Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio as a biomarker for liver health: Insights from National Health and Nutrition Examination Survey data

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Abstract. The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), a lipid-related biomarker, remains underexplored in relation to the risk of advanced fibrosis and hepatic steatosis. The present study aimed to investigate the potential association between the NHHR and these hepatic conditions. A total of 6,907 individuals aged 20 years and older from the National Health and Nutrition Examination Survey 2017-2020 were included in the present study. Advanced fibrosis and hepatic steatosis were assessed using hepatic vibration-controlled transient elastography. Multivariate regression analysis and subgroup analysis were performed to explore the independent association between the NHHR and the presence of advanced fibrosis and hepatic steatosis. Among the 6,907 adults included in the present study (mean age, 50.56±17.21 years; 3,398 male patients and 3,509 female patients), 409 (5.92%) were diagnosed with advanced fibrosis and 3,034 (43.93%) were diagnosed with hepatic steatosis. Following multivariable adjustment (age, sex, ethnicity, education level, family income-to-poverty ratio, smoking status, alcohol use and vigorous physical activity), logistic regression analysis demonstrated that an elevated NHHR was positively associated with increased possibility for advanced fibrosis [odds ratio (OR), 1.10; 95% confidence interval (CI), 1.03-1.17; P=0.005]. The restricted cubic spline model indicated a linear dose-response association between the NHHR and advanced fibrosis. The NHHR also exhibited a significant association with a higher risk of hepatic steatosis after full adjustment for covariates (OR, 1.61; 95% CI, 1.53-1.68; P<0.001). Using a two-segment linear regression model, an S-shaped relationship was identified between the NHHR and hepatic steatosis, with an inflection point at 3.83. In conclusion, the present study established a robust association of the NHHR with advanced fibrosis and hepatic steatosis. The NHHR may serve as a straightforward anthropometric index for predicting these conditions.

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing globally in tandem with rising rates of obesity and associated metabolic conditions, such as insulin resistance, dyslipidemia, central obesity and hypertension. Estimates suggest that NAFLD affects 25-30% of the adult population worldwide, which varies based on the clinical setting, ethnicity and geographical region, and NAFLD often remains undiagnosed (1,2). Consequently, the incidence of hepatic decompensation, hepatocellular carcinoma (HCC) and mortality due to non-alcoholic steatohepatitis (NASH)-associated cirrhosis is projected to rise 2- to 3-fold by 2030 (1). Therefore, early identification of hepatic steatosis and screening for advanced fibrosis are crucial for planning appropriate management strategies (3,4).

Pathological biopsy remains the gold standard for evaluating the severity of hepatic steatosis and liver fibrosis; however, vibration-controlled transient elastography (VCTE) is an increasingly utilized non-invasive alternative (5). VCTE, a non-invasive technique, employs the controlled-attenuation parameter (CAP) score to quantify the severity of hepatic steatosis, as well as the liver stiffness measurement (LSM) to assess the degree of fibrosis (6). The procedure involves

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Abbreviations: CAP, controlled-attenuation parameter; CI, confidence interval; LSM, liver stiffness measurement; HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; TC, total cholesterol; VCTE, vibration-controlled transient elastography

Key words: NHHR, advanced fibrosis, NAFLD, hepatic steatosis, NHANES

placing a probe on the patient's skin over the liver, where it emits a mechanical pulse and measures the velocity of the resulting shear wave as it travels through the liver tissue. The speed of the wave is directly related to liver stiffness, with higher velocities indicating more severe fibrosis. Therefore, VCTE serves as an effective tool for diagnosing liver fibrosis and hepatic steatosis. Furthermore, LSM provides prognostic insights beyond fibrosis staging, such as the assessment of liver stiffness changes over time, which are crucial for monitoring fibrosis progression and its complications, including cirrhosis, portal hypertension and HCC (7,8). These insights can help identify patients at higher risk for adverse outcomes and guide clinical management. Integrating LSM and CAP into nationally representative datasets offers an opportunity to accurately explore the relationship between the non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio (NHHR) and the population-level risks of liver steatosis and fibrosis.

Due to important advances in understanding the metabolic determinants of NAFLD incidence and progression, specific blood-related markers of dyslipidemia, particularly the NHHR, have been extensively associated with various conditions such as nephritis (9), abdominal aortic aneurysm (10), diabetes mellitus (11), periodontitis (12) and depression (13), demonstrating a promising predictive value. However, the association of the NHHR with liver fibrosis and hepatic steatosis remains incompletely explored. Yang *et al* (14) revealed a positive association between the NHHR and NAFLD in Chinese children and adolescents. However, this finding is constrained by its focus on a single ethnic group, the exclusion of adults, the inadequate control of complex confounders, imprecise methods for categorizing liver disease via ultrasound and the inability to assess steatosis severity.

In the present study, to further investigate the association between the NHHR and the risk of liver steatosis and fibrosis, a large, nationally representative cross-sectional study was conducted using National Health and Nutrition Examination Survey (NHANES) data.

Materials and methods

Study population. NHANES (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?Cycle=2017-2020) is a biennial cross-sectional survey conducted to assess the nutritional and physical health of the United States population. The evaluation includes standardized in-home interviews, physical examinations, records of examinations (including liver ultrasound transient elastography) and laboratory tests conducted at mobile examination centers. The NHANES protocols (NHANES 2017-2020; protocol nos. #2011-17 and #2018-01) were approved by the Centers for Disease Control and Prevention, with all participants providing written informed consent.

From the initial 15,560 patients included in NHANES (2017-2020), 6,907 individuals aged ≥20 years, who had undergone hepatic VCTE examinations, were included. The age and sex distribution of the participants are further detailed in the Results section and Table I. Individuals were excluded if they met the following criteria: i) Age <20 years (n=6,328); ii) missing elastography examination data (the examination was not performed at all; n=1,243); iii) absence of elastography examination data (fasting time <3 h, inability to obtain 10 valid measurements, interquartile range/median ratio of LSM >30% and cases where CAP was not performed; n=594); and iv) lack of complete data on the NHHR (n=488). The flowchart depicting the sample selection process is presented in Fig. 1.

Definition of NHHR. The NHHR was included as an exposure variable in the present study and calculated as follows: NHHR=non-HDL-C/HDL-C.

The computation of non-HDL-C involved subtracting HDL-C from total cholesterol (TC). The present study stratified participants based on their NHHR values, and categorized them into four quartiles (Q1: 0.67-2.71; Q2: 2.72-3.36; Q3: 3.37-4.06; and Q4: 4.07-10.58) for analytical convenience.

