With confounding factors adjusted, CMI was found to be associated with an increased risk of LF (odds ratio [OR] = 2.27, $P < .001$, 95% CI: 1.60-3.23). The stratification results showed that compared with the first quartile range, the LF risk of the second and third quartile ranges increased by 3.08 times (OR = 3.08, $P < .001$, 95% CI: 1.90-4.98) and 6.43 times (OR = 6.43, $P < .001$, 95% CI: 3.84-10.75), respectively. Further RCS analysis suggested that this association had nonlinear characteristics (P-nonlinear $< .0001$). Mediation analysis demonstrated that the intermediate proportions of serum albumin, uric acid, and GGT in the impact of CMI on LF were approximately 8.04%, 8.15%, and 5.60%, respectively.

Conclusion: This study demonstrated a significant positive linkage between CMI and LF, highlighting the mediating role of oxidative stress factors (serum albumin, uric acid, and GGT) in this linkage.

Keywords: Cardiometabolic Index, liver fibrosis, mediation analysis, National Health and Nutrition Examination Survey, oxidative stress

INTRODUCTION

Liver fibrosis (LF) is fibrous scarring induced by the accumulation of extracellular matrix proteins (mainly type 1 and type 3 cross-linked collagen).[1] Fibrosis is a common feature of chronic inflammatory disease progression.[2] If the process of LF continues to progress, it can later develop into cirrhosis or even liver cancer,[3] which seriously endangers human life and health. Liver fibrosis usually results from chronic liver injury, and risk factors include chronic hepatitis virus infection, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD) induced by metabolic syndrome (which is renamed as metabolic dysfunction-associated steatotic liver disease [MASLD]), and cholestasis.[4]

With the prevalence of obesity, MASLD has developed into one of the most common global causes of chronic liver disease in the world.[5] Metabolic dysfunction–associated steatotic liver disease is closely related to metabolic syndrome and its related hypertension, type 2 diabetes, dyslipidemia, and obesity.[6,7] Currently, commonly used scoring systems for clinical assessment of LF in MASLD, such as

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Fibrosis-4 index (FIB-4) and Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS), have included metabolic indicators such as body mass index (BMI) and blood glucose. However, these indicators often focus on a single dimension and are difficult to fully reflect the synergistic effect of central obesity and lipid metabolism disorders.[8-10]

The Cardiometabolic Index (CMI), as an integrated indicator, is calculated by multiplying the waist-to-height ratio (WHtR, reflecting central obesity) and the triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C, reflecting lipid metabolism). It combines simplicity and multidimensional evaluation advantages.[11] Although the existing fibrosis score already covers some metabolic parameters, CMI may more accurately capture the damaging effects of metabolic disorders on the liver by coupling body fat distribution with lipid metabolism abnormalities. For example, WHtR is more indicative of visceral fat accumulation than BMI,[12,13] while the TG/HDL-C ratio is closely related to insulin resistance and hepatic lipid deposition.[14] Therefore, CMI may provide additional predictive value beyond traditional single indicators. In recent years, the clinical value of CMI has been gradually revealed in metabolic diseases, including atherosclerosis,[15] ischemic stroke,[16] and hypertension.[17] A recent study found a strong positive correlation between higher CMI and the risk of NAFLD/MASLD in the general population.[18] However, there is still controversy regarding the association between CMI and LF.[19,20] For example, based on the same National Health and Nutrition Examination (NHANES) dataset, Yan et al[20] discovered that the higher CMI is indicated the higher incidence of LF (adjusted odds ratio [OR]: 1.84, 95% CI: 1.84-1.85), but Cheng et al[19] did not find an association between the 2 (OR: −0.009, 95% CI: −0.47 to 0.29). This contradiction may stem from differences in the definition of LF in research, incomplete control of confounding factors, or insufficient exploration of the potential mechanisms of CMI (such as oxidative stress).

Oxidative stress is one of the key mechanisms driving liver injury and inducing LF. Ethanol intake, chronic viral infection, and iron deposition can exacerbate the production of reactive oxygen species (ROS),[21] thereby inducing hepatic stellate cell (HSC) activation and extracellular matrix deposition.[22] Dysregulation of lipid metabolism can also exacerbate liver damage by increasing oxidative stress levels.[23] Serum albumin, uric acid, and γ-glutamyl transferase (GGT) are mediating variables of oxidative stress and are associated with the regulation of oxidative damage and the progression of LF.[24-26] Serum albumin, as an endogenous antioxidant, reduces oxidative damage by clearing ROS and chelating transition metals such as iron and copper. The decrease in its level is correlated with the severity of LF.[27,28] Uric acid has an antioxidant function at physiological concentrations, but at high concentrations, it can promote ROS generation by activating Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase, forming a "dual effect" and is associated with advanced LF.[29,30] Gamma-glutamyl transferase reflects oxidative stress status by participating in glutathione metabolism, and its elevation suggests glutathione depletion and progression of LF.[24,31,32] However, there is still a lack of population-level evidence on whether CMI affects LF by regulating oxidative stress pathways.

Therefore, this study conducted a cross-sectional study using NHANES data to investigate whether the association between CMI and LF is independent of traditional metabolic indicators. In addition, considering the crucial role of oxidative stress in the progression of liver disease, this study also investigated whether oxidative stress factors (serum albumin, uric acid, and GGT) play a mediating role in the relationship between CMI and LF. This study can provide new evidence for the clinical application of CMI in risk stratification of LF, but it does not reveal the potential mechanism of the metabolic oxidative stress axis in LF.

