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Association between lymphocyte to high-density lipoprotein cholesterol ratio and insulin resistance and metabolic syndrome in US adults: results from NHANES 2007–2018

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Abstract

Background Insulin resistance (IR) and metabolic syndrome (MetS) are significant global health challenges that increase the risk of various chronic diseases. The lymphocyte-to-high-density lipoprotein cholesterol ratio (LHR) has emerged as a novel inflammatory metabolic marker. The present study focused on evaluating the association between the LHR and both IR and MetS.

Methods We analyzed data from 14,779 adults aged ≥ 20 years from the National Health and Nutrition Examination Survey (2007–2018). To investigate the relationship between LHR and both IR and MetS, we conducted multivariable logistic regression analyses. The reliability of the results was validated through both stratified and sensitivity analyses. Furthermore, we thoroughly examined possible nonlinear associations by implementing a restricted cubic spline in conjunction with a threshold effect analysis.

Results Compared to the lowest LHR quartile, individuals in the highest quartile indicated significantly increased prevalence of IR (odds ratio = 3.72, 95% confidence intervals: 3.01–4.59) and MetS (odds ratio = 11.38, 95% confidence intervals: 8.85–14.63) in fully adjusted models. Subgroup analyses demonstrated that the association between the LHR and IR remained consistent across all subgroups, with no significant interaction effect observed. However, the association between LHR and MetS was more pronounced in female participants. Restricted cubic spline analyses revealed nonlinear associations between LHR and both IR and MetS. The threshold effect analyses identified inflection points at 0.055 for these non-linear relationships.

Conclusions An elevated LHR was positively associated with the prevalence of IR and MetS, indicating its promising role in early screening and disease prevention through biological monitoring.

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Keywords Lymphocyte to high-density lipoprotein cholesterol ratio, Insulin resistance, Metabolic syndrome, National Health and Nutrition Examination Survey

Introduction

Metabolic syndrome (MetS) manifests as systemic metabolic disturbances involving abnormal fat distribution, altered pressure regulation, dyslipidemia, and disturbed glucose metabolism [1]. Insulin resistance (IR) refers to the diminished responsiveness of peripheral tissues to insulin signaling pathways, leading to impaired glucose metabolism [2]. Accumulating evidence has indicated that IR is the core pathogenic mechanism underlying MetS [3, 4]. Globally, MetS affects 20–25% of adults, reaching 24.2% in the Chinese population [5, 6]. Concurrently, IR is prevalent in 25–30% of adults worldwide [7]. Evidence indicates that both MetS and IR substantially increase the susceptibility to chronic conditions such as nonalcoholic fatty liver disease, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) [8, 9]. Research data revealed that patients suffering from MetS face significantly increased health risks; their overall death rate exceeds normal population levels by 50%, while the likelihood of fatal cardiovascular events is 2–3 times above average [10].

The ratio of lymphocyte to high-density lipoprotein cholesterol (LHR) is an emerging marker that reflects dual pathological processes including immune activation and lipid metabolic disorders, making it a valuable indicator of inflammatory metabolism [11]. Increased LHR demonstrates a substantial association with increased cardiovascular risk and serves as a standalone indicator of the development of diabetes mellitus [12, 13]. These relationships may be mediated by chronic inflammatory conditions and dysregulation of lipid metabolism. Investigations in various populations, including Chinese, Brazilian, and Iranian cohorts, have consistently reported positive associations between LHR and MetS [11, 14, 15]. However, the current literature has several limitations. Primarily, the available studies often lack data from large-scale, multi-ethnic, and multi-regional populations. Although IR is a key pathogenic mechanism in MetS, the relationship between LHR and IR remains unclear.

Accordingly, we conducted a cross-sectional study based on the NHANES database. This study, incorporating a large-scale, multi-ethnic population, partially addressed the limitations of previous research. The research outcomes presented herein may lead to the discovery of novel diagnostic indicators for the detection of MetS and IR in its initial stages. These findings contribute to the establishment of a theoretical foundation for the implementation of preventive strategies in clinical practice.

Methods

Data source

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive nationwide health assessment conducted biennially in the United States [16]. This nationwide assessment implements a sophisticated sampling design that combines survey instruments, clinical measurements, and laboratory analyses, providing insights into the American public health status [17].

Study population

We analyzed information collected from 59,842 subjects participating in the NHANES between 2007 and 2018. We excluded participants aged < 20 years and those with incomplete records of LHR, fasting plasma glucose, fasting insulin, and MetS diagnostic information. The final analytical sample comprised 14,779 qualified participants (Fig. 1).

Exposure variable

LHR was calculated using the following formula: LHR = lymphocyte count (1000 cells/uL) / high-density lipoprotein cholesterol (HDL-C, mg/dL) [18].

Outcomes

The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated using the following formula: HOMA-IR = (fasting plasma glucose [mg/dL] × fasting insulin [uIU/mL]) / 405 [19]. Following prior research conventions, we adopted a HOMA-IR cutoff point of 2.5 to identify IR [19, 20]. MetS was diagnosed based on the guidelines established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) [21]. A diagnosis of MetS can be made if an individual fulfills three or more of the following five criteria: (a) a waist circumference of ≥ 102 cm for men or ≥ 88 cm for women; (b) triglyceride levels of ≥ 150 mg/dL (1.7 mmol/L) or being under treatment for high triglycerides; (c) HDL-C < 40 mg/dL (1.03 mmol/L) for men or < 50 mg/dL (1.3 mmol/L) for women, or receiving treatment to improve HDL-C levels; (d) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or being treated for hypertension; and (e) fasting blood glucose level of ≥ 100 mg/dL (5.6 mmol/L) or currently receiving diabetes treatment.