Measurement of liver fibrosis and hepatic steatosis. The elastography measurements at the NHANES mobile examination center were conducted using the FibroScan® model 502 V2 Touch (Echosens), which was outfitted with either a medium (M) or extra-large (XL) probe. Participants were placed in the supine position with the right arm fully extended for hepatic measurements via intercostal spaces in the right lobe. A minimum 3-h fasting period was performed by the participants before the procedure. The selection of M and XL probes was guided by the automatic selection function of the device system, the manual assessment of skin to liver envelope distance and body mass index. This selection process was performed in accordance with the manufacturer's instructions to ensure accurate and reliable measurements. The success of each measurement was evaluated by the software of the aforementioned system, with the overall validity based on meeting the following criteria: i) A minimum of 10 valid shots; ii) a success rate >60% (calculated as valid shots divided by total shots); and iii) an interquartile range <30% of the median LSM value (interquartile range/median <30%). LSM was recorded in kilopascals (kPa), while CAP was recorded in decibels per meter (dB/m). Previous studies (6,15) suggested that a CAP cut-off value of ≥274 dB/m, with a sensitivity of 90%, is indicative of hepatic steatosis. Furthermore, an LSM cut-off value of ≥9.7 kPa, with a sensitivity of 71% and specificity of 75%, is suggestive of advanced fibrosis (≥F3) (6).

Covariates. According to the literature, several covariates were analyzed in the present study, including age, sex, ethnicity, educational attainment, family income-to-poverty ratio, smoking status, alcohol abuse and vigorous activity (16-18). For the purposes of the present study, ethnicity was divided into five categories: i) Non-Hispanic White; ii) Hispanic; iii) non-Hispanic Black; iv) non-Hispanic Asian; and v) other (which encompasses multiethnic groups). Educational attainment was also classified into four distinct categories: i) Less than high school; ii) high school graduate; iii) college or associate's degree; and iv) college graduate or higher.

The ratio of family income to poverty, determined by dividing the income of the family or individual by the poverty guidelines specific to the year of the survey, classified familial income into three categories: i) Low (<1.3); ii) medium (1.3-4.9); and iii) high (≥5.0). Smoking status was determined based on the responses of the participants to two questions in

Table I. Characteristics of the study population according to non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio data.

Characteristic	Total (n=6,907)	Q1 (0.67-2.71) (n=1,727)	Q2 (2.72-3.36) (n=1,726)	Q3 (3.37-4.06) (n=1,723)	Q4 (4.07-10.58) (n=1,731)	P-value				
						Overall	Q1 vs. Q2	Q2 vs. Q3	Q3 vs. Q4	Q1 vs. Q4
Age, years	50.56±17.21	50.62±19.09	51.15±17.85	51.03±16.34	49.43±15.26	0.007	0.379	0.765	0.004	0.023
Sex, n (%)						0.007	-	-	-	-
Female	3,509 (50.80)	1,084 (62.77)	973 (56.37)	847 (49.16)	605 (34.95)					
Male	3,398 (49.20)	643 (37.23)	753 (43.63)	879 (50.84)	1,123 (65.05)					
Ethnicity, n (%)						<0.001	-	-	-	-
Non-Hispanic White	2,394 (34.66)	604 (34.97)	610 (35.34)	591 (34.30)	589 (34.03)					
Hispanic	1,586 (22.96)	283 (16.39)	381 (22.07)	424 (24.61)	498 (28.77)					
Non-Hispanic Black	1,748 (25.31)	567 (32.83)	462 (26.77)	406 (23.56)	313 (18.08)					
Non-Hispanic Asian	837 (12.12)	198 (11.46)	192 (11.12)	208 (12.07)	239 (13.81)					
Others	342 (4.95)	75 (4.34)	81 (4.69)	94 (5.46)	92 (5.31)					
Education, n (%)						<0.001	-	-	-	-
Less than high school	1,266 (18.33)	247 (14.30)	282 (16.34)	341 (19.79)	396 (22.88)					
High school graduate	2,327 (33.69)	428 (24.78)	396 (22.94)	413 (23.97)	413 (23.86)					
College or associate's degree	2,022 (29.27)	576 (33.35)	572 (33.14)	574 (33.31)	526 (30.39)					
College or above	907 (13.13)	474 (27.45)	474 (27.46)	393 (22.81)	393 (22.70)					
Ratio of family income to poverty						0.716	-	-	-	-
<1.3	1,651 (23.90)	423 (24.49)	385 (22.31%)	429 (24.90%)	414 (23.92%)					
1.3-4.9	2,327 (33.69)	564 (32.66)	580 (33.60%)	572 (33.20%)	611 (35.30%)					
≥5	2,022 (29.27)	534 (30.92)	534 (30.94%)	481 (27.92%)	473 (27.33%)					
Body mass index, n (%)						<0.001	-	-	-	-
Under weight (<18.5 kg/m^2)	84 (1.22)	52 (3.01)	17 (0.98)	8 (0.46)	7 (0.40)					
Normal weight (18.5-24.9 kg/m^2)	1,670 (24.18)	713 (41.29)	461 (26.71)	295 (17.12)	201 (11.61)					
Overweight (25.0-29.9 kg/m^2)	2,243 (32.47)	511 (29.59)	568 (32.91)	581 (33.72)	583 (33.68)					
Obese (>30.0 kg/m^2)	2,856 (41.35)	436 (25.25)	658 (38.12)	829 (48.11)	933 (53.90)					
Alcohol abuse, n (%)						0.004	-	-	-	-
Yes	1,180 (17.08)	313 (18.12)	251 (14.54)	289 (16.77)	327 (18.89)					
No	5,727 (82.92)	1,414 (81.88)	1,475 (85.46)	1,440 (83.29)	1,398 (81.11)					
Smoking status, n (%)						<0.001	-	-	-	-
Never smokers	4,040 (58.49)	1,023 (59.24)	1,054 (61.07)	1,025 (59.49)	938 (54.19)					
Former smokers	1,634 (23.66)	387 (22.41)	418 (24.22)	386 (22.40)	443 (25.59)					
Current smokers	1,233 (17.85)	317 (18.36)	254 (14.72)	312 (18.11)	350 (20.22)					

Table I. Continued.