HIGHLIGHTS

- There is a positive correlation between Cardiometabolic Index (CMI) and liver fibrosis (LF).
- Oxidative stress factors (serum albumin, uric acid, and γ-glutamyl transferase [GGT]) play a mediating role in this process.
- This project uncovered a significant positive linkage between CMI and LF, highlighting the mediating role of oxidative stress factors (serum albumin, uric acid, and GGT) in this linkage.

METHODS

Study Population

The data in this work came from the NHANES (https://www.cdc.gov/nchs/nhanes/index.html), which is a comprehensive study launched by the Centers for Disease Control and Prevention and the National Center for Health Statistics. The survey is aimed at assessing the nutritional and health status of the deinstitutionalized US population through stratified and multi-stage sampling. The relationship between CMI and LF was examined using survey data from 2017 to 2020 (n = 15 560). After excluding missing and irrelevant data on LF (n = 5860), CMI data (n = 5668), and data from subjects with other missing covariate data (n = 697), a total of 3170 individuals were included at last (non-LF samples: 2849; LF samples: 321). Figure 1 is a flowchart for screening subjects.

Dependent Variable: Liver Fibrosis

By using the FibroScan 502 V2 Touch system, NHANES staff performed liver stiffness measurement (LSM) on subjects using vibration-controlled transient elastography technology. This study used LSM ≥ 8.2 kPa as the criterion for determining LF based on the study of Eddowes et al.[33] According to liver biopsy, the study is a large cohort of NAFLD and reveals that 8.2 kPa is the optimal cutoff value for maximizing the Youden index when diagnosing significant fibrosis ($F \geq$ F2).[33]

Independent Variable: Cardiometabolic Index

CMI = WHtR × [TG (mmol/L)/HDL-C (mmol/L)], where WHtR = waist circumference (cm)/height (cm).[11] Waist circumference and height data were obtained through physical

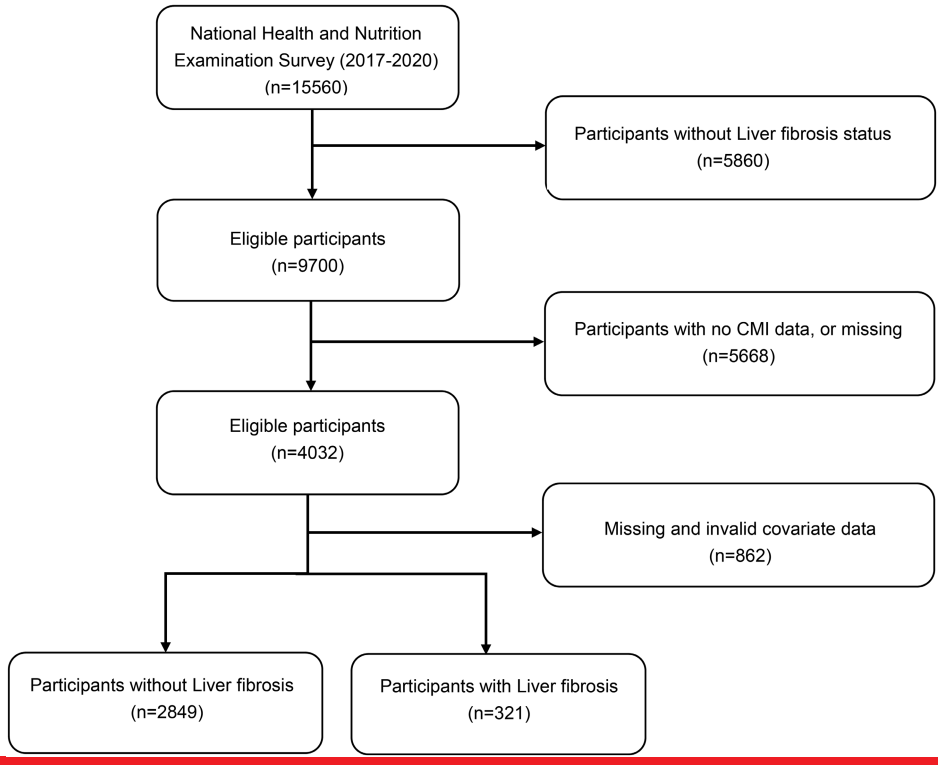

Figure 1. Flowchart of participant screening in NHANES.

examination. Triglycerides and HDL-C levels were detected by a Roche/Hitachi Cobas 6000 chemical analyzer.

Mediating Variables: Oxidative Stress Factors

Serum albumin, uric acid, and GGT were selected as the oxidative stress factors for mediation analysis in this project. In NHANES, serum albumin was obtained by the bromocresol purple staining method, and uric acid and GGT were determined by Roche Cobas 6000 (c501 module) chemistry analyzer.

Covariates

The covariates in this work included sex, race, age, BMI, serum albumin, smoking status, alcohol consumption, uric acid, blood bilirubin, alanine aminotransferase (ALT), blood urea nitrogen (BUN), aspartate transaminase (AST), GGT, history of liver disease, hepatic steatosis, MASLD, hepatitis C virus (HCV), total cholesterol (TC), TGs, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total sugar intake, and total energy intake. Non-HDL-C was calculated by subtracting HDL-C levels from TC.[34] Body mass index was calculated when body weight (kg) was divided by the square of height (m) and analyzed by the following categories: underweight/healthy weight (BMI < 25 kg/m^2) and overweight or obese (BMI ≥ 25 kg/m^2).[35] Smoking status was determined based on the concentration of serum cotinine, with a concentration $\geq$10 ng/mL indicating smokers and a concentration <10 ng/mL indicating non-smokers.[36]

The measurement or questionnaire for all variables can be queried on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.html).

