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The association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and hepatic steatosis and liver fibrosis among US adults based on NHANES

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Recently, the non-high-density to high-density lipoprotein cholesterol ratio (NHHR) has gained growing attention as an indicator for predicting diseases associated with lipid metabolism. Hepatic steatosis and fibrosis are tightly associated lipid metabolism. Our study aims to analyze the correlations among NHHR, hepatic steatosis, and fibrosis. This study analysed data from 14,578 adults in the US National Health and Nutrition Examination Survey (2005–2018). The degree of hepatic steatosis was measured through the Fatty Liver Index (FLI), while liver fibrosis severity was evaluated with the Fibrosis-4 (FIB-4) index. Multivariate linear regression assessed the association between NHHR and the FLI and FIB-4 score. Smooth curve describing the relationship between NHHR and FLI or FIB-4. Additionally, a two-part linear regression model adopted in order to more accurately account for the nonlinear relationship, with threshold effects estimated through its two components. To confirm the robustness of the findings, interaction tests and subgroup analyses were conducted. The multivariate logistic regression analysis demonstrated a significantly positive correlation of lnNHHR with FLI across all three models. In Model 3, the association was (β = 11.14, 95%CI:10.38,11.90). Curve fitting indicated a nonlinear relationship. The positive correlation between lnNHHR and FLI persists across gender, BMI, and physical activity groups. Nevertheless, a notable negative correlation between lnNHHR and FIB-4 was observed in all three models. In Model 3, the relationship between lnNHHR and FIB-4 was as follows: (β = -0.20; 95% CI: -0.22, -0.17). Curve fitting revealed a V-shaped relationship, with threshold effect analysis identifying a breakpoint at 1.51. Above this threshold, the relationship was found to be statistically insignificant (p-value = 0.424). Receiver operating characteristic (ROC) curve analysis demonstrated that NHHR exhibited better predictive performance for MASLD compared to non-HDL-C, HDL-C, and LDL-C/HDL-C. The current study's findings suggest that elevated levels of NHHR correlate with a greater risk of hepatic steatosis among adults in the U.S. Our findings imply that NHHR may be a valuable tool in improving MASLD prevention strategies in the general population.

Keywords NHHR, NHANES, NAFLD, Hepatic steatosis, Liver fibrosis

Abbreviations

NHHR	Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio
NAFLD	Non-alcoholic fatty liver disease
MASLD	Metabolic-associated fatty liver disease
HDL-C	High-density lipoprotein cholesterol
non-HDL-C	Non-high-density lipoprotein cholesterol
TC	Total cholesterol
FLI	Fatty Liver Index

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FIB-4	Fibrosis-4 Index
NCHS	National Center for Health Statistics
PIR	Income-to-Poverty Ratio
BMI	Body mass index
WC	Waist circumference
CKD	Chronic kidney disease
CVD	Cardiovascular disease

Non-alcoholic fatty liver disease (NAFLD) refers to the clustering of an abundant quantity of fatty tissue within liver cells, which develops without alcohol consumption or other commonly known causes[1]. In 2023, to reduce stigma and enhance awareness of NAFLD, an international expert committee from multiple societies decided to adopt the new term "metabolic-associated fatty liver disease" (MASLD) to replace NAFLD[2]. MASLD is the most common chronic liver disease disorder, with the possibility of advancing to severe hepatic fibrosis and, ultimately, end-stage liver failure[1,3]. It involves a range of liver conditions, starting with mild steatosis and progressing to more severe stages (cirrhosis and even hepatocellular carcinoma)[4–6].

The extant literature offers compelling evidence of a robust correlation between MASLD and a series of metabolic disorders, which include diabetes, hypertension, obesity, and cardiovascular disease[6–9]. The liver is pivotal in regulating cholesterol metabolism, overseeing its production and removal. Imbalances in hepatic cholesterol homeostasis are strongly linked to the buildup of lipids[10]. The advancement of MASLD is tightly linked to the increased buildup of cholesterols in the liver[3,10,11]. The extant evidence indicates that an excess of free cholesterol can precipitate hepatocellular injury, which may, in turn, give rise to hepatic inflammation and a subsequent development of fibrosis. The equilibrium of cholesterol is sustained through a multitude of metabolic pathways, including the processes of intestinal absorption, hepatic synthesis, and bile acid production. Nevertheless, disturbances in these pathways may contribute to the pathogenesis of MASLD. Specifically, altered cholesterol transport and storage mechanisms increase the risk of lipid toxicity, which exacerbates liver damage and promotes disease progression[10,12–14]. It can, therefore, be reasonably inferred that cholesterol metabolism exerts a pivotal role in MASLD 's pathogenesis and progressive disease development.

In recent years, NHHR has come to be regarded as an increasingly important biomarker for lipid metabolism[15–17]. Prior research has emphasized NHHR's potential as a reliable predictor for various conditions, including type 2 diabetes, depression, gallstone, and metabolic syndrome[17–20]. Yu et al. demonstrated that NHHR exhibits a U-shaped association with all-cause mortality and an L-shaped association with cardiovascular mortality in individuals with diabetes and prediabetes, underscoring its prognostic value in this population[21]. Tan et al. reported that NHHR correlates positively with type 2 diabetes mellitus (T2DM) risk, independent of age, BMI, or other demographic factors, with its relationship being particularly pronounced in males[22]. Additionally, Kim et al. found NHHR to be superior to traditional lipid ratios in predicting metabolic syndrome and insulin resistance, suggesting its broader applicability in metabolic disease management[20]. Existing research, such as the study by Yang et al. conducted on Chinese pediatric and adolescent populations, has demonstrated a significant association between the MASLD and NHHR[23]. Building on the above, the present study is focused on a U.S. adult population, aiming to provide insight into the relationship between NHHR, hepatic steatosis, and liver fibrosis. The goal is to shed light on potential variations in metabolic and disease risks across different populations. The aim is to gain further insight into the capacity of NHHR to serve as a predictive indicator for liver-related conditions, thereby contributing to earlier diagnosis and more targeted intervention strategies.

Methods

Study design and population

This study utilized data obtained from the National Health and Nutrition Examination Survey (NHANES). Conducted by the National Center for Health Statistics, uses a multistage, stratified probability-cluster sampling approach to evaluate the health and nutritional status of both U.S. adults and children. The study was ethically sanctioned by the NCHS Ethics Review Board, with all procedures conducted in adherence to the established ethical guidelines and informed permission obtained from the participants.