Characteristic	Total (n=6,907)	Q1 (0.67-2.71) (n=1,727)	Q2 (2.72-3.36) (n=1,726)	Q3 (3.37-4.06) (n=1,723)	Q4 (4.07-10.58) (n=1,731)	P-value				
						Overall	Q1 vs. Q2	Q2 vs. Q3	Q3 vs. Q4	Q1 vs. Q4
Vigorous activity, n (%)						0.147	-	-	-	-
Yes	2,487 (36.01)	617 (35.73)	609 (35.28)	599 (34.76)	662 (38.24)					
No	4,420 (63.99)	1,110 (64.27)	1,118 (64.72)	1,128 (65.24)	1,064 (61.65)					
Comorbidities, n (%)										
Diabetes						<0.001	-	-	-	-
Yes	1,312 (17.08)	283 (16.39)	301 (17.44)	330 (19.15)	398 (22.99)					
No	5,595 (81.00)	1,444 (83.61)	1,426 (82.56)	1,397 (80.85)	1,328 (77.03)					
Hypertension						0.601	-	-	-	-
Yes	2,612 (37.82)	642 (37.17)	638 (36.96)	658 (38.19)	674 (38.94)					
No	4,295 (62.18)	1,085 (62.82)	1,088 (63.04)	1,071 (61.85)	1,051 (60.93)					
Congestive heart failure						0.205	-	-	-	-
Yes	188 (2.72)	57 (3.30)	49 (2.84)	45 (2.61)	37 (2.14)					
No	6,719 (97.28)	1,670 (96.70)	1,678 (97.16)	1,684 (97.39)	1,687 (97.86)					
Coronary heart disease						0.020	-	-	-	-
Yes	274 (3.97)	84 (4.86)	78 (4.52)	55 (3.19)	57 (3.29)					
No	6,633 (96.03)	1,643 (95.14)	1,649 (95.48)	1,674 (96.81)	1,667 (96.71)					
Angina						0.148	-	-	-	-
Yes	156 (2.26)	40 (2.32)	49 (2.84)	38 (2.21)	29 (1.68)					
No	6,571 (97.74)	1,687 (97.68)	1,678 (97.16)	1,691 (97.79)	1,695 (98.32)					
Stroke						0.048	-	-	-	-
Yes	314 (4.55)	96 (5.56)	82 (4.75)	73 (4.24)	63 (3.64)					
No	6,593 (95.45)	1,631 (94.44)	1,645 (95.25)	1,656 (95.76)	1,661 (96.35)					
Asthma						0.583	-	-	-	-
Yes	1058 (15.32)	278 (16.10)	270 (15.64)	259 (15.03)	251 (14.50)					
No	5,849 (84.68)	1,449 (83.90)	1,457 (84.36)	1,468 (85.00)	1,475 (85.46)					
COPD						0.651	-	-	-	-
Yes	574 (8.31)	153 (8.86)	146 (8.46)	142 (8.24)	133 (7.68)					
No	6,333 (91.69)	1,574 (91.14)	1,581 (91.54)	1,587 (91.76)	1,591 (92.32)					
Thyroid problems						<0.001	-	-	-	-
Yes	808 (11.70)	200 (11.58)	251 (14.54)	206 (11.96)	151 (8.72)					
No	6,099 (88.30)	1,527 (88.42)	1,475 (85.46)	1,524 (88.10)	1,573 (91.24)					
Arthritis						<0.001	-	-	-	-
Yes	2,059 (29.81)	523 (30.28)	525 (30.42)	565 (32.79)	446 (25.77)					
No	4,848 (70.19)	1,204 (69.72)	1,201 (69.51)	1,162 (67.28)	1,281 (74.17)		-	-	-	-

Table I. Continued.

Characteristic	Total (n=6,907)	Q1 (0.67-2.71) (n=1,727)	Q2 (2.72-3.36) (n=1,726)	Q3 (3.37-4.06) (n=1,723)	Q4 (4.07-10.58) (n=1,731)	P-value				
						Overall	Q1 vs. Q2	Q2 vs. Q3	Q3 vs. Q4	Q1 vs. Q4
Laboratory features										
Total cholesterol (0-5.18), mmol/l	4.82±1.05	4.25±0.93	4.58±0.87	4.89±0.87	5.57±1.05	<0.001	<0.001	<0.001	<0.001	<0.001
HDL cholesterol (0-3.11), mmol/l	1.38±0.41	1.79±0.45	1.45±0.28	1.25±0.23	1.04±0.20	<0.001	<0.001	<0.001	<0.001	<0.001
Triglycerides (0-1.70), mmol/l	1.57±1.23	0.94±0.42	1.21±0.53	1.56±0.67	2.59±1.90	<0.001	<0.001	<0.001	<0.001	<0.001
Glycohemoglobin (4.00-6.00), %	5.85±1.10	5.66±0.87	5.77±0.98	5.85±0.98	6.10±1.44	<0.001	<0.001	<0.001	<0.001	<0.001
AST (0-37.00), U/l	21.96±14.44	22.50±18.51	21.45±15.89	21.03±9.30	22.86±12.27	<0.001	0.571	0.359	<0.001	<0.001
ALT (0-40.00), U/l	22.48±18.87	19.31±17.31	20.74±21.36	22.41±14.91	27.44±20.20	<0.001	<0.001	<0.001	<0.001	<0.001
ALP (40.00-129.00), U/l	77.52±25.67	73.62±25.92	76.53±23.55	77.63±22.07	82.29±29.72	<0.001	<0.001	0.098	<0.001	<0.001
γGT (11.00-51.00), U/l	32.18±45.79	30.42±52.68	29.40±41.90	29.60±33.68	39.26±51.52	<0.001	<0.001	<0.001	<0.001	<0.001
Total bilirubin (6.60-8.70), g/dl	7.84±4.70	8.41±5.43	7.86±4.47	7.57±4.57	7.51±4.18	<0.001	0.020	0.015	0.754	<0.001
Albumin (35.00-50.00), g/l	40.67±3.30	40.59±3.38	40.67±3.40	40.53±3.23	40.87±3.18	0.009	0.390	0.130	0.001	0.010
Creatinine, (45.10-84.00) μmol/l	79.52±40.22	79.24±50.00	78.34±42.00	78.43±26.94	82.05±38.38	<0.001	0.153	0.070	<0.001	<0.001
Uric acid (202.20-416.40), μmol/l	321.48±87.07	293.67±83.23	307.34±80.82	331.71±85.06	353.11±86.96	<0.001	<0.001	<0.001	<0.001	<0.001
Platelet count (150.00-450.00), $10^9/\mu$l	246.07±64.97	239.12±64.74	245.50±64.97	248.79±65.03	250.84±64.60	<0.001	0.003	0.111	0.420	<0.001
hsCRP (<5.00), mg/l	3.98±8.27	3.14±8.44	3.90±9.45	4.31±7.15	4.58±7.82	<0.001	<0.001	<0.001	<0.001	<0.001
Liver ultrasound transient elastography										
LSM value, kPa	5.82±4.58	5.58±4.10	5.68±4.20	5.73±3.99	6.30±5.75	<0.001	0.086	0.031	<0.001	<0.001
Advanced fibrosis, n (%)						0.016	-	-	-	-
Yes	409 (5.92)	86 (4.98)	102 (5.91)	93 (5.40)	128 (7.39)					
No	6,498 (94.08)	1,641 (95.02)	1,625 (94.09)	1,636 (94.60)	1,596 (92.61)					
CAP value, dB/m	265.10±62.04	237.25±57.86	255.08±58.76	275.03±58.76	292.96±58.24	<0.001	<0.001	<0.001	<0.001	<0.001
Hepatic steatosis, n (%)						<0.001	-	-	-	-
Yes	3,034 (43.93)	435 (25.19)	623 (36.10)	876 (50.84)	1,100 (63.55)					
No	3,873 (56.07)	1,292 (74.81)	1,103 (63.90)	852 (49.16)	626 (36.45)					

AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CAP, controlled-attenuation parameter; COPD, chronic obstructive pulmonary disease; γGT, γ glutamyl transferase; LSM, liver stiffness measurement; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Q, quartile; -, not applicable.

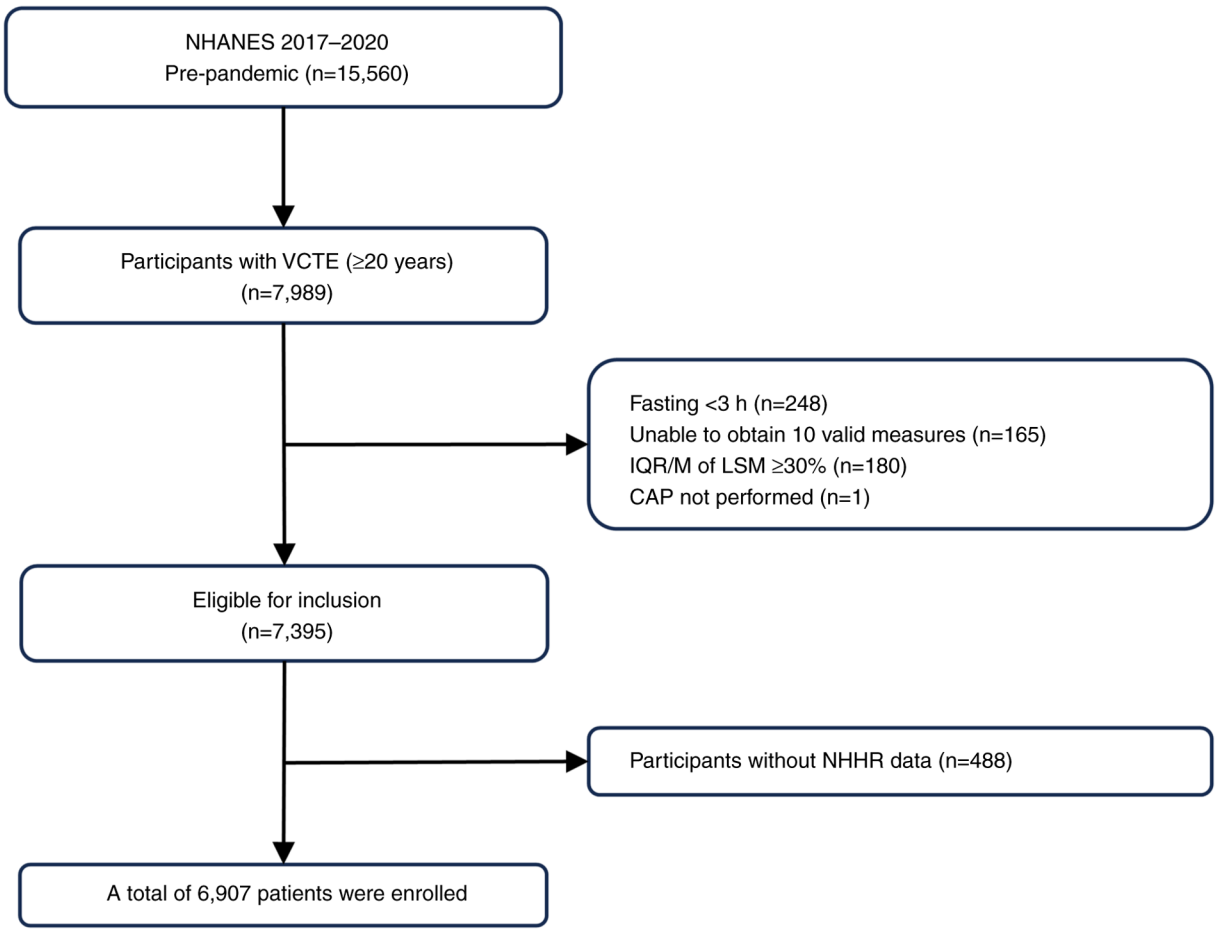

Figure 1. Flowchart of the sample selection process from NHANES 2017-2020. NHANES, National Health and Nutrition Examination Survey; VCTE, vibration-controlled transient elastography; IQR/M, interquartile range/median; LSM, liver stiffness measurement; CAP, controlled-attenuation parameter; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

the 'Smoking Cigarette Use' questionnaire: i) Whether they now smoke cigarettes; and ii) whether they have smoked at least 100 cigarettes in their entire life. Participants were categorized into three smoking status groups: i) Never smokers (<100 cigarettes in their entire life); ii) former smokers (≥100 cigarettes but had quit smoking); and iii) current smokers (19). Alcohol abuse was defined as the consumption of more than two or more than three standard drinks per day on average for female and male participants, respectively, with a standard drink defined as a 12 oz. beer, a 5 oz. glass of wine or 1.5 oz. liquor. Vigorous activity was characterized as participation in activities with a metabolic equivalent of ≥6.