Statistical Analysis

All analyses were processed using R (V4.3.3) software. The baseline table was plotted by utilizing the tableone package. The categorical variables are expressed as sample size and proportion [n (%)], and the continuous variables are expressed as mean and SD. A weighted logistics regression model was constructed using the survey package to analyze the association of CMI and its tertiles with hepatic fibrosis and to disclose its relevance in different populations through further subgroup analyses. The selection of confounding variables in this study was based on a theoretical framework supported by previous literature and the interrelationships between variables. Variance inflation factor was used to evaluate multicollinearity. To control for confounding factors that may affect the results, models were established to gradually evaluate confounding effects: in the Crude model, no adjustment for confounding factors was made. In Model 1, adjustments were made for age, sex, and race. In Model 2, age, sex, race, BMI, smoking, drinking, total bilirubin, ALT, BUN, AST, non-HDL-C, total sugar intake, and total energy intake were adjusted. A restricted cubic spline (RCS) was constructed using the rms package in a regression model after adjusting for all confounders to dissect the nonlinear relationship between CMI and hepatic fibrosis. In addition, regression analysis was employed to dig out the potential mediating role of serum albumin, uric acid, and GGT in the association of CMI with hepatic fibrosis. Mediation analysis was performed by utilizing the mediation package. Thousand non-parametric iterations were employed to estimate the 95% CI of the mediation effect and evaluate the stability of the results. Different researchers have used

weighted or unweighted methods when analyzing data. Although the complex sampling of NHANES can enhance the representativeness and applicability of research results, in some cases, weighted and unweighted analyses may yield different conclusions. Therefore, this study conducted non-weighted regression analysis as a sensitivity analysis to verify the robustness of the results of this study. $P < .05$ indicated a statistically significant difference.

RESULTS

Baseline Characteristics

A total of 3170 subjects were enrolled in this project, with an average age of 46.88 ± 17.33 years. Grouping was based on whether LF was present. The group with LF had a higher average age (52.59 vs. 46.33, $P < .001$), a significantly higher proportion of BMI ≥ 25 kg/m^2 (87.1% vs. 70.2%, $P < .001$), and a significantly higher CMI compared to the non-diseased group (0.87 vs. 0.58, $P = .001$). Biochemistry indices showed that the levels of uric acid, ALT, BUN, AST, and GGT in the population with LF were significantly higher than those in the non-diseased population. In terms of blood lipid indicators, the TG of patients with LF was significantly higher than those without LF (121.39 vs. 102.54 mg/dL, $P < .001$), while the levels of TC and HDL cholesterol were significantly lower than those without LF ($P < .05$). In addition, from the perspective of disease, a higher proportion of the LF population had a history of liver disease (9.2% vs. 4.2%, $P = .002$), steatosis (73.8% vs. 38.9%, $P < .001$), MASLD (82.2% vs. 40.1%, $P < .001$), and HCV (6.2% vs. 1.8%, $P = .035$) (Table 1).

Association Between Cardiometabolic Index and Liver Fibrosis

Table 2 displays the results of the weighted logistics regression model between CMI and LF. In the Crude model, CMI was associated with increased risk of LF (OR = 2.16, $P < .001$, 95% CI: 1.71-2.74). After preliminary adjustments for age, sex, and race (Model 1), the trend remained unchanged (OR = 2.09, $P < .001$, 95% CI: 1.64-2.65). After further adjustment of BMI, smoking, drinking, total bilirubin, ALT, BUN, AST, non-HDL-C, total sugar intake, and total energy intake (Model 2), the association between CMI and LF remains statistically significant (OR = 2.27, $P < .001$, 95% CI: 1.60-3.23). Additionally, the CMI was stratified by tertiles. The trend test uncovered that the risk of LF increased significantly with the increase of the CMI tertile interval (P for trend < .001). In Model 2, the risk of LF increased by 3.08 (OR = 3.08, $P < .001$, 95% CI: 1.90-4.98) and 6.43 (OR = 6.43, $P < .001$, 95% CI: 3.84-10.75) times for the second and third quartile intervals, respectively, compared to the first quartile interval.

Further subgroup analysis identified the association between CMI and LF in different subgroups (Table 3). After adjusting for all confounding factors, in both male (OR = 2.04, $P < .001$, 95% CI: 1.49-2.81) and female populations (OR = 2.62, $P < .01$, 95% CI: 1.48-4.65), CMI was associated with an increased risk of LF. Additionally, participants who were overweight or obese (BMI ≥ 25 kg/m^2) (OR = 2.30, $P < .001$, 95% CI: 1.63-3.25), who were drinkers (OR = 2.34, $P < .001$, 95% CI: 1.57-3.48), and with hepatic steatosis (OR = 1.58, $P < .05$, 95% CI: 1.08-2.32) were also significantly connected with an elevated risk of LF.

Nonlinear Relationship Between Cardiometabolic Index and Liver Fibrosis

After adjusting for all confounding factors, the nonlinear relationship between CMI and LF was explored using the RCS in a weighted logistic regression model. The results revealed that the overall trend between CMI and LF was significant (P-overall < .0001). With the increase in CMI, the risk of LF was significantly elevated. When CMI was greater than 0.451, the risk of LF was further increased. In addition, a significant nonlinear relationship between CMI and LF (P-nonlinear < .0001) was also detected (Figure 2).

Mediation Analysis

In the mediation analysis, the potential mediating roles of oxidative stress factors (serum albumin, uric acid, and GGT) in the association between CMI and LF were assessed. The results demonstrated that in the overall effect of CMI on LF, about 8.04% (95% CI: 3.61, 14.00) of the effect was attributed to the mediation of serum albumin (Figure 3A). In addition, uric acid and GGT accounted for approximately 8.15% (95% CI: 2.33, 14.00) and 5.60% (95% CI: 1.98, 10.00) of the mediating effect on LF in CMI, respectively (Figure 3B and C). These findings suggested that oxidative stress factors play an instrumental mediating role between CMI and LF.