The data were analyzed from U.S. adults aged 20 and above who participated in seven NHANES cycles between 2005–2006 and 2017–2018. Of the 79,501 participants enrolled in NHANES during this period, we focused on those meeting the inclusion criteria. Participants were excluded if they: (1) those who are under the age of 20 (n = 35,427); (2) Missing data on NHHR and FLI and FIB-4 (n = 6619); (3) other pre-existing liver conditions or alternative causes of chronic liver disease, including positive hepatitis B virus surface antigen (HBsAg) and hepatitis C virus (HCV) RNA (n = 835); (4) excessive alcohol consumption based on questionnaires (n = 4699); (5) Weighted data are missing or equal to 0 (n = 17,334). After the necessary exclusions were applied, the final analysis was based on the data from 14,587 participants (Fig. 1).

Independent and dependent variables

In this study, the main exposure variable was the NHHR. The non-HDL cholesterol to HDL cholesterol ratio is utilized to ascertain the non-HDL cholesterol level, which is abbreviated as NHHR. The non-HDL-C is computed by deducting the HDL-C value of the total cholesterol (TC) value[16,17].

FibroScan is a relatively standard method for assessing hepatic steatosis and liver fibrosis. However, data prior to 2017 in NHANES lack FibroScan measurements. Therefore, we utilized the widely applicable Fatty Liver Index (FLI) and Fibrosis-4 (FIB-4) index to evaluate the severity of hepatic steatosis and liver fibrosis, respectively.

FLI and FIB-4 were defined as the dependent variable. FLI is a non-invasive evaluation tool based on straightforward clinical parameters that is utilized extensively for the purpose of assessing hepatic steatosis

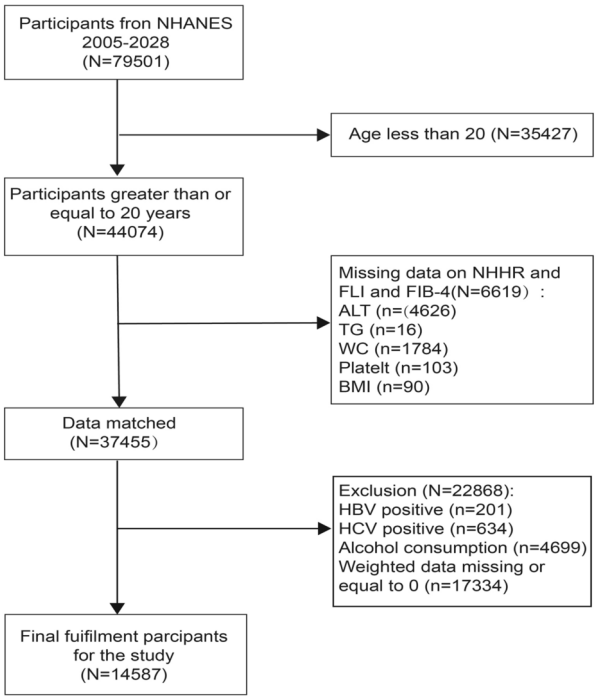

Fig. 1. Flow chart of participants selection. NHANES, National Health and Nutrition Examination Survey.

associated with MASLD and metabolic liver disorders[24–26].The FLI is typically categorized into three primary ranges: FLI < 30, Reflects a low likelihood of hepatic steatosis; FLI 30 < FLI < 60, Represents an intermediate likelihood, suggesting the possibility of moderate steatosis and the need for further clinical evaluation; FLI ≥ 60, Signifies a high probability of significant liver steatosis, and it Can be recognized as fatty liver. FLI has been confirmed as a dependable instrument for evaluating hepatic steatosis[24,27].

FIB-4 is a commonly utilized non-invasive examination intended for evaluating liver fibrosis, especially in individuals with chronic liver conditions like hepatitis or metabolic-associated steatotic liver disease[28–30]. FIB-4 allows clinicians to stratify the risk of advanced liver fibrosis: FIB-4 < 1.45 suggests a low likelihood of fibrosis; FIB-4 range of 1.45 to 3.25 represents an indeterminate zone; FIB-4 > 3.25 signifies a high probability of advanced fibrosis or cirrhosis[28,29,31], often prompting further diagnostic intervention or consideration of more aggressive treatment options.

Covariates

To more precisely assess the independent effects of NHHR on FLI and FIB-4, we incorporated covariates that could influence these relationships into the model for adjustment. The covariates were based on data obtained from the questionnaires, including age, gender, race, family income-to-poverty ratio (PIR), education level, body mass index (BMI), waist circumference (WC), hypertension, diabetes, physical activity and smoke.

Statistical analysis

The statistical analysis was calculated utilizing the R software (version 4.1.3) alongside EmpowerStats (version 4.1). The normality test indicated that the NHHR data were skewed. As a result, we applied a logarithmic transformation using ln transformed NHHR to normalize the data for subsequent analyses. The participants were sorted into three equal parts according to the lnNHHR values: < 0.736, 0.736 ≤ lnNHHR ≤ 1.124, and > 1.124. This transformed variable was used in all analyses throughout the study. Baseline characteristics of the study population were stratified by FLI and FIB-4 subgroups. Continuous variables were depicted as mean ± Se and proportions for categorical variables and weighted linear regression models were applied. Beta coefficients and 95% confidence intervals (CI) were derived through multivariate linear regression to assess the associations between lnNHHR, FLI, and FIB-4. For the analysis, three distinct models were developed with varying levels of adjustment: Model 1 had no adjustments, Model 2 included partial adjustments, and Model 3 was fully adjusted. Simultaneous variable adjustments were performed using smoothed curve fitting, and a threshold effect analysis model was applied to assess evaluate the correlation and inflection point between lnNHHR and FLI and FIB-4. The same analytical method was utilized for the subgroups, with statistical significance defined as P-value < 0.05. The receiver operating characteristic (ROC) curve was used to evaluate the performance of NHHR in diagnosing MASLD. The diagnostic efficacy of NHHR and other lipid parameters was determined by calculating the area under the curve (AUC). Moreover, a weighting technique was mitigated dataset variability and enhance the stability of the results.

Result

Participants characteristics

Table 1 illustrates the baseline characteristics of the participants, classified accordingly with FLI. Of 14,587 individuals were selected for enrolment in the study. The average participant age was 46.12 years (Se = 0.46). Of the research participants, 55.45% were female, and 43.12% identified as non-Hispanic white. As Table 1 illustrates, the FLI was classified into three categories based on the extent of hepatic steatosis. Compared to the group with the lowest FLI, those with higher FLI group were more likely to identify as male and belong to either Mexican American or non-Hispanic Black ethnic backgrounds and exhibited a higher prevalence of diabetes and hypertension. Also, participants with more severe hepatic steatosis exhibited higher WC, TC, BMI, TG, and NHHR, along with elevated HDL-C.