Covariables

Based on previous similar studies, we included the following covariables [14, 15, 22]: age, sex, race, educational level, poverty income ratio (PIR), marital status,

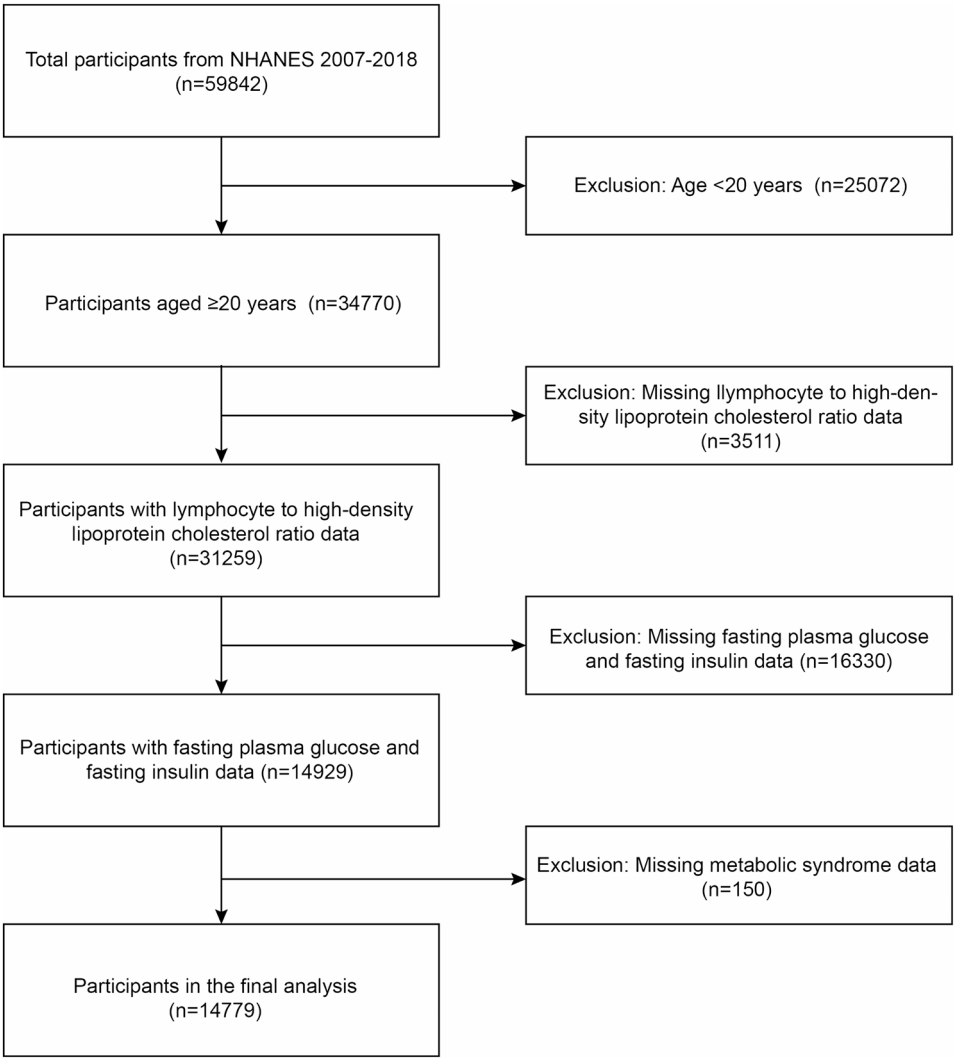

Fig. 1 Flowchart of the study design. *Note*: NHANES: National Health and Nutrition Examination Survey

daily energy intake (kcal), smoking status, alcohol status, physical activity, hypertension, diabetes mellitus (DM), cardiovascular disease (CVD), body mass index (BMI, kg/m^2), waist circumference (cm), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), creatinine (CR, mg/dL), uric acid (UA, mg/dL), blood urea nitrogen (BUN, mg/dL), total cholesterol (TC, mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), monocyte count (1000 cells/μL), and neutrophil count (1000 cells/μL). Race was categorized as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other. Educational level was classified into three categories depending on the number of years of schooling: less than high school, high school, and higher than high school. PIR was classified into three levels: low income (PIR ≤ 1.3), middle income (PIR: 1.3–3.5), and high income (PIR > 3.5) [23]. Participants were categorized based on their marital status as married, unmarried, living with a partner, or other (widowed, divorced, or separated). Dietary recall interviews were conducted to obtain the participants' total energy intake over a 24-hour period. Smoking behavior was classified into three groups: nonsmokers (lifetime consumption below 100 cigarettes), past smokers (discontinued smoking after exceeding 100 cigarettes), and active smokers (continued smoking after exceeding 100 cigarettes) [24]. Participants were classified based on alcohol consumption as non-drinkers (fewer than 12 drinking occasions in the past 12 months) or drinkers (12 or more drinking occasions in the past 12 months). Data on physical activity were collected using a global physical activity questionnaire. Physical activity was converted into metabolic equivalent (MET)-minutes per week for moderate-to-vigorous physical activity. Based on the American physical activity guidelines, we classified physical activity as inactive (< 600 MET-min/week) and active (≥ 600 MET-min/

week) [25, 26]. Hypertension was diagnosed based on self-reported history or the current use of antihypertensive medications. The diagnosis of diabetes was based on any of the following: fasting plasma glucose (FPG) ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, use of any antidiabetic medication, or self-reported history of diabetes [27]. The diagnoses of coronary heart disease, congestive heart failure, angina, myocardial infarction, and stroke were based on self-reported history. CVD can be diagnosed if at least one of the five aforementioned conditions is present.