Further analysis was conducted on the potential mediating roles of oxidative stress factors such as serum albumin, uric acid, and GGT in the association between CMI and LF in sex subgroups. The results showed that in males, GGT accounted for approximately 4.65% (95% CI: 0.03, 11.00) of the mediating proportion in the process of CMI affecting LF. In females, approximately 9.18% (95% CI: 1.96, 19.00) of the total effect of CMI on LF was attributed to the mediating role of serum albumin. Uric acid and GGT accounted for 13.55% (95% CI: 2.53, 27.00) and 5.21% (95% CI: 0.78, 10.00) of the mediating proportion in the process of CMI affecting LF, respectively (Table 4).

Sensitivity Analysis

Sensitivity analysis of non-weighted logistic analysis showed that in Model 2, the risk of LF increased by 2.95 (OR = 2.95, $P < .001$, 95% CI: 1.93-4.61) and 6.87 (OR = 6.87, $P < .001$, 95% CI: 4.46-10.86) times for the second and third quartiles, respectively, compared to the first quartile. These results indicate a strong correlation between CMI and the increased risk of LF (Table 5).

DISCUSSION

Based on the data from the NHANES, this investigation probed into the association between CMI and LF as well as the mediating role of oxidative stress factors (serum albumin, uric acid, GGT) in this association. The results indicated that CMI was associated with an increased risk of LF. Furthermore, the mediation analysis further revealed that serum albumin, uric acid, and GGT played mediating roles in the association between CMI and LF, with mediation proportions of 8.04%, 8.15%, and 5.60%, respectively.

Since its introduction in 2015, CMI has become a novel anthropometric measure for assessing an individual's metabolic health. CMI was originally used for the recognition

Table 1. Baseline Characteristics of Study Participants

Characters	Total, n (%)	Normal, n (%)	Liver Fibrosis, n (%)	*P*
Overall	3170	2849 (91.1)	321 (8.9)	
Demographic information				
Age (years)	46.88 (17.33)	46.33 (17.37)	52.59 (15.89)	<.001
Race				.507
Mexican American	427 (9.3)	376 (9.2)	51 (10.4)	
Other Hispanic	316 (6.7)	287 (6.7)	29 (6.4)	
Non-Hispanic White	1123 (63.7)	998 (63.4)	125 (66.5)	
Non-Hispanic Black	790 (10.9)	710 (11.0)	80 (9.9)	
Other race	514 (9.4)	478 (9.6)	36 (6.8)	
Sex				.138
Male	1564 (49.7)	1377 (48.9)	187 (58.2)	
Female	1606 (50.3)	1472 (51.1)	134 (41.8)	
BMI (kg/m^2)				.001
<25	844 (28.3)	809 (29.8)	35 (12.9)	
≥25	2326 (71.7)	2040 (70.2)	286 (87.1)	
Alcohol				.049
No	290 (6.7)	259 (6.2)	31 (10.9)	
Yes	2880 (93.3)	2590 (93.8)	290 (89.1)	
Smoke				.995
Non-smoker	2423 (77.5)	2180 (77.5)	243 (77.5)	
Active smoker	747 (22.5)	669 (22.5)	78 (22.5)	
Biochemical parameters				
CMI	0.61 (0.52)	0.58 (0.51)	0.87 (0.61)	<.001
Serum albumin (g/L)	40.77 (3.24)	40.84 (3.17)	40.04 (3.83)	.026
Uric acid (mg/dL)	5.40 (1.38)	5.35 (1.37)	5.97 (1.40)	<.001
Total bilirubin (mg/dL)	0.51 (0.32)	0.51 (0.32)	0.55 (0.29)	.110
ALT (U/L)	22.43 (17.40)	21.50 (16.44)	32.00 (23.20)	<.001
BUN (mmol/L)	5.20 (1.82)	5.13 (1.70)	5.90 (2.66)	<.001
AST (U/L)	21.56 (11.30)	20.90 (10.09)	28.36 (18.57)	.003
GGT (IU/L)	27.87 (30.16)	25.66 (24.24)	50.56 (60.55)	<.001
Total cholesterol (mg/dL)	184.19 (39.48)	184.90 (39.01)	176.91 (43.43)	.009
Triglycerise (mg/dL)	104.21 (61.57)	102.54 (61.20)	121.39 (62.82)	<.001
LDL-C (mg/dL)	109.37 (34.70)	109.89 (34.33)	103.99 (38.01)	.056
HDL-C (mg/dL)	54.00 (15.64)	54.52 (15.76)	48.67 (13.28)	<.001
Non-HDL-C (mg/dL)	130.19 (39.15)	130.38 (38.73)	128.23 (43.25)	.481
Total sugars intake (gm)	106.99 (78.73)	107.25 (78.78)	104.31 (78.30)	.499
Total energy intake (kcal)	2178.05 (964.84)	2174.09 (956.85)	2218.78 (1044.29)	.399
Comorbidity information				
Liver disease history				.002
No	3015 (95.3)	2733 (95.8)	282 (90.8)	
Yes	155 (4.7)	116 (4.2)	39 (9.2)	
Steatosis				<.001
No	1801 (58.0)	1718 (61.4)	83 (26.2)	
Yes	1369 (42.0)	1131 (38.9)	238 (73.8)	
MASLD				<.001
No	1735 (56.1)	1684 (59.9)	51 (17.8)	
Yes	1435 (43.9)	1165 (40.1)	270 (82.2)	
HCV				.035
No	3101 (97.8)	2805 (98.2)	296 (93.8)	
Yes	69 (2.2)	44 (1.8)	25 (6.2)	

n (%) represented the categorical variable and mean (SD) represented the continuous variable. n was unweighted. n (%), mean, and SD were weighted.
ALT, alanine aminotransferase; AST, aspartate transferase; BMI, body mass index; BUN, blood urea nitrogen; CMI, Cardiometabolic Index; GGT, γ-glutamyl transferase; HCV, hepatitis C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction–associated steatotic liver disease.