Table 2 illustrates the baseline characteristics of the participants, classified accordingly with FIB-4. In accordance with the findings of previous research, FIB-4 was classified into three categories, each corresponding to a distinct degree of liver fibrosis. Compared to the group with the FIB-4 lowest, those with higher FIB-4 group were more prone to be male and non-Hispanic white, with an increased likelihood of having diabetes and hypertension. Additionally, individuals with elevated FIB-4 scores were typically older, had higher TG, WC, and FLI scores, lower NHHR values, and engaged in less vigorous physical activity (Table 2).

The association between lnNHHR and FLI

Multiple logistic regression models were constructed to ascertain whether there is an inherent correlation between lnNHHR concentration and FLI. Table 3 illustrates a markedly positive correlation between lnNHHR and FLI across all models, including the unadjusted model 1 [β = 31.22, (30.11,32.33)], the partially adjusted model 2 [β = 30.82, (29.69,31.96)], and the fully adjusted model 3 [β = 11.14, (10.38,11.90)]. In the model 3, an additional analysis was conduced to further clarify the association between lnNHHR and FLI by dividing lnNHHR into tertiles. Compared to Tertile 1, a higher lnNHHR (Tertile2 and Tertile3) to exhibit a strong association with FLI [β = 3.65, (2.88,4.42), and 10.87, (10.04,11.7), p for trend < 0.0001]. Moreover, the results from the smoothed curve fitting provided further confirmation of the nonlinear positive relationship between lnNHHR and FLI score (Fig. 2).

Table 4 presents the results of subgroup analysis and interaction effects based on stratified population variables. The positive correlation between lnNHHR and FLI persists across gender, BMI, and physical activity groups. Nevertheless, no notable interaction effects were identified in the stratified groups based on educational level, PIR, diabetes status, smoke, or hypertension.

The association between lnNHHR and FIB-4

The findings from the multiple regression analysis revealed a notable association was observed between lnNHHR and FIB-4, with a negative correlation evident across all models (Table 5), including the crude model 1 [β = −0.19, (−0.21, −0.16)], the partially adjusted model 2 [β = −0.24, (−0.26, −0.22)], and the fully adjusted model 3 [β = −0.20, (−0.22, −0.17)]. In model 3, lnNHHR was also divided into three categories. Compared to Tertile1, higher lnNHHR (Tertile2 and Tertile3) had significantly negative association with FIB-4 [β = −0.13, (−0.15, −0.10) and −0.19, (−0.21, −0.16), p for trend < 0.001]. The potential nonlinear relationship between lnNHHR and FIB-4 was evaluated through the use of smooth curve fitting and threshold effect analysis. Depending on Fig. 3; Table 6, a significant V-shaped nonlinear association was identified between lnNHHR and FIB-4, with an inflection point of 1.51 (Fig. 3). The effect below the threshold β coefficient is −0.24 (95% CI: −0.27, −0.22), is indicating a statistically significance inverse relationship between the two variables (p-valve < 0.0001). Above the threshold, the β coefficient is 0.06 (95% CI: −0.08, 0.19), indicating a weak and statistically non-significant association (p-valve = 0.4242).

Subgroup analyses and interaction tests were conducted to evaluate how stratified population variables influence the relationship between lnNHHR and FIB-4, as presented in Table 7. The negative correlation between lnNHHR and FIB-4 shows an interaction effect across different physical activity levels. The analysis suggests that individuals who engage in non-vigorous physical activity [β = −0.23, (−0.27, −0.18)] are at a higher risk of developing advanced liver fibrosis than those involved in vigorous physical activity [β = −0.12, (−0.18, −0.06)]. It is to be noted that no substantial interactions were identified between the negative association and variables such as gender, educational level, BMI, PIR, diabetes, smoke and hypertension.

NHHR as a predictor of MASLD*: ROC analysis*

In previous studies, HDL-C, non-HDL-C, and the LDL-C/HDL-C ratio have been identified as significant predictors of MASLD. In this study, we compared NHHR with these factors using ROC curve analysis. Figure 4 presents the ROC curves, demonstrating that the area under the curve (AUC) for NHHR was significantly larger than those of the other three factors. As shown in Supplementary Table 1, the AUC for NHHR was 0.700, with a sensitivity of 0.7204 and a specificity of 0.6906 for predicting NAFLD. Compared to the other groups, NHHR exhibited notably higher sensitivity and specificity.

Discussion

The results of this study, which analyzed data from 14,587 participants, indicate a meaningful positive correlation between the NHHR and hepatic steatosis. Moreover, the positive correlation persists across gender, BMI, and physical activity groups. The curve results indicate a nonlinear relationship between lnNHHR and FLI. Furthermore, our results indicate a negative association between lnNHHR and hepatic fibrosis. Smoothing curve and threshold effect analysis revealed a V-shaped relationship, with a turning point at 1.51. Prior to the