Statistical analysis

This study adhered to the analytical guidelines set forth by NHANES, accounting for its intricate sampling design and corresponding sampling weights [28]. The sampling weights for the years 2007–2018 were calculated using the following formula: WTSAF2YR / 6. The incomplete covariable information was subjected to multiple imputations using chained equations. LHR levels were categorized into quartiles and baseline differences among the four groups were compared. The Kolmogorov-Smirnov test was used to determine whether the variable followed a normal distribution. Descriptive statistics for normally distributed quantitative data were presented as weighted mean ± standard deviation (SD), and group differences were analyzed using one-way analysis of variance. For non-normally distributed quantitative data, descriptive statistics were reported as weighted median (interquartile range, IQR), with group differences assessed using the Kruskal-Wallis test. For qualitative data, raw counts and weighted proportions were reported, with chi-square tests used for between-group analyses. Owing to the small LHR values, we multiplied them by 100 prior to subsequent statistical analyses. We employed multivariable logistic regression models to explore the associations between LHR quartiles and the prevalence of IR and MetS across different models. We assessed the potential multicollinearity among covariables using the variance inflation factor (VIF). Covariables with VIF ≥ 5, indicating significant multicollinearity, such as waist circumference and TC, were not included as adjusting variables. Finally, we constructed three models: Model 1 was unadjusted; Model 2 was adjusted for age, sex, race, educational level, PIR, and marital status; and Model 3 was adjusted for age, sex, race, educational level, PIR, marital status, daily energy intake, smoking, alcohol consumption, physical activity, hypertension, DM, CVD, BMI, ALT, AST, CR, UA, BUN, LDL-C, monocyte count, and neutrophil count. Furthermore, we stratified the study population by the following characteristics: age (< 65, ≥ 65 years), sex, race, BMI (< 30, ≥ 30 kg/m^2), smoking status, alcohol status, and physical activity. We then employed multivariable logistic regression models for subgroup analyses and conducted likelihood ratio tests to assess the interaction effects across the subgroups. Subgroup analyses can reveal variations among various subgroups, aiding in a more comprehensive understanding of the association between LHR and the prevalence of IR and MetS. Furthermore, analyzing different subgroups allows us to assess the consistency and robustness of the study findings across diverse populations. Moreover, after adjusting for the covariables in Model 3, we performed restricted cubic spline (RCS) regression using the 25th, 50th, and 75th percentiles of LHR to evaluate the nonlinear relationships between LHR, IR, and MetS. When nonlinear associations were detected, piecewise logistic regression was employed to identify significant inflection points. Additionally, to assess the robustness of the study findings across different populations, three sensitivity analyses were conducted. First, participants with LHR outliers were excluded from the analysis. Outliers were defined as values falling below the lower bound or exceeding the upper bound. The upper bound was calculated as quartile 3 + 1.5 × IQR, and the lower bound as quartile 1 – 1.5 × IQR. Second, individuals who received lipid-lowering treatments were excluded. Third, participants with missing covariable data were excluded. Finally, we assessed the diagnostic ability of LHR to diagnose IR and MetS using receiver operating characteristic (ROC) curves and the area under the curve (AUC). The optimal cut-off values for LHR in diagnosing IR and MetS were determined using the maximum Youden index.

Analyses were performed using R (version 4.2.2; https://www.r-project.org; The R Foundation, Vienna, Austria) and Free Statistics software (version 1.9.2; Beijing Free Clinical Medical Technology Co., Ltd, Beijing, China). Throughout the statistical evaluation, results yielding bilateral p-values below 0.05 were deemed significant.

Results

Population characteristics

The study population comprised 14,779 individuals, all being 20 years or above. The median age of the study population was 47 years, of which 51.10% were female (n = 7,541). Baseline analyses were stratified according to LHR quartiles (Table 1). Demographically, age decreased from the initial to the final quartile, whereas the proportion of males increased ($p < 0.05$). The first quartile consisted predominantly of well-educated and non-Hispanic whites ($p < 0.05$). Conversely, lower income and unmarried status were most prevalent in the fourth quartile ($p < 0.05$). Regarding lifestyle factors, individuals in the fourth quartile exhibited the highest energy intake and smoking rates ($p < 0.05$). The prevalence of diabetes, IR, and MetS showed an increasing trend from the lowest to the highest quartiles ($p < 0.05$). In terms of physical and laboratory examinations, participants in the higher

Table 1 Characteristics of the study population from NHANES 2007–2018

Variables	Overall	LHR				*p*-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Unweighted number	14,779	3690	3692	3700	3697	
Weighted number	219,089,334	57,004,174	54,442,967	55,428,224	52,213,969	
Age, years, Median (IQR)	47.00 (33.00, 60.00)	54.00 (40.00, 66.00)	47.00 (33.00, 60.00)	45.00 (32.00, 58.00)	42.00 (30.00, 55.00)	< 0.001
Sex, n (%)						< 0.001
Female	7541 (51.10)	2261 (63.88)	2009 (54.70)	1766 (46.08)	1505 (38.72)	
Male	7238 (48.90)	1429 (36.12)	1683 (45.30)	1934 (53.92)	2192 (61.28)	
Race, n (%)						< 0.001
Mexican American	2271 (8.68)	359 (4.76)	575 (8.66)	624 (9.34)	713 (12.30)	
Other Hispanic	1625 (5.96)	329 (4.09)	401 (6.13)	438 (6.26)	457 (7.49)	
Non-Hispanic White	6128 (66.24)	1742 (72.69)	1514 (66.40)	1471 (65.48)	1401 (59.81)	
Non-Hispanic Black	2939 (11.09)	815 (11.28)	752 (11.22)	701 (10.81)	671 (11.04)	
Other Race	1816 (8.03)	445 (7.18)	450 (7.58)	466 (8.11)	455 (9.36)	
Educational level, n (%)						< 0.001
< High school	3739 (16.38)	730 (11.20)	888 (15.93)	980 (17.59)	1141 (21.24)	
High school	3336 (22.93)	773 (20.45)	816 (22.02)	867 (24.26)	880 (25.18)	
> High school	7704 (60.69)	2187 (68.36)	1988 (62.05)	1853 (58.16)	1676 (53.58)	
PIR, n (%)						< 0.001
Low (≤ 1.3)	4859 (22.56)	982 (16.33)	1106 (21.35)	1266 (23.76)	1505 (29.36)	
Medium (1.3–3.5)	5634 (36.50)	1400 (34.96)	1466 (37.22)	1398 (35.98)	1370 (37.98)	
High (> 3.5)	4286 (40.94)	1308 (48.71)	1120 (41.43)	1036 (40.26)	822 (32.66)	
Marital status, n (%)						< 0.001
Married	7634 (55.25)	1921 (59.00)	1947 (55.92)	1919 (54.17)	1847 (51.62)	
Never married	2619 (18.22)	553 (14.23)	667 (18.80)	694 (19.12)	705 (21.01)	
Living with partner	1204 (8.36)	226 (6.48)	262 (7.24)	326 (8.82)	390 (11.11)	
Other	3322 (18.17)	990 (20.30)	816 (18.03)	761 (17.89)	755 (16.26)	
Daily energy intake, kcal, Median (IQR)	2015.00 (1493.00, 2674.00)	1919.12 (1451.11, 2529.38)	1970.00 (1492.00, 2600.85)	2078.00 (1530.00, 2734.00)	2130.00 (1520.93, 2824.00)	< 0.001
Smoking status, n (%)						< 0.001
Never	8189 (55.72)	2219 (60.12)	2159 (59.04)	2058 (55.69)	1753 (47.49)	
Former	3610 (25.19)	998 (27.90)	912 (24.97)	914 (24.90)	786 (22.77)	
Current	2980 (19.09)	473 (11.99)	621 (15.99)	728 (19.41)	1158 (29.74)	
Alcohol status, n (%)						0.743
No	4329 (23.52)	1119 (23.52)	1104 (24.35)	1083 (23.18)	1023 (23.00)	
Yes	10,450 (76.48)	2571 (76.48)	2588 (75.65)	2617 (76.82)	2674 (77.00)	
Physical activity, n (%)						0.607
Inactive	5977 (35.27)	1508 (34.47)	1474 (36.32)	1464 (34.88)	1531 (35.46)	
Active	8802 (64.73)	2182 (65.53)	2218 (63.68)	2236 (65.12)	2166 (64.54)	
Hypertension, n (%)						0.179
No	8377 (61.98)	2024 (62.37)	2170 (63.63)	2089 (60.27)	2094 (61.65)	
Yes	6402 (38.02)	1666 (37.63)	1522 (36.37)	1611 (39.73)	1603 (38.35)	
DM, n (%)						< 0.001
No	11,482 (83.70)	3032 (88.44)	2954 (85.82)	2853 (82.24)	2643 (77.87)	
Yes	3297 (16.30)	658 (11.56)	738 (14.18)	847 (17.76)	1054 (22.13)	
CVD, n (%)						0.291
No	13,045 (90.67)	3231 (90.49)	3270 (91.19)	3301 (91.18)	3243 (89.79)	
Yes	1734 (9.33)	459 (9.51)	422 (8.81)	399 (8.82)	454 (10.21)	
IR, n (%)						< 0.001
No	7447 (53.96)	2628 (76.07)	2114 (60.19)	1620 (45.25)	1085 (32.58)	
Yes	7332 (46.04)	1062 (23.93)	1578 (39.81)	2080 (54.75)	2612 (67.42)	
MetS, n (%)						< 0.001
No	9332 (65.56)	2954 (83.19)	2643 (73.20)	2228 (60.55)	1507 (43.69)	
Yes	5447 (34.44)	736 (16.81)	1049 (26.80)	1472 (39.45)	2190 (56.31)	