Table 2. The Associations Between Cardiometabolic Index and Liver Fibrosis

Participants	Crude Model	Model 1	Model 2
CMI (continuous)	OR = 2.16, *P* < .001, 95% CI: 1.71-2.74	OR = 2.09, *P* < .001, 95% CI: 1.64-2.65	OR = 2.27, *P* < .001, 95% CI: 1.60-3.23
CMI (categorical)			
T1 (<0.296)	Ref.	Ref.	Ref.
T2 (0.296-0.646)	OR = 2.78, *P* < .001, 95% CI: 1.63-4.72	OR = 2.45, *P* = .006, 95% CI: 1.33-4.49	OR = 3.08, *P* < .001, 95% CI: 1.90-4.98
T3 (≥0.646)	OR = 5.17, *P* < .001, 95% CI: 3.32-8.05	OR = 4.50, *P* < .001, 95% CI: 2.74-7.39	OR = 6.43, *P* < .001, 95% CI: 3.84-10.75
P_{trend}	<.001	<.001	<.001

Crude model: no adjustment for confounding factors. Model 1: adjustments for age, sex, and race. Model 2: adjustments for age, sex, race BMI, smoking, alcohol consumption, total bilirubin ALT, BUN, AST, Non-HDL-C, total sugar intake, total energy intake.
CMI, Cardiometabolic Index; OR, odds ratio.

Table 3. Relationship Between Cardiometabolic Index and Liver Fibrosis by Subgroup Analysis

Participants	Crude	Model 1	Model 2
Sex			
Male	OR = 1.85, *P* < .001, 95% CI: 1.36-2.51	OR = 1.83, *P* < .001, 95% CI: 1.35-2.48	OR = 2.04, *P* < .001, 95% CI: 1.49-2.81
Female	OR = 2.62, *P* < .001, 95% CI: 1.89-3.63	OR = 2.58, *P* < .001, 95% CI: 1.85-3.60	OR = 2.62, *P* = .004, 95% CI: 1.48-4.65
BMI			
BMI < 25	OR = 0.69, *P* = .589, 95% CI: 0.17-2.77	OR = 0.29, *P* = .153, 95% CI: 0.05-1.66	OR = 0.52, *P* = .493, 95% CI: 0.06-4.18
BMI ≥ 25	OR = 1.95, *P* < .001, 95% CI: 1.49-2.55	OR = 1.97, *P* < .001, 95% CI: 1.51-2.56	OR = 2.30, *P* < .001, 95% CI: 1.63-3.25
Alcohol			
No	OR = 2.62, *P* = .050, 95% CI: 1.00-6.83	OR = 2.56, *P* = .077, 95% CI: 0.89-7.32	OR = 2.66, *P* = .084, 95% CI: 0.85-8.30
Yes	OR = 2.13, *P* < .001, 95% CI: 1.61-2.80	OR = 2.04, *P* < .001, 95% CI: 1.54-2.69	OR = 2.34, *P* < .001, 95% CI: 1.57-3.48
Steatosis			
No	OR = 1.49, *P* = .420, 95% CI: 0.55, 4.02	OR = 1.17, *P* = .803, 95% CI: 0.31, 4.39	OR = 2.88, *P* = .057, 95% CI: 0.96-8.64
Yes	OR = 1.51, *P* = .005, 95% CI: 1.14, 1.98	OR = 1.55, *P* = .003, 95% CI: 1.19, 2.03	OR = 1.58, *P* = .025, 95% CI: 1.08-2.32

Crude model: no adjustment for confounding factors. Model 1: adjustments for age, sex, and race. Model 2: adjustments for age, sex, race BMI, smoking, alcohol consumption, total bilirubin ALT, BUN, AST, Non-HDL-C, total sugar intake, total energy intake.
BMI, body mass index; OR, odds ratio.

of diabetes. A study has confirmed its significant association with hyperglycemia,[11] which can reflect obesity and lipid metabolism. Obesity and dyslipidemia are strongly linked with the onset of MASLD.[37,38] Cardiometabolic Index is positively linked with the risk of MASLD in the general population.[18] This linkage has also been confirmed in the Chinese adult population, where CMI is a convenient indicator for MASLD screening and quantification.[39] Metabolic dysfunction–associated steatotic liver disease activates liver regeneration and fibrosis processes in the context of pathological damage such as liver fat accumulation, oxidative stress, inflammation, and apoptosis and facilitates the development of LF.[40] These findings indicated a significant positive correlation between CMI and LF, which is in line with previous studies.[20]