Statistical analysis. All statistical analyses were performed using R software v.4.1.3 (Posit Software). Continuous variables are presented as the mean ± SD, while categorical variables are presented as counts and percentages. Baseline differences between NHHR quartile (Q) groups were compared using one-way ANOVA followed by Bonferroni post hoc test for continuous variables or χ^2 test for categorical variables. For study variables of primary interest (such as the NHHR), records containing missing values were removed entirely. For important covariates that required adjustment (such as educational attainment, smoking status and alcohol abuse), the missing records were filled in by transforming them into categorical variables ('missing' category). The association between the NHHR and the presence of steatosis and fibrosis was explored using multivariate logistic regression analyses. Odds ratio (OR) and 95% (confidence interval) CI values for the NHHR were calculated, treating it as both a continuous and categorical variable. The multivariate analysis comprised three models: i) Model 1, unadjusted; ii) model 2, adjusted for age, sex and ethnicity; and iii) model 3, additionally adjusted for education level, family income-to-poverty ratio, smoking status, alcohol use and vigorous physical activity.

In addition, a restricted cubic spline (RCS) regression model was utilized to analyze dose-response associations of the NHHR with liver fibrosis and hepatic steatosis. Subgroup analyses were performed to evaluate the robustness of these associations across diverse population factors. A log-likelihood ratio test was applied to ascertain the presence of a threshold, contrasting a single-linear model (non-segmented) with a two-piecewise linear regression model. The inflection point (K) was determined through a two-step recursive method.

Several sensitivity analyses were performed to evaluate the robustness of the results. First, hepatic steatosis was defined using a CAP cut-off value of ≥285 dB/m, which was selected to optimize sensitivity (80%) and specificity (77%) (20). Second, an optimal LSM cut-off of ≥8.6 kPa was applied (sensitivity of 66% and specificity of 80%) to indicate clinically significant

Table II. Association between NHHR and advanced fibrosis.

	Model 1		Model 2		Model 3	
NHHR category	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
NHHR total	1.10 (1.03-1.17)	0.002	1.10 (1.03-1.17)	0.005	1.10 (1.03-1.17)	0.007
NHHR quartile						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.20 (0.89-1.61)	0.229	1.16 (0.86-1.56)	0.340	1.16 (0.86-1.57)	0.324
Q3	1.09 (0.81-1.47)	0.580	1.03 (0.76-1.40)	0.831	1.02 (0.75-1.39)	0.889
Q4	1.52 (1.15-2.02)	0.003	1.45 (1.08-1.95)	0.012	1.44 (1.07-1.93)	0.016
P-value for trend		0.008		0.027		0.038

Model 1, no variables adjusted; model 2, age, sex and ethnicity adjusted; model 3, further adjustments for education level, ratio of family income to poverty, smoking status, alcohol abuse and vigorous activity. NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval; Q, quartile.

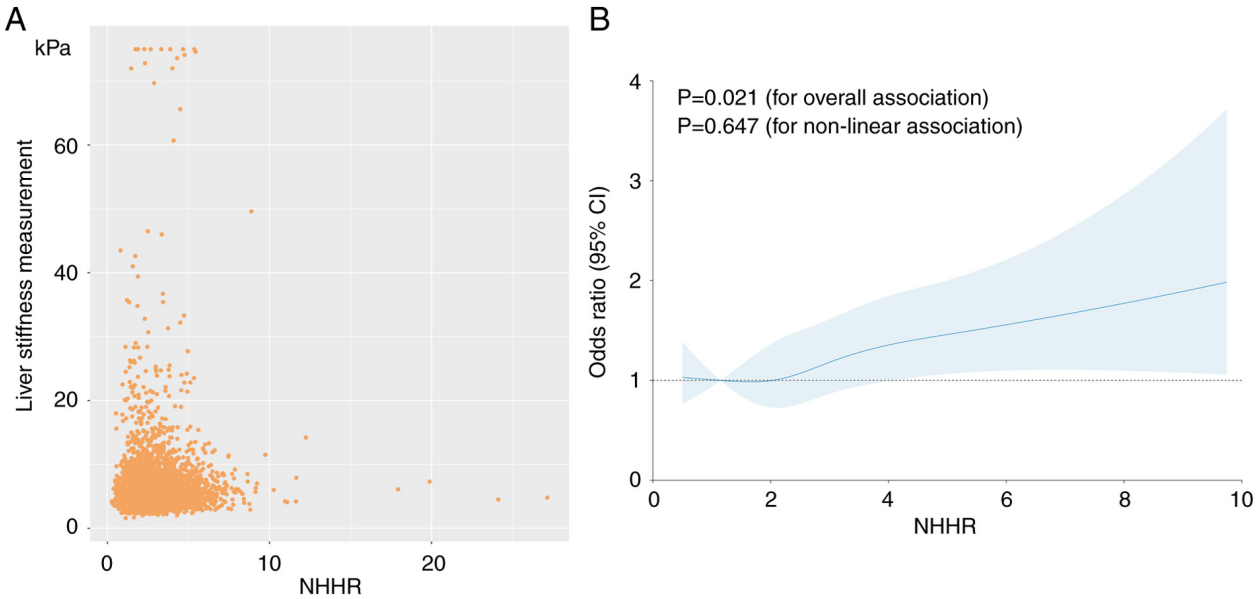

Figure 2. Association between the NHHR and advanced fibrosis. (A) Scatter plot depicting the association between NHHR and liver stiffness values, with each yellow point representing a sample. (B) Restricted cubic spline model of the association between the NHHR and advanced fibrosis. NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; CI, confidence interval.

fibrosis (stage F2-F4) (4,5). Third, the analysis was restricted to patients with NAFLD (n=5,478) to exclude confounding factors on steatosis. Patients with alcohol consumption (n=1,234), use of steatogenic medications for >6 months (n=89) and hepatitis B (n=38) or C (n=157) were excluded (3,4). Certain patients had more than one of these conditions; therefore, the number of excluded patients may overlap.

A two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. Among the 15,560 participants enrolled in NHANES between 2017 and 2020, 8,653 individuals were excluded due to their age being <20 years, missing or absent elastography data or incomplete NHHR records. This resulted in a final analytical cohort of 6,907 patients. The average age of these adults was 50.56±17.21 years, with 3,398 male patients and 3,509 female patients. The baseline characteristics of the NHANES participants from 2017 to 2020 are presented in Table I, stratified by the following NHHR Qs: i) 0.67-2.71; ii) 2.72-3.36; iii) 3.37-4.06; and iv) 4.07-10.58. Significant differences were observed among the groups. Compared with subjects in the lowest Q of the NHHR, those in the highest Q were more likely to be male, more obese as assessed by body mass index, had higher percentage of diabetes and worse liver function (higher aspartate aminotransferase and alanine aminotransferase levels). The mean ± SD values of CAP and LSM were 265.10±62.04 dB/m and 5.82±4.58 kPa, respectively. The overall prevalence of advanced fibrosis was 5.92%, with rates by Q (Q1 to Q4) of 4.98, 5.91, 5.40 and 7.39%, respectively (P=0.016). Hepatic steatosis occurred in 43.93%

Table III. Two-segment piecewise linear regression model for the analysis of threshold effects between the NHHR, advanced fibrosis and hepatic steatosis.