Table 1 (continued)

Variables	Overall	LHR				*p*-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
BMI, kg/m2, Median (IQR)	27.90 (24.11, 32.57)	25.30 (22.50, 28.90)	27.40 (23.70, 31.90)	28.91 (25.46, 33.80)	30.22 (26.60, 35.10)	< 0.001
Waist circumference, cm, Median (IQR)	97.84 (87.50, 109.20)	91.20 (82.50, 101.50)	96.00 (85.57, 107.70)	101.00 (90.80, 112.00)	103.90 (94.50, 115.30)	< 0.001
ALT, U/L, Median (IQR)	21.00 (16.00, 28.00)	19.00 (15.00, 24.00)	20.00 (15.00, 26.00)	22.00 (17.00, 30.00)	24.00 (17.00, 34.00)	< 0.001
AST, U/L, Median (IQR)	22.00 (19.00, 27.00)	22.00 (19.00, 27.00)	22.00 (18.00, 26.00)	22.00 (19.00, 27.00)	23.00 (19.00, 28.00)	0.004
CR, mg/dL, Median (IQR)	0.84 (0.72, 0.98)	0.82 (0.70, 0.96)	0.83 (0.72, 0.97)	0.85 (0.72, 0.99)	0.86 (0.73, 1.00)	< 0.001
UA, mg/dL, Median (IQR)	5.40 (4.50, 6.40)	4.90 (4.10, 5.90)	5.30 (4.40, 6.20)	5.60 (4.70, 6.50)	5.90 (5.00, 6.80)	< 0.001
BUN, mg/dL, Median (IQR)	13.00 (10.00, 16.00)	13.00 (11.00, 17.00)	13.00 (10.00, 16.00)	13.00 (10.00, 16.00)	13.00 (10.00, 16.00)	0.001
TC, mg/dL, Median (IQR)	188.00 (164.00, 215.13)	195.00 (169.00, 222.00)	187.00 (163.00, 214.00)	186.00 (163.00, 213.00)	184.00 (158.00, 213.00)	< 0.001
HDL-C, mg/dL, Median (IQR)	51.00 (42.37, 63.00)	69.00 (59.00, 79.00)	55.00 (49.00, 63.00)	48.00 (42.00, 54.00)	40.00 (34.96, 45.00)	< 0.001
LDL-C, mg/dL, Median (IQR)	111.00 (89.00, 135.00)	108.00 (86.00, 132.00)	111.00 (89.00, 134.00)	113.00 (92.00, 137.00)	111.00 (89.00, 136.00)	< 0.001
FPG, mg/dL, Median (IQR)	100.00 (93.00, 109.00)	98.00 (91.00, 105.00)	100.00 (93.00, 107.00)	101.00 (95.00, 111.00)	103.00 (96.00, 114.00)	< 0.001
Fasting insulin, uU/mL, Median (IQR)	9.48 (6.03, 15.47)	6.69 (4.59, 9.98)	8.61 (5.68, 13.92)	11.12 (7.13, 16.58)	13.97 (8.70, 22.08)	< 0.001
HOMAIR, Median (IQR)	2.41 (1.44, 4.17)	1.63 (1.08, 2.54)	2.15 (1.36, 3.60)	2.83 (1.75, 4.53)	3.65 (2.17, 6.40)	< 0.001
Lymphocyte number, 1000 cells/uL, Median (IQR)	1.90 (1.60, 2.30)	1.40 (1.20, 1.60)	1.80 (1.60, 2.00)	2.10 (1.80, 2.40)	2.60 (2.20, 3.03)	< 0.001
Monocyte number, 1000 cells/uL, Median (IQR)	0.50 (0.40, 0.60)	0.40 (0.40, 0.50)	0.50 (0.40, 0.60)	0.50 (0.40, 0.60)	0.60 (0.50, 0.70)	< 0.001
Neutrophils num, 1000 cells/uL, Median (IQR)	3.70 (2.90, 4.70)	3.20 (2.50, 4.10)	3.50 (2.80, 4.50)	3.90 (3.00, 4.90)	4.30 (3.40, 5.40)	< 0.001

