

## ORIGINAL ARTICLE

# The Association between NHHR and Nonalcoholic Fatty Liver Disease: Result from NHANES 2017 - 2023

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## SUMMARY

**Background:** The non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio (NHHR) has emerged as a novel lipid biomarker with potential relevance to nonalcoholic fatty liver disease (NAFLD), yet its role remains underexplored.

**Methods:** Utilizing data from the National Health and Nutrition Examination Survey (NHANES) spanning 2017 through 2023, we investigated the relationship between NHHR and NAFLD. NHHR values were log-transformed (LnNHHR) to achieve normal distribution. Multivariate logistic regression and restricted cubic spline (RCS) models were applied to examine the association between NHHR and both NAFLD and hepatic fibrosis. Robustness was evaluated through subgroup and sensitivity analyses.

**Results:** NHHR levels were significantly elevated in individuals with NAFLD and hepatic fibrosis compared to those without ( $p < 0.001$ ). Multivariate logistic regression indicated a positive correlation between increased LnNHHR and NAFLD risk [odds ratio (OR): 2.94,  $p < 0.001$ ], whereas no significant association was found with hepatic fibrosis (OR: 1.02,  $p = 0.870$ ). Participants in the highest LnNHHR quartile (Q4) had a 3.09-fold higher likelihood of NAFLD compared to those in the lowest quartile (Q1) [95% confidence interval (CI): 2.60 - 3.67,  $p < 0.001$ ]. However, no significant trend was observed for hepatic fibrosis across quartiles ( $p > 0.05$ ). RCS analysis revealed a J-shaped relationship between LnNHHR and both NAFLD ( $p_{\text{interaction}} < 0.001$ ) and hepatic fibrosis ( $p_{\text{interaction}} = 0.006$ ). Stratified analyses further demonstrated that NHHR's impact on NAFLD varied across age groups ( $p_{\text{interaction}} = 0.024$ ), while its effect on hepatic fibrosis differed by education level ( $p_{\text{interaction}} = 0.048$ ).

**Conclusions:** NHHR is strongly linked to an increased risk of NAFLD, suggesting that improving NHHR levels may help mitigate hepatic steatosis.

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## Supplementary Data

Table S1. Baseline characteristics of the study participants.

Characteristics	Overall	Without NAFLD	With NAFLD	p-value	Without hepatic fibrosis	With hepatic fibrosis	p-value
	n = 8,350	n = 4,886 (58.5%)	n = 3,464 (41.5%)		n = 7,552 (90.4%)	n = 798 (9.6%)	
Age group (years)							
< 60	5,237 (62.7%)	3,193 (65.3%)	2,044 (59.0%)	< 0.001	4,808 (63.7%)	429 (53.8%)	< 0.001
≥ 60	3,113 (37.3%)	1,693 (34.7%)	1,420 (41.0%)		2,744 (36.3%)	369 (46.2%)	
Gender							
Female	5,326 (63.8%)	3,260 (66.7%)	2,066 (59.6%)	< 0.001	4,856 (64.3%)	470 (58.9%)	0.003
Male	3,024 (36.2%)	1,626 (33.3%)	1,398 (40.4%)		2,696 (35.7%)	328 (41.1%)	
Race							
Mexican american	771 (9.2%)	341 (7%)	430 (12.4%)	< 0.001	685 (9.1%)	86 (10.8%)	< 0.001
Other hispanic	820 (9.8%)	481 (9.8%)	339 (9.8%)		752 (10%)	68 (8.5%)	
Non - hispanic white	3,968 (47.5%)	2,305 (47.2%)	1,663 (48%)		3,548 (47%)	420 (52.6%)	
Non - hispanic black	1,586 (19.0%)	1,014 (20.8%)	572 (16.5%)		1,440 (19.1%)	146 (18.3%)	
Other/multiracial	1,205 (14.4%)	745 (15.2%)	460 (13.3%)		1,127 (14.9%)	78 (9.8%)	
BMI group (kg/m <sup>2</sup> )							
< 25	2,207 (26.4%)	1,967 (40.3%)	240 (6.9%)	< 0.001	2,127 (28.2%)	80 (10%)	< 0.001
25 - 30	2,668 (32%)	1,715 (35.1%)	953 (27.5%)		2,526 (33.4%)	142 (17.8%)	
≥ 30	3,475 (41.6%)	1,204 (24.6%)	2,271 (65.6%)		2,899 (38.4%)	576 (72.2%)	
Smoking							
Never	5,133 (61.5%)	3,112 (63.7%)	2,021 (58.3%)	< 0.001	4,676 (61.9%)	457 (57.3%)	0.018
Past	1,966 (23.5%)	1,034 (21.2%)	932 (26.9%)		1,749 (23.2%)	217 (27.2%)	
Current	1,251 (15.0%)	740 (15.1%)	511 (14.8%)		1,127 (14.9%)	124 (15.5%)	
Education							
Less than 9th grade	359 (4.3%)	179 (3.7%)	180 (5.2%)	< 0.001	317 (4.2%)	42 (5.3%)	< 0.001
9 - 11th grade	667 (8.0%)	375 (7.7%)	292 (8.4%)		593 (7.9%)	74 (9.3%)	
High School graduate/GED	1,761 (21.1%)	966 (19.8%)	795 (23.0%)		1,564 (20.7%)	197 (24.7%)	
College or AA degree	2,769 (33.2%)	1,547 (31.7%)	1,222 (35.3%)		2,479 (32.8%)	290 (36.3%)	
College graduate or above	2,794 (33.5%)	1,819 (37.2%)	975 (28.1%)		2,599 (34.4%)	195 (24.4%)	