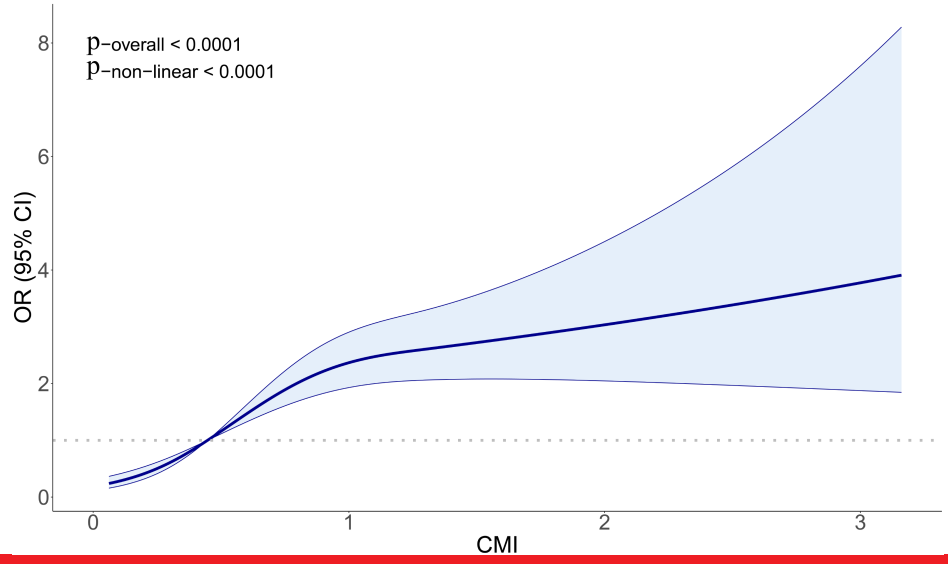

Figure 2. The nonlinear associations between CMI and LF. Adjustments were made based on age, sex, race, BMI, smoking, alcohol consumption, total bilirubin, ALT, BUN, AST, non-HDL-C, total sugar intake, and total energy intake. The solid line and the blue area represent the estimated value and its corresponding 95% CI, respectively.

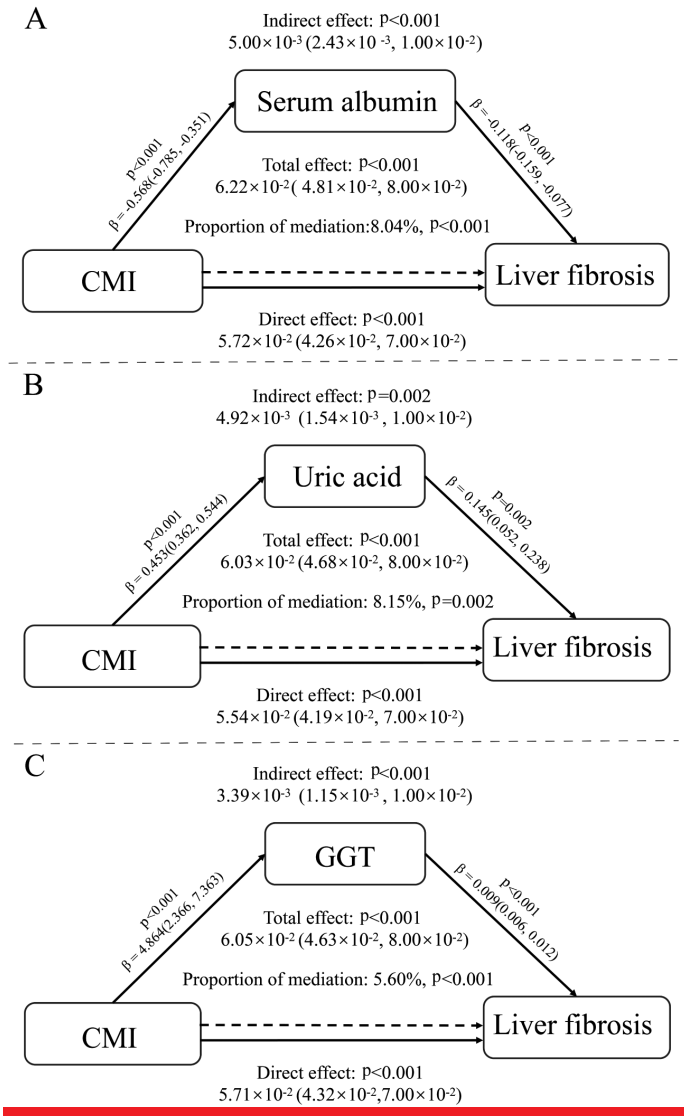

Figure 3. Mediation analysis of oxidative stress factors on the relationship between CMI and LF. In the mediation analysis, the following variables were adjusted: age, sex, race, BMI, smoking, alcohol consumption, total bilirubin, ALT, BUN, AST, non-HDL-C, total sugar intake, and total energy intake.

In addition, this study also included non-HDL-C, a key lipid indicator, in the analysis. Numerous studies have shown that non-HDL-C is not only closely associated with cardiovascular metabolic abnormalities but also with the occurrence and progression of hepatic steatosis and fibrosis.[41,42] A previous study has confirmed that this indicator is an independent predictor of NAFLD.[43] In a high-quality meta-analysis, the good predictive efficacy of non-HDL-C and its ratio (non-HDL-C/HDL-C) is confirmed in the occurrence and diagnosis of MASLD.[42] A large sample study based on NHANES indicated that elevated levels of non-HDL-C/HDL-C were independently associated with an increased risk of LF.[44] In the baseline characteristics of this study, there was no significant difference in non-HDL-C levels between the LF group and the non-LF group. However, after incorporating multiple confounding factors (Model 2), the association between CMI and LF remained robust (OR = 2.27). This result suggests that although non-HDL-C itself did not show differences between different LF states, incorporating it into the model still helps to more comprehensively control potential metabolic confounding factors, and CMI still exhibits predictive ability independent of non-HDL-C. Therefore, non-HDL-C may have additional or complementary value in the risk assessment of liver metabolic injury, while CMI provides a convenient indicator for integrating obesity and lipid metabolism abnormalities. The 2 may have the potential for synergistic application in identifying the risk of LF.