Note NHANES: National Health and Nutrition Examination Survey; LHR: lymphocyte to high-density lipoprotein cholesterol ratio; Quartile 1: 0.004–0.028; Quartile 2: 0.028–0.038; Quartile 3: 0.038–0.051; Quartile 4: ≥0.051; PIR: poverty income ratio; DM: diabetes mellitus; CVD: cardiovascular disease; IR: insulin resistance; MetS: metabolic syndrome; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CR: creatinine; UA: uric acid; BUN: blood urea nitrogen; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; HOMA-IR: homeostatic model assessment of insulin resistance; IQR: interquartile range

Table 2 Multivariable logistic regression models of LHR and IR

	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
LHR quartile						
Q1 (0.004, 0.028)	Reference		Reference		Reference	
Q2 (0.028, 0.038)	2.10 (1.81, 2.45)	< 0.001	2.38 (2.03, 2.79)	< 0.001	1.65 (1.38, 1.96)	< 0.001
Q3 (0.038, 0.051)	3.84 (3.34, 4.43)	< 0.001	4.67 (4.04, 5.39)	< 0.001	2.51 (2.15, 2.92)	< 0.001
Q4 (≥ 0.051)	6.58 (5.57, 7.77)	< 0.001	8.44 (7.10, 10.03)	< 0.001	3.72 (3.01, 4.59)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Note

Model 1: No covariables were adjusted

Model 2: Age, sex, race, educational level, poverty income ratio, and marital status were adjusted

Model 3: Age, sex, race, educational level, poverty income ratio, marital status, daily energy intake, smoking status, alcohol status, physical activity, hypertension, diabetes mellitus, cardiovascular disease, body mass index, alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid, blood urea nitrogen, low-density lipoprotein cholesterol, monocyte count, and neutrophils count were adjusted

LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4

quartiles of LHR showed significantly higher BMI, waist circumference, ALT, AST, CR, UA, LDL-C, FPG, fasting insulin levels, HOMA-IR, and lymphocyte, monocyte, and neutrophil counts ($p < 0.05$). However, lower TC and HDL-C levels were observed ($p < 0.05$).

Association between LHR, IR, and MetS

Multiple regression analyses identified a significant association between elevated LHR and a higher prevalence of IR and MetS (Tables 2 and 3). This relationship remained robust even after adjusting for potential confounding variables. Compared to those in the lowest LHR quartile in Model 3, the prevalence of IR increased 2.72-fold

Table 3 Multivariable logistic regression models of LHR with MetS

	Model 1		Model 2		Model 3	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
LHR quartile						
Q1 (0.004, 0.028)	Reference		Reference		Reference	
Q2 (0.028, 0.038)	1.81 (1.51, 2.17)	< 0.001	2.83 (2.31, 3.46)	< 0.001	2.08 (1.66, 2.60)	< 0.001
Q3 (0.038, 0.051)	3.22 (2.73, 3.81)	< 0.001	6.65 (5.51, 8.01)	< 0.001	4.02 (3.26, 4.96)	< 0.001
Q4 (≥ 0.051)	6.38 (5.24, 7.76)	< 0.001	18.37 (14.78, 22.84)	< 0.001	11.38 (8.85, 14.63)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Note

Model 1: No covariables were adjusted

Model 2: Age, sex, race, educational level, poverty income ratio, and marital status were adjusted

Model 3: Age, sex, race, educational level, poverty income ratio, marital status, daily energy intake, smoking status, alcohol status, physical activity, hypertension, diabetes mellitus, cardiovascular disease, body mass index, alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid, blood urea nitrogen, low-density lipoprotein cholesterol, monocyte count, and neutrophils count were adjusted

LHR: lymphocyte to high-density lipoprotein cholesterol ratio; MetS: metabolic syndrome; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4

for IR (OR = 3.72, 95% CI: 3.01–4.59, $p < 0.001$), and the prevalence of MetS increased 10.38-fold (OR = 11.38, 95% CI: 8.85–14.63, $p < 0.001$) among individuals in the higher quartiles.

Subgroup analyses

The association between LHR and IR was not significantly modified by any of the subgroup factors in stratification analyses (p for interaction > 0.05) (Additional File 1). Similarly, the association between the LHR and MetS revealed no significant interaction effects across most subgroups (p for interaction > 0.05) (Additional File 2). However, a unique finding emerged from sex stratification: females exhibited a markedly stronger association between LHR and MetS (OR = 13.48, 95% CI: 9.54–19.06) compared to males (OR = 9.76, 95% CI: 6.97–13.68), with statistical confirmation of this sex difference (p for interaction = 0.020).

Non-linear relationships

RCS analysis revealed nonlinear relationships between LHR and both IR and MetS (p for nonlinearity < 0.001) (Figs. 2 and 3). Threshold effect analysis using a two-piecewise logistic regression model identified an inflection point at 0.055 for both relationships (Tables 4 and 5). When LHR remained under the threshold of 0.055, every 0.01−unit elevation corresponded to a 46% higher prevalence of IR (OR = 1.46, 95% CI: 1.39–1.53, $p < 0.001$). Above the threshold (LHR ≥ 0.055), the association remained significant but attenuated, with each 0.01−unit increase in LHR corresponding to a 14% increase in IR prevalence (OR = 1.14, 95% CI: 1.04–1.24, $p = 0.004$). Similarly, the data indicated that for LHR values under 0.055, each unit increase corresponded to an 82% higher MetS prevalence (OR = 1.82, 95% CI: 1.72–1.92, $p < 0.001$). Beyond this point, the prevalence elevation moderated to 34% (OR = 1.34, 95% CI: 1.24–1.46, $p < 0.001$).