Characteristic	Fatty Liver Index (FLI)			
	FLI < 30 N = 6765	30 ≤ FLI < 60 N = 2909	FLI ≥ 60 N = 4913	P-value
Age(years)	43.28 ± 0.41	49.04 ± 0.62	48.32 ± 0.41	< 0.0001
Gender, %				< 0.0001
Male	2736 (40.44)	1379 (47.40)	2381 (48.46)	
Female	4029 (59.36)	1530 (53.60)	2532 (51.54)	
Race/Ethnicity, %				< 0.0001
Mexican American	881 (13.02)	492 (16.91)	920 (18.73)	
Non-Hispanic White	2999 (44.33)	1246 (42.83)	2045 (41.62)	
Non-Hispanic Black	1246 (18.42)	580 (19.94)	1079 (21.96)	
Other Race	1639 (24.23)	591 (20.32)	869 (17.69)	
Educational level, %				< 0.0001
< High school	1352 (19.98)	646 (22.21)	1189 (24.20)	
High school	1369 (20.24)	640 (22.00)	1159 (23.59)	
Some college or above	4044 (59.78)	1623 (55.79)	2565 (52.21)	
PIR, %				< 0.0001
< 1.0	1153 (17.04)	471 (16.19)	906 (18.44)	
1.0–3.0	2716 (40.15)	1266 (43.52)	2239 (20.21)	
> 3.0	2896 (42,81)	1172 (40.29)	1768 (35.99)	
BMI, %				< 0.0001
< 25.0	3931 (58.23)	368 (12.65)	59 (1.20)	
25.0–29.9	2169 (32.06)	1634 (56.17)	993 (20.21)	
≥ 30.0	665 (9.83)	907 (31.18)	3861 (78.59)	
Smoke, %				0.0001
Yes	2463 (36.41)	1144 (39.33)	2091 (42.56)	
No	4302 (63.59)	1765 (60.67)	2822 (57.44)	
Diabetes, %				< 0.0001
Yes	726(10.73)	590 (20.28)	1538 (31.30)	
No	6039 (89.27)	2319 (79.72)	3375 (68.70)	
Physical activity, %				< 0.0001
Vigorous	1673 (24.73)	865 (29.74)	1595 (32.46)	
No Vigorous	5092 (75.27)	2044 (70.26)	3318 (67.54)	
Hypertension, %				< 0.0001
Yes	2658 (39.29)	1573 (54.07)	3207 (65.28)	
No	4107 (60.71)	1336 (45.93)	1706 (34.72)	
Waist circumference (cm)	86.91 ± 0.27	98.95 ± 0.23	113.47 ± 0.34	
HDL-C, (mmol/L)	1.56 ± 0.01	1.40 ± 0.01	1.24 ± 0.01	< 0.0001
Total cholesterol, (mmol/L)	4.87 ± 0.02	5.05 ± 0.03	5.15 ± 0.03	< 0.0001
Triglycerid, (mg/dL)	68.17 ± 1.34	111.02 ± 2.07	168.91 ± 4.80	< 0.0001
FIB-4 score	1.03 ± 0.01	1.12 ± 0.03	1.03 ± 0.02	0.0341
NHHR	2.31 ± 0.02	2.78 ± 0.02	3.38 ± 0.03	< 0.0001

Table 1. Basic characteristics of participants by fatty liver index (FLI) among U.S. adults. Mean ± Se for continuous variables: the P value was calculated by the weighted linear regression model; n (%) for categorical variables: the P value was calculated by the weighted chi-square test. Abbreviation: NHHR: non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PIR: Poverty Income Ratio; BMI: Body Mass Index; HDL-C: high-density lipoprotein cholesterol; FIB-4: Fibrosis-4 Index.

inflection point, a reduction in the lnNHHR correlated positively with FIB-4. However, after this point, the correlation did not achieve statistical significance.

Liver fibrosis is a complex process driven by chronic liver injury and sustained inflammatory responses, involving dynamic interactions between hepatic and extrahepatic cell populations[32]. In the early stages of liver fibrosis, dysregulation of lipid metabolism, characterized by elevated non-HDL-C and reduced HDL-C, may promote the progression of fibrosis through oxidative stress, the release of inflammatory cytokines, and the activation of hepatic stellate cells. NHHR, as an indicator of lipid metabolism imbalance, reflects the extent of the lipid-toxic environment. As fibrosis progresses, the fibrotic tissue microenvironment may impose restrictions on lipid metabolism, leading to a redistribution or attenuation of metabolic load. Furthermore, in advanced fibrosis, liver dysfunction may weaken the direct effects of lipid toxicity on hepatocytes[32,33], which may explain why the positive correlation between NHHR and FIB-4 becomes statistically insignificant beyond a certain threshold.

This study also revealed that the association between the NHHR and hepatic steatosis is influenced by gender, BMI, and physical activity, consistent with findings from previous studies. However, within our study population, the proportion of severe hepatic steatosis cases was slightly higher among females than males. We speculate that this discrepancy may be attributed to the significantly larger sample size of females compared to males in our cohort. Furthermore, when exploring the relationship between NHHR and liver fibrosis, physical activity levels also emerged as a significant influencing factor. Recent research has demonstrated that 12 weeks of aerobic exercise can significantly improve histological features, including hepatocellular ballooning and liver fibrosis, in patients with MASLD[34]. Other studies have reported that high-intensity exercise is associated with reductions in body weight, visceral fat, and liver fat[35]. However, the required amount and intensity of physical activity to achieve weight loss, as well as its impact on MASLD risk, remain unclear. Additionally, exercise interventions have been shown to favorably regulate serum pro-inflammatory cytokines, such as interleukin-6, and metabolic regulators, such as fibroblast growth factor 21 (FGF21), in individuals with MASLD[36,37]. Moreover, recent studies indicate that vigorous physical activity, compared to moderate-intensity exercise, is more effective in reducing all-cause mortality among adults with MASLD[38]. This benefit is particularly pronounced in those with obesity, hypertension, or metabolic syndrome[39–41]. We hypothesize that vigorous physical activity may serve as an effective therapeutic strategy for MASLD management.

NHHR represents an emerging methodology for the comprehensive assessment of atherogenic lipids, encompassing HDL-C and non-HDL cholesterol. It has been linked to disorders of lipid metabolism and is associated with a number of diseases that are related to dyslipidemia[18,20,21]. In dyslipidemia management, the primary focus typically centers on LDL-C levels[42]. Nonetheless, research indicates that non-HDL-C, comprising all plasma lipoproteins other than HDL-C, has emerged as a major risk factor for MASLD[23]. XuDong Huang et al. used NHANES data from 2017 to 2020 and found that the prevalence of MASLD among US adults increases with the elevation of NHHR, which is consistent with our findings[43]**.** However, our study did not observe a significant interaction between NHHR and hepatic steatosis in hypertensive and diabetic populations ($p > 0.05$). Additionally, our study further reveals a significant negatively correlation between NHHR and liver fibrosis, with a significant interaction effect at different levels of physical activity ($p < 0.05$).

MASLD is closely associated with TC, LDL-C, HDL-C, and TG, highlighting the central role of dysregulated lipid metabolism in its pathogenesis. Patients with MASLD often exhibit elevated TG and LDL-C levels, with small dense LDL particles posing a higher risk for atherosclerosis[44,45]. This is primarily attributed to increased hepatic cholesterol synthesis and impaired cholesterol clearance. Concurrently, HDL-C levels are significantly reduced, leading to compromised reverse cholesterol transport, which exacerbates both hepatic steatosis and cardiovascular disease risk. Moreover, hypertriglyceridemia is a hallmark of MASLD, with studies reporting that increased very-low-density lipoprotein (VLDL) secretion and impaired lipid clearance in the liver contribute to elevated TG levels in MASLD patients[44–47].