Liver function parameter	OR (95% CI)	P-value
Advanced fibrosis		
Fitting by standard linear model	1.10 (1.03-1.17)	0.007
Fitting by two-piecewise linear model		
<5.01	1.13 (1.02-1.24)	0.014
≥5.01	1.04 (0.90-1.21)	0.589
Log-likelihood ratio	0.402	
Hepatic steatosis		
Fitting by standard linear model	1.61 (1.53-1.68)	<0.001
Fitting by two-piecewise linear model		
<3.83	1.96 (1.84-2.09)	<0.001
≥3.83	1.07 (0.98-1.16)	0.135
Log-likelihood ratio	0.039	

The multivariate logistic regression model was adjusted for age, sex, ethnicity, education level, family income-to-poverty ratio, smoking status, alcohol use and vigorous physical activity. NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval.

of cases, showing a significant increase with higher NHHR Qs (Q1, 25.19%; Q2, 36.10%; Q3, 50.84%; and Q4, 63.55%; P<0.001).

Association between the NHHR and advanced fibrosis. The results of the multivariate logistic regression analysis are presented in Table II. In the unadjusted model, an elevated NHHR exhibited a positive association with increased possibility for advanced fibrosis (OR, 1.10; 95% CI, 1.03-1.17; P=0.002), which remained consistent after adjusting for multiple confounding factors (Model 2: OR, 1.10; 95% CI, 1.03-1.17; P=0.005; Model 3: OR, 1.10; 95% CI, 1.03-1.17; P=0.007). Stratifying the NHHR into Qs for further analysis revealed that individuals in the highest Q (Q4) had a higher risk of advanced fibrosis compared with those in the lower Qs (Q1-Q3) in a fully adjusted model (OR, 1.44; 95% CI, 1.07-1.93; P=0.016). This finding highlights the association between higher NHHR levels and advanced fibrosis risk. The association between the NHHR and advanced fibrosis is shown in Fig. 2A, where each yellow point represents a sample. The RCS model indicated a linear dose-response relationship between the NHHR and advanced fibrosis (P=0.647 for non-linearity; Fig. 2B; Table III). When NHHR is <5.01, the chance of developing advanced fibrosis increases by 13% (OR, 1.13; 95% CI, 1.02-1.24; P=0.014) for every additional unit of NHHR. Conversely, when the NHHR was ≥5.01, no significant change in the relative risk of advanced fibrosis was observed.

Table IV. Sensitivity analyses of the association between NHHR and advanced fibrosis or hepatic steatosis.

Analysis	OR (95% CI)	P-value
Advanced fibrosis		
LSM cut-off of ≥8.6 kPa	1.10 (1.03-1.16)	0.003
Patients with NAFLD	1.08 (1.01-1.17)	0.042
Hepatic steatosis		
CAP cut-off value of ≥285 dB/m	1.56 (1.49-1.63)	<0.001
Patients with NAFLD	1.55 (1.47-1.64)	<0.001

CAP, controlled-attenuation parameter; LSM, liver stiffness measurement; OR, odds ratio; CI, confidence interval.

The robustness of the association between the NHHR and advanced fibrosis was assessed through subgroup analysis (Fig. 3). The results revealed significant associations between the NHHR and advanced fibrosis among men (OR, 1.09; 95% CI, 1.01-1.18; P=0.028), individuals aged 20-39 years (OR, 1.24; 95% CI, 1.11-1.40; P=0.001) and non-Hispanic Black individuals (OR, 1.38; 95% CI, 1.17-1.62; P=0.001). Furthermore, significant associations were observed in individuals without heavy alcohol use (OR, 1.08; 95% CI, 1.00-1.17; P=0.042), former smokers (OR, 1.23; 95% CI, 1.07-1.41; P=0.003) and those without vigorous physical activity (OR, 1.13; 95% CI, 1.04-1.22; P=0.005).

Using an LSM cut-off of ≥8.6 kPa to define clinically significant fibrosis, the association between the NHHR and clinically significant fibrosis remained statistically significant (OR, 1.10; 95% CI, 1.03-1.16; P=0.003). To reduce the influence of other factors contributing to hepatic steatosis, the analysis was restricted to patients with NAFLD. In a logistic regression sensitivity analysis, the NHHR was significantly associated with advanced fibrosis in patients with NAFLD (OR, 1.08; 95% CI, 1.01-1.17; P=0.042) (Table IV).

Association between the NHHR and hepatic steatosis. The association between the NHHR and hepatic steatosis is presented in Table V. In the continuous model, the NHHR exhibited a significant association with an increased risk of hepatic steatosis after full adjustment for covariates (OR, 1.61; 95% CI, 1.53-1.68; P<0.001). In the fully adjusted categorical model, compared with the lowest Q reference, participants in the second, third and fourth Qs had an OR of 1.60 (95% CI, 1.37-1.85; P<0.001), 2.91 (95% CI, 2.51-3.38; P<0.001) and 4.86 (95% CI, 4.17-5.67; P<0.001) for hepatic steatosis risk, respectively, which demonstrated a significant trend (P<0.001). The association between the NHHR and hepatic steatosis is demonstrated in Fig. 4A. As shown in Fig. 4B, the NHHR was non-linearly linked with the prevalence of hepatic steatosis (P<0.001 for non-linearity). Utilizing biphasic linear models and recursive algorithms, the present study identified an inflection point at an NHHR value of 3.83 (Table III). Below an NHHR of 3.83, there was a 96% increase in the likelihood of developing hepatic steatosis per unit increase in the NHHR (OR, 1.96; 95% CI, 1.84-2.09; P<0.001). Conversely, NHHR

Table V. Association between NHHR and hepatic steatosis.

	Model 1		Model 2		Model 3	
NHHR category	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
NHHR total	1.64 (1.56- 1.71)	<0.001	1.59 (1.52-1.67)	<0.001	1.61 (1.53-1.68)	<0.001
NHHR quartile						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.68 (1.45-1.94)	<0.001	1.59 (1.37-1.85)	<0.001	1.60 (1.37-1.85)	<0.001
Q3	3.07 (2.66-3.55)	<0.001	2.88 (2.48-3.33)	<0.001	2.91 (2.51-3.38)	<0.001
Q4	5.18 (4.47-5.99)	<0.001	4.76 (4.09-5.55)	<0.001	4.86 (4.17-5.67)	<0.001
P-value for trend		<0.001		<0.001		<0.001

Model 1, no variables adjusted; model 2, age, sex and ethnicity adjusted; model 3, further adjustments for education level, ratio of family income to poverty, smoking status, alcohol abuse and vigorous activity. NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; CI, confidence interval; Q, quartile.