Table S1. Baseline characteristics of the study participants (continued).

Characteristics	Overall	Without NAFLD	With NAFLD	p-value	Without hepatic fibrosis	With hepatic fibrosis	p-value
	n = 8,350	n = 4,886 (58.5%)	n = 3,464 (41.5%)		n = 7,552 (90.4%)	n = 798 (9.6%)	
<b>PIR group</b>							
≥ 1.3	6,435 (77.1%)	3,750 (76.7%)	2,685 (77.5%)	0.400	5,807 (76.9%)	628 (78.7%)	0.200
< 1.3	1,915 (22.9%)	1,136 (23.3%)	779 (22.5%)		1,745 (23.1%)	170 (21.3%)	
Age (years)	52 (37, 65)	49 (34, 64)	55 (41, 65)	< 0.001	51 (36, 64)	58 (44, 67)	< 0.001
BMI (kg/m <sup>2</sup> )	28.5 (24.7, 33.5)	26 (23.1, 29.9)	32.4 (28.5, 37.4)	< 0.001	28.1 (24.4, 32.6)	35.2 (29.3, 41.0)	< 0.001
PIR	2.74 (1.39, 4.93)	2.78 (1.38, 5.00)	2.66 (1.40, 4.76)	0.200	2.77 (1.38, 4.97)	2.54 (1.47, 4.62)	0.300
Waist circumference (cm)	98.7 (88.0, 110.3)	91.6 (82.7, 101.2)	108.6 (99.4, 119.1)	< 0.001	97.4 (87.1, 108.2)	115.2 (102.0, 126.6)	< 0.001
TC (mmol/L)	4.81 (4.16, 5.55)	4.76 (4.11, 5.48)	4.89 (4.22, 5.64)	< 0.001	4.84 (4.16, 5.56)	4.68 (3.96, 5.46)	< 0.001
HDL-C (mmol/L)	1.37 (1.14, 1.66)	1.47 (1.24, 1.76)	1.24 (1.06, 1.47)	< 0.001	1.40 (1.16, 1.68)	1.22 (1.05, 1.47)	< 0.001
HbA1c (%)	5.50 (5.30, 5.90)	5.40 (5.20, 5.70)	5.70 (5.40, 6.20)	< 0.001	5.50 (5.20, 5.80)	5.90 (5.50, 6.60)	< 0.001
FBG (mmol/L)	5.66 (5.27, 6.16)	5.50 (5.16, 5.88)	5.94 (5.50, 6.72)	< 0.001	5.61 (5.22, 6.11)	6.16 (5.55, 7.22)	< 0.001
<b>DM</b>							
No	6,909 (82.7%)	4,423 (90.5%)	2,486 (71.8%)	< 0.001	6,441 (85.3%)	468 (58.6%)	< 0.001
Yes	1,441 (17.3%)	463 (9.5%)	978 (28.2%)		1,111 (14.7%)	330 (41.4%)	
SBP (mmHg)	121 (110, 133)	118 (108, 131)	123 (112, 136)	< 0.001	120 (109, 133)	127 (114, 139)	< 0.001
DBP (mmHg)	74 (67, 81)	72 (66, 79)	76 (69, 84)	< 0.001	74 (67, 81)	76 (68, 84)	< 0.001
<b>Hypertension</b>							
No	5,080 (61.0%)	3,341 (68.0%)	1,739 (50.0%)	< 0.001	4,762 (63%)	318 (40%)	< 0.001
Yes	3,270 (39.0%)	1,545 (32.0%)	1,725 (50.0%)		2,790 (37%)	480 (60%)	
NHHR	2.41 (1.79, 3.22)	2.15 (1.64, 2.84)	2.84 (2.15, 3.72)	< 0.001	2.39 (1.78, 3.19)	2.66 (1.94, 3.52)	< 0.001
LnNHHR	0.88 (0.58, 1.17)	0.76 (0.49, 1.4)	14 (0.77, 1.31)	< 0.001	0.87 (0.58, 1.16)	0.98 (0.66, 1.26)	< 0.001
LSM (kPa)	4.9 (4, 6.1)	4.6 (3.8, 5.5)	5.6 (4.5, 7.1)	< 0.001	4.7 (3.9, 5.7)	10.5 (9, 13.9)	< 0.001
CAP (dB/m)	259 (218, 305)	225 (199, 248)	315 (292, 346)	< 0.001	254 (215, 297)	319 (274, 359)	< 0.001
<b>Severe hepatic steatosis</b>							
No	6,125 (73.4%)	4,886 (100%)	1,239 (35.8%)	< 0.001	5,825 (77.1%)	300 (37.6%)	< 0.001
Yes	2,225 (26.6%)	0 (0%)	2,225 (64.2%)		1,727 (22.9%)	498 (62.4%)	