Cholesterol metabolism imbalances and insulin resistance are strongly linked to the development and advancement of MASLD[48]. Lee et al. observed that individuals with sustained elevations in non-HDL-C had a notably higher risk of developing MASLD than those maintaining stable or lower levels of non-HDL-C[49]. This increased risk may be attributed to non-HDL-C's role in lipid buildup within the liver, which initiates inflammation and oxidative stress, ultimately leading to liver damage[13,50,51]. A study demonstrated that remnant cholesterol, a non-HDL-C component, is positively correlated with the severity of hepatic steatosis. Elevated levels of remnant cholesterol markedly elevate the probability of developing mild to moderate MASLD, with the risk intensifying in tandem with rising cholesterol levels. This association underscores the role of remnant cholesterol in exacerbating liver lipid accumulation and subsequent liver damage[52]. Additionally, research has shown that elevated LDL-C levels can exacerbate liver inflammation and fibrosis through their hepatotoxic effects. This progression plays a crucial role in advancing MASLD toward more severe stages, such as liver fibrosis and cirrhosis[10]. Recent research has shown that as MASLD advances, the likelihood of developing liver fibrosis rises considerably. In this context, non-HDL cholesterol plays a critical role, with evidence suggesting that controlling its levels may help slow the advancement of MASLD and mitigate the risk of fibrosis development[53]. Researchers have identified a close association between abnormal HDL-C levels and the onset of various diseases, including depression, cardiovascular disease (CVD) and bone fractures[54–56]. It has been suggested that elevated or reduced HDL-C concentrations may influence health outcomes due to the role of HDL-C in lipid metabolism and inflammation regulation. Moreover, while HDL-C is typically viewed as protective against CVD owing to its anti-inflammatory and antioxidant properties, recent studies indicate that high HDL-C levels may paradoxically increase fracture risk and even exacerbate certain cardiovascular conditions under specific inflammatory states[55,56]. These intricate relationships highlight the necessity for a nuanced comprehension of the function of HDL-C in the context of diverse pathological processes. Prior research has identified HDL-C as a crucial element in lipid metabolism, citing its involvement in reverse cholesterol transport, antioxidant defense mechanisms, and anti-inflammatory processes[57–59]. A substantial body of published research has shown

Characteristic	Fibrosis-4 Index (FIB-4)			
	FIB-4 < 1.45 N = 11,140	1.45 ≤ FIB-4 ≤ 3.25 N = 3236	FIB-4 > 3.25 N = 211	P value
Age, (years)	41.26 ± 0.24	65.64 ± 0.38	70.88 ± 1.24	< 0.0001
Gender				0.2704
Male	4790 (43.00)	1592 (49.20)	114 (54.03)	
Female	6350 (57.00)	1644 (50.80)	97 (45.97)	
Race/Ethnicity				< 0.0001
Mexican American	1921 (17.24)	352 (10.88)	20 (9.48)	
Non-Hispanic White	4465 (40.08)	1693 (52,32)	132 (62.56)	
Non-Hispanic Black	2281 (20.48)	596 (18.42)	28 (13.27)	
Other Race	2473 (22.20)	595 (18.38)	31 (14.69)	
Educational level				0.0141
< High school	2293 (20.59)	844 (26.08)	50 (23.70)	
High school	2361 (21.19)	755 (23.33)	52 (24.64)	
Some college or above	6486 (58.22)	1637 (50.59)	109 (51.66)	
PIR				0.0003
< 1.0	2046 (18.37)	460 (14.22)	24 (11.37)	
1.0–3.0	4647 (41.71)	1462 (45.18)	112 (53.08)	
> 3.0	4447 (39.92)	1314 (40.60)	75 (35.55)	
BMI				< 0.0001
< 25.0	3204 (28.76)	1090 (33.68)	64 (30.33)	
25.0–29.9	3559 (31.95)	1158 (35.78)	79 (37.44)	
≥ 30.0	4377 (39.29)	988 (30.53)	68 (32.23)	
Smoke				0.0138
Yes	4220 (37.88)	1365 (42.18)	113 (53.55)	
No	6920 (62.12)	1871 (57.82)	98 (46.45)	
Diabetes				< 0.0001
Yes	1765 (14.55)	998 (30.57)	91 (37.66)	
No	9375 (85.45)	2238 (69.43)	120 (62.34)	
Physical activity				< 0.0001
Vigorous	3343 (30.01)	738 (22.81)	52 (24.64)	
No vigorous	7797 (69.99)	2498 (77.19)	159 (75.36)	
Hypertension				< 0.0001
Yes	4867 (43.69)	2412 (74.54)	159 (75.36)	
No	6273 (56.31)	824 (25.46)	52 (24.64)	
Waist circumference, cm	97.98 ± 0.33	98.56 ± 0.44	99.54 ± 1.11	0.2609
HDL-C, (mmol/L)	1.39 ± 0.01	1.57 ± 0.02	1.57 ± 0.09	< 0.0001
Total cholesterol (TC), (mmol/L)	4.99 ± 0.02	5..04 ± 0.03	4.51 ± 0.14	0.0012
Triglyceride (TG), (mg/dL)	110.13 ± 2.42	104.25 ± 2.82	129.66 ± 29.13	0.1545
FLI	41.40 ± 0.63	39.59 ± 0.99	45.57 ± 3.36	0.0860
NHHR	2.83 ± 0.02	2.44 ± 0.03	2.28 ± 0.15	< 0.0001

Table 2. Basic characteristics of participants by Fibrosis-4 Index (FIB-4) among U.S. adults. Mean ± Se for continuous variables: the P value was calculated by the weighted linear regression model; n (%) for categorical variables: the P value was calculated by the weighted chi-square test. Abbreviation: NHHR: non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PIR: Poverty Income Ratio; BMI: Body Mass Index; HDL-C: high-density lipoprotein cholesterol; FLI: Fatty Liver Index.

Characteristic	Model 1, Beta coefficient (95%CI)	Model 2, Beta coefficient (95%CI)	Model 3, Beta coefficient (95%CI)
lnNHHR	31.22 (30.11, 32.33)	30.82 (29.69,31.96)	11.14(10.38,11.90)
Categories			
Tertile 1 (< 0.736)	0	0	0
Tertile 2 (0.736—1.124)	15.40 (14.18, 16.63)	14.99 (13.78,16.20)	3.65 (2.88, 4.42)
Tertile 3 (> 1.124)	32.01 (30.77, 33.25)	31.20 (29.94,32.46)	10.87(10.04,11.70)
P for trend	< 0.0001	< 0.0001	< 0.0001

Table 3. Weighted Multivariate logistic regression models of association lnNHHR with FLI. Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3: age, gender, race, education level, PIR, BMI, diabetes, hypertension, physical activity and smoke were adjusted. Abbreviation: NHHR: non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PIR: the ratio of income to poverty, BMI: body mass index.