Sensitivity analyses

To validate our findings, we performed sensitivity analyses using three approaches: excluding individuals with extreme LHR values, excluding subjects who received lipid-lowering therapy, and excluding participants with missing covariable data. The results of the sensitivity analyses confirmed that the LHR was significantly and positively correlated with IR and MetS across all alternatively processed datasets (Tables 6 and 7, and 8).

ROC curve analysis

The predicted AUC for IR was 0.702 (95% CI: 0.691–0.714) in the female population and 0.668 (95% CI: 0.655–0.680) in the male population (Fig. 4). The optimal threshold for LHR in predicting IR was lower in females (0.037) compared to males (0.041) (Table 9). In predicting MetS, LHR also exhibited comparable performance (AUC: 0.709, 95% CI: 0.697–0.721 for females; AUC: 0.673, 95% CI: 0.660–0.686 for males) (Fig. 5). Analogously, the optimal LHR threshold for predicting MetS in females (0.038) was lower than that in males (0.043) (Table 10).

Discussion

Our study evaluated the potential connections between the LHR and two metabolic disorders, IR and MetS. A total of 14,779 adults aged ≥ 20 years from the NHANES database (2007–2018) were included in the analysis. Research outcomes indicated that a 0.01-unit increment in LHR was linked to heightened prevalence: 20% for IR and 59% for MetS. Further analyses revealed nonlinear relationships, with more pronounced prevalence observed when the LHR was below 0.055. Subgroup analyses indicated that these associations were generally consistent across different populations, except for a more pronounced relationship between the LHR and MetS in females. To enhance the clinical utility and practical

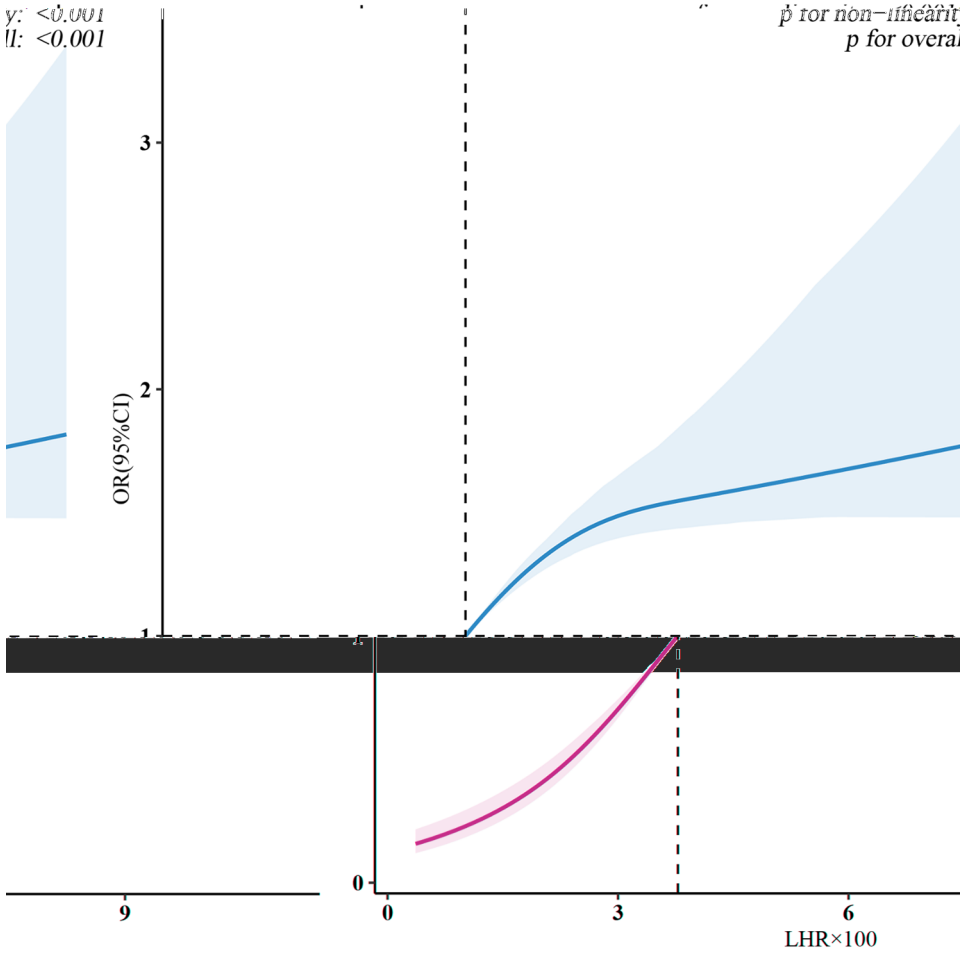

Fig. 2 Restricted cubic spline analysis of the relationship between LHR and IR. *Note*: LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance

application of LHR, we investigated sex-specific LHR thresholds. ROC curve analysis revealed that the optimal cut-off values for predicting IR and MetS were consistently lower in females (0.037 and 0.038, respectively) compared to males (0.041 and 0.043, respectively).

A research team led by Chen examined 852 adults from coastal southern China through a cross-sectional analysis, confirming a significant positive association between LHR and MetS [29]. Yu et al., following 4,980 rural residents in northeastern China for over four years, identified the LHR as an effective predictor of MetS [15]. In a cross-sectional study comprising 581 Brazilian adults, Flávia Galvão Cândido et al. demonstrated that an elevated LHR was not only independently associated with an increased prevalence of MetS but was also significantly correlated with the number of MetS components [30]. These findings strongly align with our results, further validating the LHR as a novel indicator of MetS. Tong Chen et al. revealed that after adjusting for confounding factors, LHR remained a significant predictor of MetS in females but lost its predictive value in males [18]. Similarly, Ahari et al. investigated over 8,000 Iranian participants and found stronger associations between the LHR and MetS in females than in males [14]. These findings are consistent with those of our subgroup analysis, suggesting sex-specific differences in the relationship between the LHR and MetS. This observed sex difference may be attributed to female-specific adipose tissue distribution patterns and higher body fat percentages, which are associated with the production of pro-inflammatory cytokines [31]. These inflammatory mediators may interfere with estrogen-mediated metabolic regulation, thereby amplifying the association between LHR and MetS. However, systematic investigations of the relationship between LHR and insulin resistance are still insufficient. Examining a large American cohort, Quispe et al. documented characteristic lipid patterns in subjects: increased triglyceride (TG) accompanied by decreased HDL-C levels [32]. Yeh et al., in a study of 398 participants, identified the TG/HDL-C ratio as an effective predictor of IR [33]. Additionally, a cross-sectional study by Guo et al. demonstrated a significant relationship between an elevated