There is a positive linkage between CMI and LF, especially in overweight or obese individuals, alcohol drinkers, and people with a history of liver steatosis. Obesity is a key risk factor for the progression of MASLD to LF.[45] Obesity may develop insulin resistance by activating pro-inflammatory M1-type macrophages in adipose tissue and releasing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α.[46] Obesity and insulin resistance may upregulate the expression of pro-inflammatory cytokines[47] and activate HSCs, thereby reinforcing the development of hepatic fibrosis. Furthermore, long-term alcohol consumption is a known cause of alcoholic liver disease and LF.[48] The main metabolite of ethanol, acetaldehyde, is highly toxic to hepatocytes and can lead to hepatocyte death and apoptosis. Meanwhile, ROS generated during ethanol catabolism causes oxidative stress and further induces hepatocyte death.[49] This persistent damage to hepatocytes causes mesenchymal cells to proliferate, thus resulting in fibrosis. Hepatic steatosis is also closely related to insulin resistance.[50,51] Fatty liver further exacerbates the development of insulin resistance by hindering the elimination of insulin from the portal vein, forming a vicious cycle. The imbalance of pro-inflammatory cytokines, free fatty acids, and adiponectin resulting from the vicious cycle can exacerbate the inflammatory response and is considered the main pathological mechanism of LF in patients with fatty liver.[52] Therefore, lifestyle management is particularly essential for these high-risk groups, including dietary adjustments, increasing physical activity, controlling alcohol consumption, and improving metabolic health. These measures may help reduce the risk of LF and refine the prognosis of liver disease.

The mediation analysis highlighted the mediating roles of oxidative stress factors, serum albumin, uric acid, and GGT in the association between CMI and LF. Serum albumin acts as an essential antioxidant in the human body.[27] The level of serum albumin reflects the body's oxidative stress state. A negative linkage between albumin levels and stages of LF has been revealed,[28] which is in line with the results showing that elevated levels of serum albumin can reduce the risk of LF ($\beta = -0.118$). Uric acid has dual properties of an antioxidant and a pro-oxidant.[53,54] Under physiological conditions, uric acid may elevate oxidative stress levels by increasing the production of ROS.[29] Hyperuricemia is connected with advanced LF in patients with MASLD.[30] Gamma-glutamyl transferase is not only a marker of liver damage, but also

Table 4. Mediation Analysis of Oxidative Factors on the Relationship Between Cardiometabolic Index and Liver Fibrosis by Sex Subgroup Analysis

Oxidative Stress	Direct Effect	Indirect Effect	Mediated Proportion % (95% CI)
Male			
Serum albumin	OR = 0.057, *P*<.001, 95% CI: 0.034, 0.080	OR = 0.002, *P* = .140, 95% CI: −0.001, 0.010	4.13 (−1.18, 12.00)
Uric acid	OR = 0.056, *P*<.001, 95% CI: 0.033, 0.080	OR = 0.002, *P* = .210, 95% CI: −0.001, 0.010	3.30 (−1.99, 11.00)
GGT	OR = 0.055, *P*<.001, 95% CI: 0.033, 0.070	OR = 0.003, *P* = .050, 95% CI: 0, 0.010	4.65 (0.03, 11.00)*
Female			
Serum albumin	OR = 0.062, *P*<.001, 95% CI: 0.039, 0.080	OR = 0.006, *P* = .012, 95% CI: 0.002, 0.010	9.18 (1.96, 19.00)*
Uric acid	OR = 0.058, *P*<.001, 95% CI: 0.035, 0.080	OR = 0.009, *P* = .018, 95% CI: 0.002, 0.020	13.55 (2.53, 27.00)*
GGT	OR = 0.065, *P*<.001, 95% CI: 0.042, 0.090	OR = 0.004, *P* = .010, 95% CI: 0.001, 0.010	5.21 (0.78, 10.00)*

Adjustments for age, sex, race BMI, smoking, alcohol consumption, total bilirubin, ALT, BUN, AST, non-HDL-C, total sugar intake, and total energy intake.
GGT, gamma-glutamyl transferase; OR, odds ratio.
*$P < .05$.
**$P < .01$.
***$P < .001$.

plays a pivotal role in the metabolism of glutathione, with its elevation usually indicating oxidative damage to liver cells.[55] In a cross-sectional study, elevated GGT can affect metabolic syndrome and progressive LF in patients with MASLD.[32]

It is worth noting that interesting differences in sex stratification analysis were observed. In females, the mediating ratio of serum albumin and uric acid is higher than that in males, while the mediating effect of GGT exists in both males and females, but in a lower proportion. The sex dimorphism of this association strength suggests potential biological mechanism differences. Estrogen has been found to exhibit potential protective effects in preventing or delaying the progression of LF. Estrogen can alleviate liver lipid deposition,[56] reduce oxidative stress induced by lipotoxicity in liver mitochondria, alleviate inflammation, and protect liver cells from damage.[57,58] Therefore, in women, pathways related to antioxidant capacity, such as albumin and uric acid, may play a more prominent role in liver damage associated with metabolic disorders. On the contrary, the association between CMI observed in males and LF may be related to the involvement of Y chromosome genes (especially *SRY* genes) in regulating fibrosis response. According to previous animal and molecular studies, the *SRY* gene can transcriptionally regulate platelet-derived growth factor receptor α (*Pdgfr*α) expression and promote HMGB1 release and subsequent activation of HSCs. By upregulating the expression of profibrotic genes, males are more likely to experience liver tissue repair imbalance and fibrosis exacerbation when subjected to oxidative stress or increased metabolic load.[59] It should be emphasized that these explanations are still speculative at present, and further clarification of the role of sex in metabolism-related LF is needed at the genetic and molecular levels in the future.