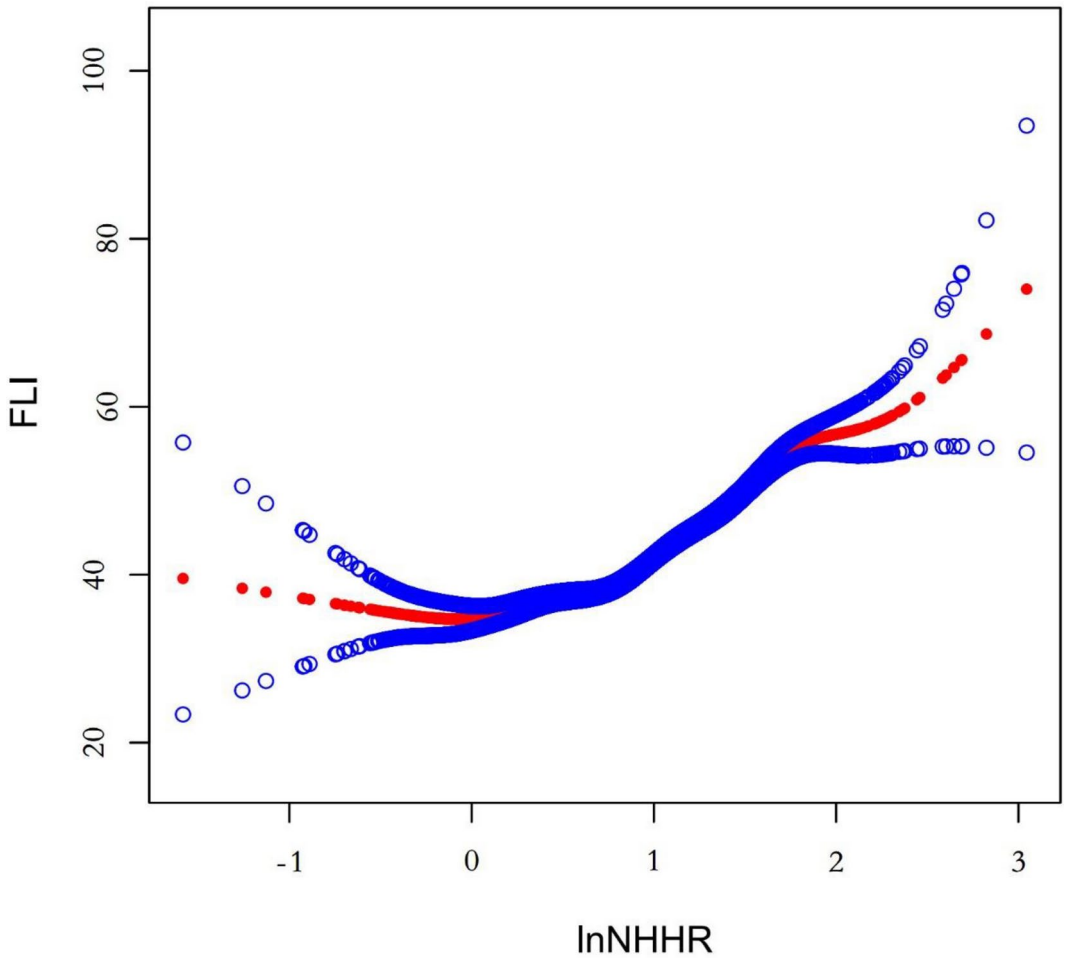

Fig. 2. The nonlinear associations between lnNHHR and FLI. The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit.

a robust association between reduced HDL-C levels and an elevated risk of developing hepatic steatosis and liver fibrosis[60–62]. However, despite HDL-C traditionally being regarded as protective for cardiovascular health, this study reveals that high levels of HDL-C may be associated with an elevating mortality risk[63]. This finding underscores the complexity of HDL-C's role in metabolic diseases and liver health, suggesting that elevated HDL-C levels may not always be beneficial. In certain MASLD patients, despite elevated HDL-C levels, the

Characteristic	Total (n)	β (95%CI)	P for interaction
Gender			0.0087
Male	6496	12.79 (10.80, 14.77)	
Female	8091	9.77 (8.44, 11.09)	
Educational level			0.1596
< High school	3187	10.79 (8.48, 13.10)	
High school	3168	13.19 (11.00, 15.38)	
Some college or above	8232	10.55 (8.86, 12.25)	
BMI			< 0.0001
< 25.0	4318	8.88 (7.42, 10.33)	
25.0–29.9	4796	17.90(15.74,20.07)	
≥ 30.0	5433	11.43 (8.87,14.00)	
PIR			0.6442
< 1.0	2530	11.64 (9.15, 14.14)	
1.0–3.0	6221	11.73 (10.23, 13.23)	
> 3.0	5836	10.58 (8.64, 12.53)	
Diabetes			0.3667
Yes	2854	12.08 (9.70, 14.45)	
No	11,733	10.95 (9.67, 12.22)	
Physical activity			0.0021
Vigorous	4133	13.37 (11.55, 15.19)	
No vigorous	10,454	10.19 (8.82, 11.57)	
Smoke			0.6487
Yes	5698	10.83 (8.99, 12.66)	
No	8889	11.37 (9.82, 12.91)	
Hypertension			0.9883
Yes	7438	11.15 (9.40, 12.89)	
No	7149	11.13 (9.71, 12.55)	

Table 4. Subgroup analysis for the association between lnNHHR and FLI. The subgroup analyses shown in the table were conducted based on Model 3, with the inclusion of covariates including: age, gender, race, PIR, BMI, educational level, diabetes, physical activity, smoke and hypertension. Abbreviation: PIR, the ratio of income to poverty, BMI, body mass index.