**Table S1. Baseline characteristics of the study participants (continued).**

Characteristics	Overall	Without NAFLD	With NAFLD	p-value	Without hepatic fibrosis	With hepatic fibrosis	p-value
	n = 8,350	n = 4,886 (58.5%)	n = 3,464 (41.5%)		n = 7,552 (90.4%)	n = 798 (9.6%)	
<b>Hepatic fibrosis</b>							
F1	7,552 (90.4%)	4,687 (95.9%)	2,865 (82.7%)	< 0.001	7,552 (100%)	0 (0%)	< 0.001
F2	299 (3.6%)	81 (1.7%)	218 (6.3%)		0 (0%)	299 (37.5%)	
F3	291 (3.5%)	67 (1.4%)	224 (6.5%)		0 (0%)	291 (36.5%)	
F4	208 (2.5%)	51 (1%)	157 (4.5%)		0 (0%)	208 (26.1%)	

ALB albumin, ALP alkaline phosphatase, ALT alanine transaminase, AST aspartate aminotransferase, BMI body mass index, CAP controlled attenuation parameter, DM diabetes mellitus, DBP diastolic blood pressure, FBG fasting blood glucose, GGT gamma-glutamyl transpeptidase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, LSM liver stiffness measurement, NAFLD nonalcoholic fatty liver disease, NHHR non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio, PIR poverty-to-income ratio, SBP systolic blood pressure, TC total cholesterol, TG triglyceride, TP total protein.