Table 5. Unweighted Logistic Regression Analysis on the Associations Between Cardiometabolic Index and Liver Fibrosis in Sensitive Analysis

Participants	Crude Model	Model 1	Model 2
CMI (continuous)	OR = 2.16, *P*<.001, 95% CI: 1.82-2.57	OR = 2.14, *P*<.001, 95% CI: 1.78-2.56	OR = 2.24, *P*<.001, 95% CI: 1.81-2.77
CMI (categorical)			
T1 (<0.296)	Ref.	Ref.	Ref.
T2 (0.296-0.641)	OR = 2.82, *P*<.001, 95% CI: 1.92-4.24	OR = 2.56, *P*<.001, 95% CI: 1.73-3.86	OR = 2.95, *P*<.001, 95% CI: 1.93-4.61
T3 (≥0.641)	OR = 5.77, *P*<.001, 95% CI: 4.03-8.50	OR = 5.34, *P*<.001, 95% CI: 3.69-7.95	OR = 6.87, *P*<.001, 95% CI: 4.46-10.86
P_{trend}	<.001	<.001	<.001

Crude model: no adjustment for confounding factors. Model 1: adjustments for age, sex, and race. Model 2: adjustments for age, sex, race BMI, smoking, alcohol consumption, total bilirubin ALT, BUN, AST, non-HDL-C, total sugar intake, total energy intake.
CMI, Cardiometabolic Index; OR, odds ratio.

This study confirmed that CMI, as a simple tool based on conventional metabolic indicators such as WHtR and TG/HDL-C, can integrate the dual risks of metabolic abnormalities and oxidative stress, providing a new strategy for early screening of LF. By combining oxidative stress markers such as serum albumin, uric acid, and GGT, CMI can not only identify high-risk populations (such as obesity and metabolic syndrome patients) but also suggest potential oxidative damage mechanisms, thereby optimizing primary stratified management. For example, prioritizing FIB-4 scores or imaging examinations for individuals with elevated CMI can achieve efficient resource allocation. In addition, this study revealed for the first time at the population level the specific pathway through which CMI mediates LF through oxidative stress (mediation ratio ranging from 5.60% to 8.15%), providing direct evidence for the pathological mechanism of the "metabolism-oxidative stress-fibrosis" axis. This discovery suggests that combined interventions targeting metabolic and oxidative pathways, such as lipid-lowering therapy combined with antioxidants, may be an effective strategy for delaying fibrosis progression. Future research needs to further validate the universality of CMI in non-obese MASLD, different ethnic and regional populations, or verify the predictive value of CMI dynamic changes on intervention effectiveness through longitudinal cohort studies.

It should be pointed out that although this study focuses on the mediating role of oxidative stress, the influence of other unmeasured mediating pathways cannot be ruled out. Chronic low-grade inflammatory response remains an important biological mechanism between metabolic disorders and LF, and this study did not include inflammatory biomarkers such as C-reactive protein (CRP) and IL-6 for evaluation. In addition, dietary structure and physical activity level can independently affect metabolic status, liver lipid deposition, and fibrosis risk. These unmeasured behaviors or inflammation-related factors may interact with the oxidative stress pathway, thereby participating in or amplifying the association between CMI and LF to some extent. Future research needs to combine more comprehensive inflammatory biomarkers, dietary survey data, and physical activity data, and further use multi-omics methods to systematically analyze the interactions of different pathways in order to more accurately characterize the complex mechanism network of CMI acting on LF.

Although this investigation provides evidence of a positive association between oxidative stress-mediated CMI and hepatic fibrosis, certain limitations persist. Firstly, this study is a cross-sectional study that limits causal inference. The time sequence of exposure mediation outcome cannot be determined, and mediation effects may be influenced by reverse causality and residual confounding. The observed mediation effects should be considered as preliminary evidence, and their robustness needs to be further validated through longitudinal cohorts or intervention studies. Secondly, the extrapolation of research needs to be carefully evaluated. The NHANES data are mainly based on the American population, whose racial structure, dietary habits, and prevalence of liver disease differ from regions such as Asia, the Middle East, and Europe. Therefore, the applicability of the research results to other populations is limited. Thirdly, confounding factors cannot be completely ruled out. Although this study controlled for bias through complex sampling weighting and statistical analysis, this cross-sectional study may still contain unknown or unmeasured confounding factors that affect the observed associations. Finally, the sample for this study was from the general population, and the incidence of LF (especially advanced fibrosis) is relatively low, which may have an impact on the positive predictive value of imaging tools such as FibroScan. However, through stratified analysis and a tiered screening strategy, the limitations of low prevalence rates were partially alleviated. In the future, it is necessary to verify the synergistic application value of CMI and imaging tools in higher-risk populations (such as MASLD outpatient patients) and develop composite models to optimize diagnostic efficiency. Taken together, these findings revealed a positive correlation between CMI and LF and highlighted the key role of oxidative stress factors in it. These findings can proffer a new perspective on the complex relationship between CMI and liver diseases, offering scientific evidence for the prevention and clinical management of LF in the future.

CONCLUSION

Based on the NHANES data, this work systematically revealed a significant positive correlation between CMI and LF and emphasized the mediating role of oxidative stress factors (serum albumin, uric acid, and GGT) in this association. These findings not only deepen the interpretation of the relationship between metabolic abnormalities and LF but also provide a scientific basis for the early prevention of LF. Future studies should further validate these findings in different populations to provide stronger evidence and guidance for the prevention and clinical management of LF.

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