Characteristic	Model 1, Beta coefficient (95%CI)	Model 2, Beta coefficient (95%CI)	Model 3, Beta coefficient (95%CI)
lnNHHR	−0.19 (−0.21, −0.16)	−0.24 (−0.26, −0.22)	−0.20 (−0.22, −0.17)
Categories			
Tertile1 (< 0.736)	0	0	0
Tertile2 (0.736—1.124)	−0.12 (−0.15, −0.09)	−0.16 (−0.18, −0.13)	−0.13 (−0.15, −0.10)
Tertile3 (> 1.124)	−0.18 (−0.21, −0.15)	−0.24 (−0.26, −0.21)	−0.19 (−0.21, −0.16)
P for trend	< 0.0001	< 0.0001	< 0.0001

Table 5. Weighted Multivariate logistic regression models of association lnNHHR with FIB-4. Model 1: no covariates were adjusted. Model 2: age, gender, and race were adjusted. Model 3: age, gender, race, education level, PIR, BMI, diabetes, hypertension, physical activity and smoke were adjusted. Abbreviation: NHHR: non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PIR: the ratio of income to poverty, BMI: body mass index.

quality of HDL particles may decline, leading to the loss of its protective effects[33]. This suggests that an increase in HDL-C levels may not be beneficial for all patients. Additionally, studies have reported a significant association between low HDL-C levels and the progression of liver fibrosis as well as an increased incidence of hepatocellular carcinoma in MASLD populations[64], further supporting the notion that HDL-C may have a protective role within a certain range. However, there is currently no conclusive evidence to demonstrate that elevated HDL-C levels are consistently beneficial for hepatic steatosis and fibrosis. Therefore, current research underscores the

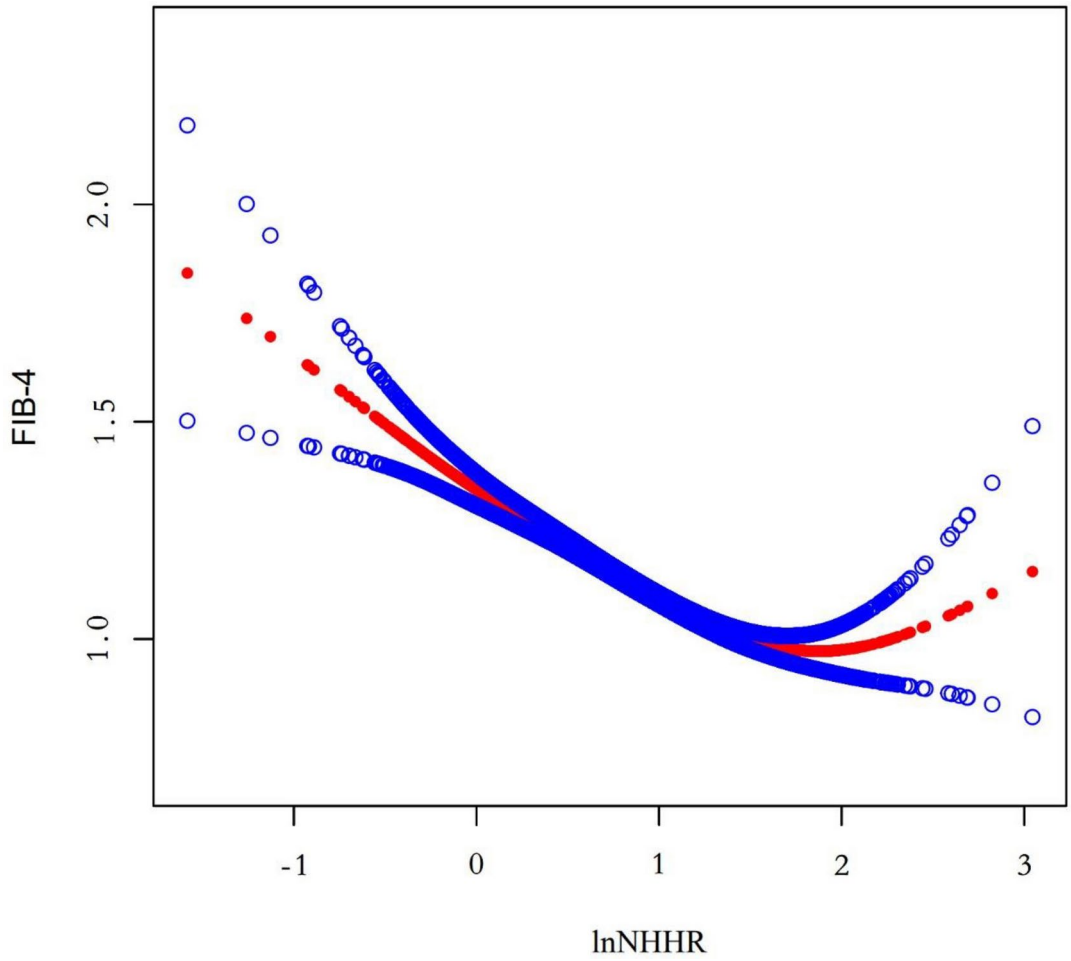

Fig. 3. The V-shaped curve associations between lnNHHR and FIB-4. The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit.

lnNHHR	Adjust β (95% CI)	P value
Linear model (model I)	−0.22 (−0.24, −0.19)	< 0.0001
Two-piecewise linear regression model (model I)		
Inflection point	1.51	
< 0.77	−0.24 (−0.27, −0.22)	< 0.0001
> 0.77	0.06 (−0.08, 0.19)	0.4242
Log likelihood ratio test		< 0.001

Table 6. Threshold effect analysis of the association between lnNHHR and FIB-4. Adjusted for age, gender, race, PIR, BMI, educational level, diabetes, physical activity, smoke and hypertension. Abbreviation: NHHR: non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PIR: the ratio of income to poverty, BMI: body mass index.

necessity for a more sophisticated comprehension and cautious assessment of the effects of HDL-C, particularly in the context of metabolic disorders.