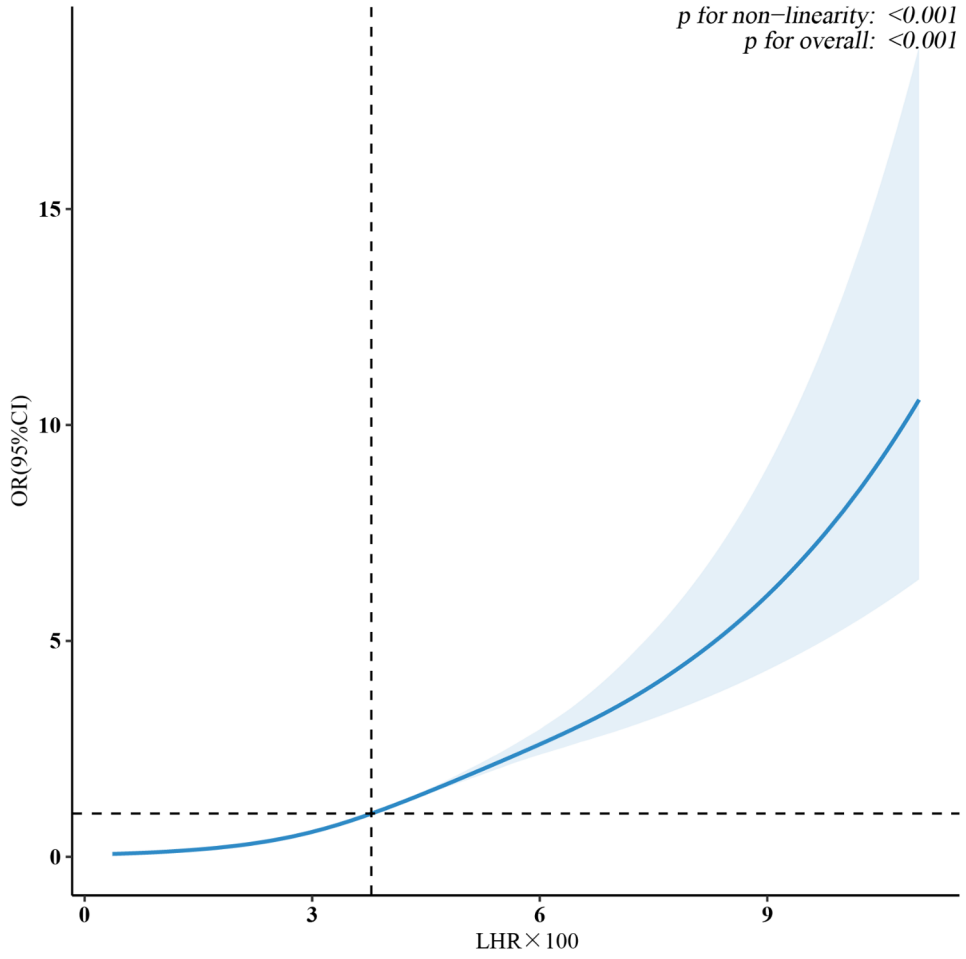

Fig. 3 Restricted cubic spline analysis of the relationship between LHR and MetS. Note: LHR: lymphocyte to high-density lipoprotein cholesterol ratio; MetS: metabolic syndrome

Table 4 Threshold effect analysis of LHR on IR using a two-part logistic regression model

UHR×100	OR	95% CI	*p*-value
< 5.51	1.46	1.39–1.53	< 0.001
≥ 5.51	1.14	1.04–1.24	0.004
likelihood ratio test			< 0.001

Note LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; OR: odds ratio; 95% CI: 95% confidence interval

Table 5 Threshold effect analysis of LHR on MetS using a two-part logistic regression model

UHR×100	OR	95% CI	*p*-value
< 5.51	1.82	1.72–1.92	< 0.001
≥ 5.51	1.34	1.24–1.46	< 0.001
likelihood ratio test			< 0.001

Note LHR: lymphocyte to high-density lipoprotein cholesterol ratio; MetS: metabolic syndrome; OR: odds ratio; 95% CI: 95% confidence interval

systemic immune-inflammation (SII) index, which incorporates the lymphocyte count and IR [34]. These studies indirectly support our findings regarding the association between LHR and IR.

The pathophysiological mechanisms linking elevated LHR levels to IR and MetS are complex and multifaceted. Increased lymphocyte count, reflected by a higher LHR, triggers several inflammatory cascades. Nishimura et al. showed that cytotoxic T lymphocytes (CD8 + T cells) play a stimulatory role in recruiting and activating macrophages within adipose tissue [35]. Upon activation, adipose tissue macrophages secrete pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1-beta (IL-1β) [36]. The induction of IR by these cytokines occurs mainly via two inflammatory signaling routes: the JNK1 and IKKβ pathways [37, 38]. In a mouse model of diet-induced obesity, Winer et al. revealed that B cells promote glucose intolerance and insulin resistance through multiple mechanisms, including the activation of CD8 + and CD4 + T cells, and production of pathogenic immunoglobulin G (IgG) [39]. Zhang et al. demonstrated that HDL-C binds to its receptor, the scavenger receptor type I (SR-BI), activates the PI3K/Akt pathway, and promotes AMP-activated protein kinase (AMPK)

Table 6 Multivariable logistic regression models of LHR with IR and MetS. (we excluded participants with outlier LHR values.)