**Table S2. Multivariable regression analysis of associations between NHHR and NAFLD and hepatic fibrosis.**

Characteristics	Model 1 †			Model 2 ‡			Model 3 §		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
NAFLD									
LnNHHR	4.77	4.20, 5.42	< 0.001	4.98	4.37, 5.68	< 0.001	2.94	2.54, 3.40	< 0.001
<b>LnNHHR quartile</b>									
Q1	-	-		-	-		-	-	
Q2	1.63	1.41, 1.89	< 0.001	1.64	1.42, 1.89	< 0.001	1.24	1.04, 1.47	0.017
Q3	2.93	2.49, 3.45	< 0.001	3.00	2.54, 3.54	< 0.001	1.92	1.59, 2.33	< 0.001
Q4	5.37	4.66, 6.18	< 0.001	5.60	4.85, 6.47	< 0.001	3.09	2.60, 3.67	< 0.001
<b>Hepatic fibrosis</b>									
LnNHHR	1.69	1.40, 2.03	< 0.001	1.73	1.42, 2.10	< 0.001	1.02	0.80, 1.31	0.870
<b>LnNHHR quartile</b>									
Q1	-	-		-	-		-	-	
Q2	1.16	0.97, 1.40	0.110	1.16	0.96, 1.39	0.120	0.90	0.74, 1.10	0.310
Q3	1.34	1.14, 1.58	< 0.001	1.36	1.14, 1.61	< 0.001	0.86	0.72, 1.03	0.091
Q4	1.79	1.43, 2.24	< 0.001	1.83	1.45, 2.31	< 0.001	1.00	0.77, 1.30	> 0.990

CI confidence interval, NAFLD nonalcoholic fatty liver disease, NHHR non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio, OR odds ratio.

† Crude model: unadjusted.

‡ Partial-adjusted model: adjusted for gender, age, and race.

§ Fully-adjusted model: adjusted for gender, age, race, education level, body mass index, waist circumference, smoking status, diabetes mellitus, and hypertension.

**Table S3. Threshold effect analysis of NHHR on NAFLD and hepatic fibrosis.**

Inflection point	OR	95% CI	p-value
<b>NAFLD</b>			
< 0.885	1.62	1.12, 2.34	0.012
≥ 0.885	3.16	2.40, 4.17	< 0.001
<b>Hepatic fibrosis</b>			
< 0.885	0.73	0.46, 1.14	0.160
≥ 0.885	1.54	1.04, 2.29	0.031

CI confidence interval, NAFLD nonalcoholic fatty liver disease, NHHR non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio, OR odds ratio.

**Table S4. Sensitivity analyses.**

Characteristics	Model 1 †			Model 2 ‡			Model 3 §		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
<b>NAFLD</b>									
<b>NHHR group</b>									
< 0.838	-	-		-	-		-	-	
≥ 0.838	3.00	2.71, 3.33	< 0.001	3.18	2.86, 3.53	< 0.001	1.95	1.72, 2.20	< 0.001
<b>LnNHHR quartile</b>									
Q1	-	-		-	-		-	-	
Q2	1.57	1.33, 1.85	< 0.001	1.61	1.36, 1.90	< 0.001	1.30	1.06, 1.59	0.014
Q3	2.55	2.11, 3.09	< 0.001	2.65	2.18, 3.23	< 0.001	1.65	1.32, 2.07	< 0.001
Q4	5.09	4.34, 5.98	< 0.001	5.66	4.79, 6.71	< 0.001	2.78	2.22, 3.49	< 0.001
<b>Hepatic fibrosis</b>									
<b>NHHR group</b>									
< 0.897	-	-		-	-		-	-	
≥ 0.897	1.58	1.39, 1.79	< 0.001	1.64	1.44, 1.87	< 0.001	1.02	0.87, 1.19	0.840
<b>LnNHHR quartile</b>									
Q1	-	-		-	-		-	-	
Q2	1.23	0.98, 1.54	0.072	1.24	0.99, 1.54	0.060	1.01	0.79, 1.30	0.940
Q3	1.28	0.99, 1.65	0.058	1.29	1.00, 1.66	0.052	0.84	0.65, 1.10	0.210
Q4	1.90	1.57, 2.30	< 0.001	2.00	1.64, 2.45	< 0.001	0.96	0.77, 1.21	0.720

CI confidence interval, NAFLD nonalcoholic fatty liver disease, NHHR non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio, OR odds ratio.

† Crude model: unadjusted.

‡ Partial-adjusted model: adjusted for gender, age, and race.

§ Fully-adjusted model: adjusted for gender, age, race, education level, body mass index, waist circumference, smoking status, diabetes mellitus, and hypertension.