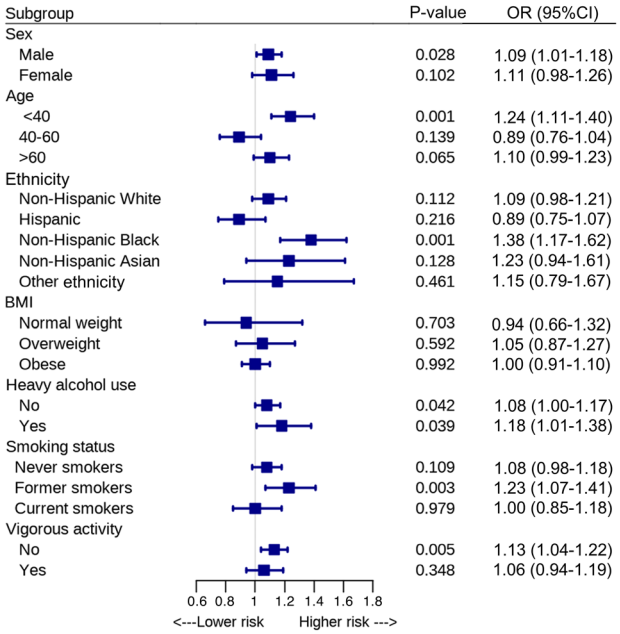

Figure 3. Subgroup analysis for the association between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and advanced fibrosis. Stratification was performed for age, sex, ethnicity, smoking status, alcohol abuse and vigorous activity. BMI, body mass index; OR, odds ratio; CI, confidence interval.

values ≥3.83 were not significantly associated with the relative risk of hepatic steatosis (OR, 1.07; 95% CI, 0.98-1.16; P=0.135).

The subgroup analyses results are shown in Fig. 5. The NHHR exhibited a significant association with hepatic steatosis across all subgroups, including those stratified by age, sex, ethnicity, smoking status, alcohol use and vigorous physical activity (all P<0.001).

Using a CAP cut-off of ≥285 dB/m to define hepatic steatosis, the association between the NHHR and hepatic steatosis was significant (OR, 1.56; 95% CI, 1.49-1.63; P<0.001). To minimize the influence of other factors contributing to hepatic steatosis, the analysis focused exclusively on patients with NAFLD. In a logistic regression sensitivity analysis, the NHHR remained significantly associated with hepatic steatosis in patients with NAFLD (OR, 1.55; 95% CI, 1.47-1.64; P<0.001) (Table IV).

Discussion

Lipoprotein metabolism serves a crucial role in the pathogenesis of NAFLD. The present study aimed to investigate the potential associations between the NHHR and the presence of advanced fibrosis and hepatic steatosis. Utilizing a nationally representative sample of United States adults, it was observed that an elevated NHHR was significantly associated with an increased likelihood of advanced fibrosis. The RCS model demonstrated a linear dose-response relationship between the NHHR and advanced fibrosis. Additionally, the NHHR was significantly associated with a higher risk of hepatic steatosis after adjusting for covariates. An S-shaped relationship was identified between the NHHR and hepatic steatosis, with an inflection point at 3.83. Given the use of the NHANES design to obtain national estimates, these findings are likely generalizable to the broader adult outpatient population in the United States.

NAFLD encompasses a spectrum of pathological features, ranging from the ectopic accumulation of triglycerides in hepatocytes (hepatic steatosis) to inflammation and hepatocellular injury, known as NASH. This condition can lead to fibrosis, cirrhosis, end-stage liver disease or HCC (21). Dyslipidemia serves a crucial role in the pathogenesis of NAFLD. The underlying metabolic mechanisms reflect an imbalance in hepatic energy metabolism, where excess energy, primarily from carbohydrates and fats, is stored as triglycerides in the liver (22). Adipocyte dysfunction also contributes to the development of NAFLD (23). Severe forms of NAFLD and NASH can occur as complications of congenital lipodystrophy, where the absence of adipose tissue forces the liver to store excess fatty acids, leading to notable insulin resistance (24). Increased visceral adipose tissue is associated with hyperlipidemia, insulin resistance and NAFLD (25). It is widely accepted that visceral adipose tissue contributes to NAFLD and its metabolic complications,

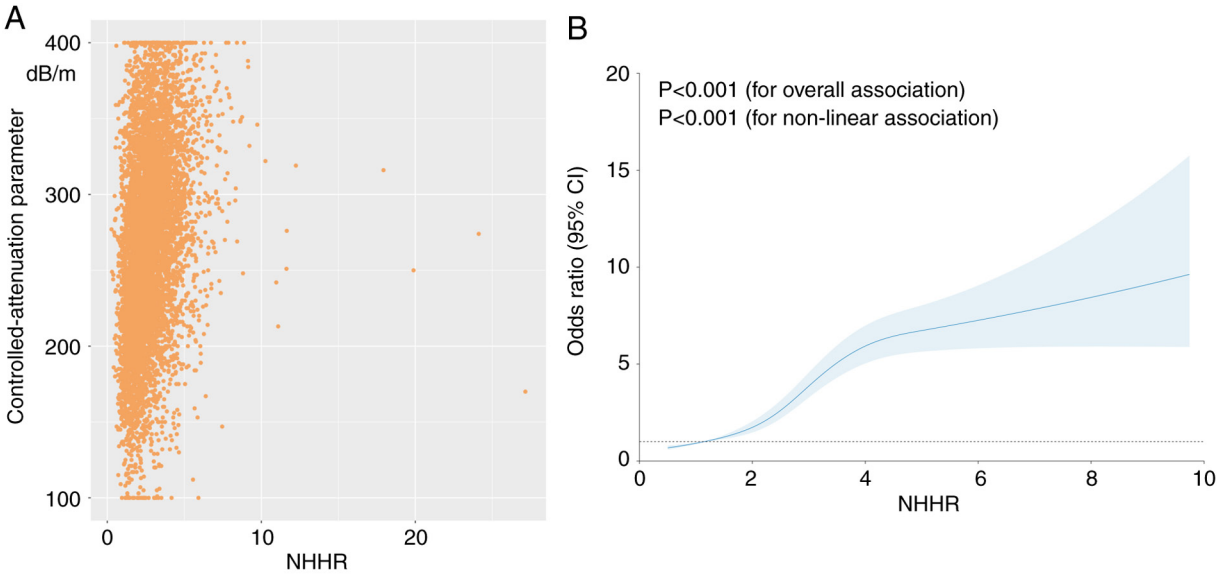

Figure 4. Association between the NHHR and hepatic steatosis. (A) Scatter plot depicting the association between NHHR and hepatic steatosis, with each yellow point representing a sample. (B) Restricted cubic spline model of the association between the NHHR and hepatic steatosis. NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; CI, confidence interval.