The pathophysiological mechanisms of MASLD are complex. Free cholesterol and its derivatives, such as ceramides and diacylglycerol, have been demonstrated to disrupt mitochondrial function in the liver and to trigger lipotoxic stress responses in the endoplasmic reticulum. These effects play a role in the onset of hepatic steatosis and liver damage[45,65,66]. The accumulation of free cholesterol within Kupffer cells has been demonstrated to initiate a cascade of events that result in inflammatory responses, oxidative stress, and immune activation. Collectively, these processes drive Kupffer cell activation[67]. Furthermore, intracellular cholesterol accumulation can activate hepatic stellate cells via a toll-like receptor 4 (TLR4) receptor-dependent signaling pathway, thereby contributing to liver fibrosis progression[67]. Studies indicate that oxidative stress and lipid toxicity in hepatocytes

Characteristic	Total	β(95%CI)	P for interaction
Gender			0.6797
Male	6496	−0.96 (−0.26, −0.11)	
Female	8091	−0.24 (−0.21, −0.17)	
Educational level			0.5876
< High school	3187	−0.23 (−0.27, −0.18)	
High school	3168	−0.20 (−0.26, −0.15)	
Some college or above	8232	−0.19 (−0.25, −0.12)	
BMI			0.3570
< 25.0	4318	−0.24 (−0.29, −0.19)	
25.0–29.9	4796	−0.18 (−0.25, −0.12)	
≥ 30.0	5433	−0.18 (−0.27, −0.09)	
PIR			
< 1.0	2530	−0.18 (−0.22, −0.14)	0.5262
1.0–3.0	6221	−0.21 (−0.24, −0.18)	
> 3.0	5836	−0.19 (−0.26, −0.12)	
Diabetes			0.8754
Yes	2854	−0.20 (−0.30, −0.11)	
No	11,733	−0.20 (−0.24, −0.15)	
Physical activity			0.0003
Yes	4133	−0.12 (−0.18, −0.06)	
No	10,454	−0.23 (−0.27, −0.18)	
Smoke			0.4199
Yes	5698	−0.18 (−0.23, −0.14)	
No	8889	−0.21 (−0.26, −0.15)	
Hypertension			0.6192
Yes	7438	−0.21 (−0.26, −0.15)	
No	7149	−0.19 (−0.25, −0.12)	

Table 7. Subgroup analysis for the association between lnNHHR and FIB-4. The subgroup analyses shown in the table were conducted based on Model 3, with the inclusion of covariates including: age, gender, race, PIR, BMI, educational level, diabetes, physical activity, smoke and hypertension. Abbreviation: PIR, the ratio of income to poverty, BMI, body mass index.

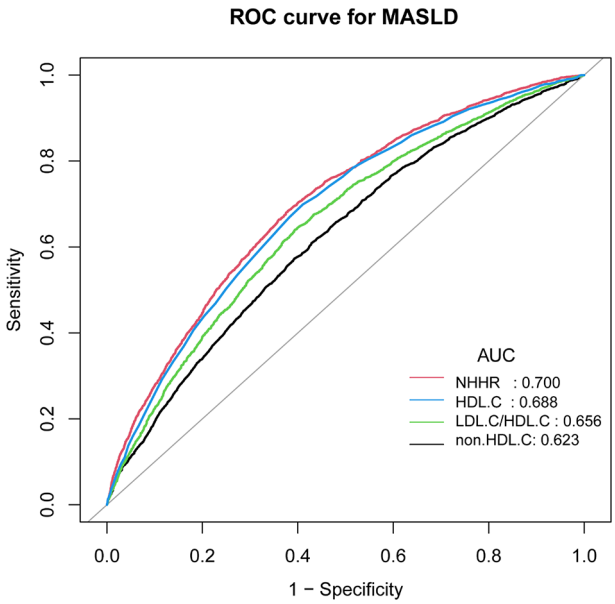

Fig. 4. ROC curves for NHHR, compared to non-HDL-C, HDL-C and LDL-C/HDL-C for MASLD onset. As determined by AUC, the predictive value for NHHR is more significant than other factor.

are key drivers in the progression from MASLD to the more advanced state of nonalcoholic steatohepatitis (NASH). Oxidized low-density lipoprotein (Ox-LDL) appears to compromise hepatocyte repair mechanisms and elevate apoptosis rates. Additionally, it activates Kupffer cells to release pro-inflammatory cytokines, thereby exacerbating hepatic lipid accumulation and cellular injury, ultimately heightening the risk of developing liver fibrosis and cirrhosis[68].

In light of our findings, NHHR has the potential to be an essential marker for evaluating liver health, MASLD, and the progression of liver fibrosis in the adult United States population. Its positive correlation with the FLI suggests potential utility in the detection of fatty liver. The negative correlation and V-shaped relationship with the FIB-4 index may offer insights into the progression of fibrosis at different stages. These associations indicate that NHHR might be instrumental in early screening and monitoring MASLD progression.

Study strengths and limitations

This study offers several notable advantages. Firstly, it is based on the NHANES dataset, which provides large-scale, nationally representative data. Second, the covariates adjustment enhances the findings' reliability and generalizability. Finally, this study explores the nonlinear relationship between NHHR and hepatic steatosis and fibrosis by employing stratified analysis, smoothing curve fitting, and assessments of threshold effects.

However, the study has several limitations. First, FLI and FIB-4 are indirect assessment tools rather than direct liver fat and fibrosis measures, which may introduce some errors. Secondly, the cross-sectional nature of NHANES restricts the capacity to determine a definitive causal relationship between NHHR and hepatic steatosis and fibrosis. Furthermore, many medications, such as antipsychotics and antidepressants, can directly impact the liver, worsening hepatic steatosis and fibrosis. However, the NHANES dataset lacks detailed information on medication use, leaving this potential confounder insufficiently addressed. Additionally, self-reported alcohol consumption in NHANES may not accurately reflect long-term drinking habits, limiting a comprehensive evaluation of alcohol's impact on liver disease.

Moreover, due to the broader diagnostic scope of MASLD, some cases that were originally classified as NAFLD may be redefined in different study populations because of the diversity of metabolic abnormalities. This could further impact the accuracy of non-invasive biomarkers used in our study.

Conclusion

The results suggest that higher levels of NHHR are linked to a more significant occurrence of hepatic steatosis among adults in the United States. The NHHR has the capacity to function as a potential predictive biomarker for MASLD, thereby facilitating early diagnosis and more targeted intervention strategies. Furthermore, Moreover, the calculation of NHHR is highly straightforward.

Although the results of this study suggest that the NHHR index is a promising tool for predicting MASLD, some outcomes may not reach clinical significance due to factors such as study design, sample size, or other limitations. In clinical settings, it is essential to consider not only statistical significance but also the practical applicability, cost-effectiveness, and the real-world benefits for patients. To better assess its clinical value, future research with a larger sample size and broader clinical context may be necessary.

Data availability

The survey data are publicly available on the internet for data users and researchers throughout the world (www.cdc.gov/nchs/nhanes/).

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Author contributions
BL, XM and XG designed the research. BL, XM and YL collected, analyzed the data, and drafted the manuscript. XM and XG revised the manuscript. All author scontributed to the article and approved the submitted version.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical statement
The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Additional information
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