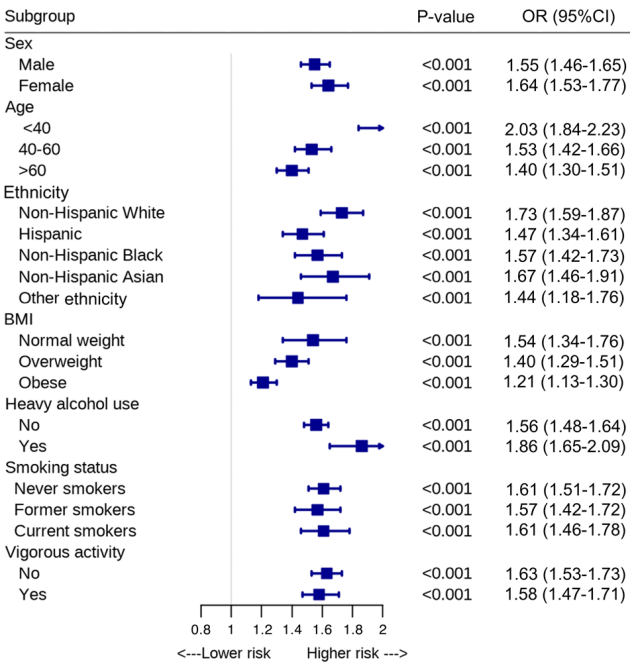

Figure 5. Subgroup analysis for the association between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and hepatic steatosis. Stratification was performed for age, sex, ethnicity, smoking status, alcohol abuse and vigorous activity. BMI, body mass index; OR, odds ratio; CI, confidence interval.

partly due to a higher rate of lipolysis, which typically occurs during conditions such as insulin resistance, excess caloric intake, or inflammation. This increased lipolysis may be mediated by interleukin-6 and results in an increased influx of fatty acids to the liver, promoting hepatic steatosis, insulin resistance and dyslipidemia (26). Additionally, the gut microbiota influences hepatic triglyceride metabolism by increasing endotoxin levels, affecting nutrient absorption, and altering the composition and levels of metabolites such as amino acids, fatty acids and bile acids (27).

Non-HDL-C represents cholesterol carried by atherogenic particles containing apolipoprotein B, including triglyceride-rich lipoproteins, such as low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and its remnants, chylomicrons and lipoprotein (a). Guidelines emphasize the importance of monitoring non-HDL-C levels, particularly in patients with diabetes, obesity or metabolic syndrome, as these individuals frequently exhibit elevated non-HDL-C and triglyceride levels, along with reduced HDL-C levels, even when low-density lipoprotein-cholesterol levels are not significantly elevated (28,29). The value of non-HDL-C is obtained by subtracting HDL-C from TC. This measurement is advantageous because it is unaffected by fasting conditions and triglyceride variability, making it a reliable indicator. On the other side, the NHHR provides a more comprehensive assessment of lipid dysregulation and offers a superior capacity for evaluating the risk of lipid metabolism-related diseases.

The present study demonstrated that the NHHR is an independent predictor of advanced fibrosis and hepatic steatosis. The present findings are consistent with previous research and contribute to the understanding of the causal relationship between dyslipidemia and NAFLD. For example, Wang *et al* (30) revealed that the NHHR was associated with an increased risk of NAFLD, with a hazard ratio (HR) of 2.66 (95% CI, 1.13-6.24; P=0.025) in women and an HR of 2.11 (95% CI, 1.15-3.90; P=0.016) in men, demonstrating that the NHHR was a stronger predictor than non-HDL-C in the Chinese population. Similarly, Yang *et al* (14) reported that the prevalence of NAFLD was positively associated with the NHHR, with an OR of 8.61 (95% CI, 5.90-12.57; P<0.001) in the highest NHHR tertile compared with the lowest tertile. However, a small number of studies have explored the association between the NHHR and advanced fibrosis.

The present study has a number of strengths. First, to the best of our knowledge, this is the first study to examine the potential association of the NHHR with advanced fibrosis and hepatic steatosis as estimated by VCTE, which allows for a more accurate assessment of hepatic fibrosis and steatosis. Furthermore, since the selection of LSM and CAP thresholds may influence diagnostic performance, sensitivity analyses were conducted using different LSM and CAP thresholds to demonstrate a strong association of the NHHR with advanced fibrosis and hepatic steatosis. This suggested that the original findings were not overly dependent on a specific threshold, reinforcing the reliability and consistency of the association across different sensitivity analyses. Second, the present study sample was nationally representative, and all participants had comprehensive data. This broad representation enhanced the generalizability of the present findings and permitted robust subgroup analyses with high statistical power. Additionally, the study employed rigorous exclusion criteria and effectively controlled potential confounding factors by collecting comprehensive data on various lifestyle factors.

Several limitations of the present study should be acknowledged. First, advanced fibrosis and hepatic steatosis were diagnosed using VCTE rather than liver histopathology. Although VCTE is widely recognized as an accurate and reliable tool for detecting advanced fibrosis and hepatic steatosis, certain inaccuracies in the diagnosis may not be excluded. Second, the cross-sectional nature of the present analysis precludes establishing causality or identifying associations with clinical outcomes. Longitudinal and interventional studies are necessary to address this limitation. Third, although numerous potential confounding variables were adjusted for, residual and unmeasured confounding factors could not be entirely ruled out.

In conclusion, the present findings demonstrated a strong association of the NHHR with advanced fibrosis and hepatic steatosis. The NHHR may serve as a simple and effective anthropometric index for predicting these conditions. However, further large-scale prospective studies are necessary to validate the present results in different nations and ethnic groups.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LH and YS designed the study, performed the statistical analysis, and drafted the manuscript. XL collected and reviewed the clinical data. XX revised the manuscript and was responsible for the study conception, design, data collection and analysis. LH and XX confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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