	Model 1		Model 2		Model 3	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
IR						
LHR quartile						
Q1 (0.004, 0.027)	Reference		Reference		Reference	
Q2 (0.027, 0.037)	2.03 (1.75, 2.35)	< 0.001	2.30 (1.97, 2.67)	< 0.001	1.61 (1.36, 1.90)	< 0.001
Q3 (0.037, 0.050)	3.77 (3.25, 4.38)	< 0.001	4.58 (3.94, 5.33)	< 0.001	2.48 (2.10, 2.92)	< 0.001
Q4 (≥ 0.050)	6.27 (5.31, 7.41)	< 0.001	8.03 (6.77, 9.53)	< 0.001	3.62 (2.93, 4.47)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
MetS						
LHR quartile						
Q1 (0.004, 0.027)	Reference		Reference		Reference	
Q2 (0.027, 0.037)	1.75 (1.45, 2.10)	< 0.001	2.72 (2.22, 3.34)	< 0.001	2.02 (1.61, 2.55)	< 0.001
Q3 (0.037, 0.050)	3.08 (2.61, 3.65)	< 0.001	6.31 (5.24, 7.59)	< 0.001	3.88 (3.15, 4.78)	< 0.001
Q4 (≥ 0.050)	5.72 (4.70, 6.95)	< 0.001	15.98 (12.84, 19.89)	< 0.001	10.09 (7.85, 12.96)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Note

Model 1: No covariables were adjusted

Model 2: Age, sex, race, educational level, poverty income ratio, and marital status were adjusted

Model 3: Age, sex, race, educational level, poverty income ratio, marital status, daily energy intake, smoking status, alcohol status, physical activity, hypertension, diabetes mellitus, cardiovascular disease, body mass index, alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid, blood urea nitrogen, low-density lipoprotein cholesterol, monocyte count, and neutrophils count were adjusted

LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; MetS: metabolic syndrome; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4

Table 7 Multivariable logistic regression models of LHR with IR and MetS. (we excluded participants who were taking lipid-lowering medications.)

	Model 1		Model 2		Model 3	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
IR						
LHR quartile						
Q1 (0.004, 0.028)	Reference		Reference		Reference	
Q2 (0.028, 0.038)	2.29 (1.92, 2.74)	< 0.001	2.54 (2.11, 3.06)	< 0.001	1.83 (1.51, 2.22)	< 0.001
Q3 (0.038, 0.052)	4.00 (3.43, 4.66)	< 0.001	4.62 (3.93, 5.42)	< 0.001	2.50 (2.08, 3.01)	< 0.001
Q4 (≥ 0.052)	7.33 (6.16, 8.73)	< 0.001	8.72 (7.20, 10.58)	< 0.001	3.94 (3.13, 4.95)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
MetS						
LHR quartile						
Q1 (0.004, 0.028)	Reference		Reference		Reference	
Q2 (0.028, 0.038)	1.91 (1.51, 2.42)	< 0.001	2.98 (2.29, 3.88)	< 0.001	2.32 (1.72, 3.12)	< 0.001
Q3 (0.038, 0.052)	3.85 (3.16, 4.69)	< 0.001	7.50 (6.02, 9.34)	< 0.001	4.86 (3.70, 6.37)	< 0.001
Q4 (≥ 0.052)	8.36 (6.79, 10.30)	< 0.001	21.33 (16.70, 27.26)	< 0.001	13.94 (10.31, 18.86)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Note

Model 1: No covariables were adjusted

Model 2: Age, sex, race, educational level, poverty income ratio, and marital status were adjusted

Model 3: Age, sex, race, educational level, poverty income ratio, marital status, daily energy intake, smoking status, alcohol status, physical activity, hypertension, diabetes mellitus, cardiovascular disease, body mass index, alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid, blood urea nitrogen, low-density lipoprotein cholesterol, monocyte count, and neutrophils count were adjusted

LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; MetS: metabolic syndrome; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4

phosphorylation. This signaling cascade subsequently induces glucose transporter 4 (GLUT4) translocation to the cell membrane and thereby enhancing insulin sensitivity [40, 41]. Studies by Rütti et al. revealed that HDL-C prevents glucose-mediated β-cell apoptosis in pancreatic islets from both humans and mice [42]. Multiple studies have shown that HDL-C protects β-cells by inhibiting the activation of nuclear factor κB (NF-κB). This mechanism

Table 8 Multivariable logistic regression models of LHR with IR and MetS. (we excluded participants with missing covariable data)

	Model 1		Model 2		Model 3	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
IR						
LHR quartile						
Q1 (0.004, 0.027)	Reference		Reference		Reference	
Q2 (0.027, 0.038)	1.89 (1.60, 2.22)	< 0.001	2.18 (1.83, 2.58)	< 0.001	1.50 (1.23, 1.83)	< 0.001
Q3 (0.038, 0.050)	3.63 (3.10, 4.26)	< 0.001	4.54 (3.84, 5.37)	< 0.001	2.36 (1.94, 2.87)	< 0.001
Q4 (≥ 0.050)	5.63 (4.75, 6.67)	< 0.001	7.44 (6.15, 9.00)	< 0.001	3.33 (2.65, 4.19)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
MetS						
LHR quartile						
Q1 (0.004, 0.027)	Reference		Reference		Reference	
Q2 (0.027, 0.038)	1.67 (1.33, 2.11)	< 0.001	2.69 (2.08, 3.48)	< 0.001	1.99 (1.46, 2.72)	< 0.001
Q3 (0.038, 0.050)	3.00 (2.44, 3.70)	< 0.001	6.62 (5.22, 8.40)	< 0.001	3.84 (2.94, 5.02)	< 0.001
Q4 (≥ 0.050)	5.50 (4.34, 6.98)	< 0.001	17.26 (13.08, 22.79)	< 0.001	11.18 (8.15, 15.33)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Note

Model 1: No covariables were adjusted

Model 2: Age, sex, race, educational level, poverty income ratio, and marital status were adjusted

Model 3: Age, sex, race, educational level, poverty income ratio, marital status, daily energy intake, smoking status, alcohol status, physical activity, hypertension, diabetes mellitus, cardiovascular disease, body mass index, alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid, blood urea nitrogen, low-density lipoprotein cholesterol, monocyte count, and neutrophils count were adjusted

LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; MetS: metabolic syndrome; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4

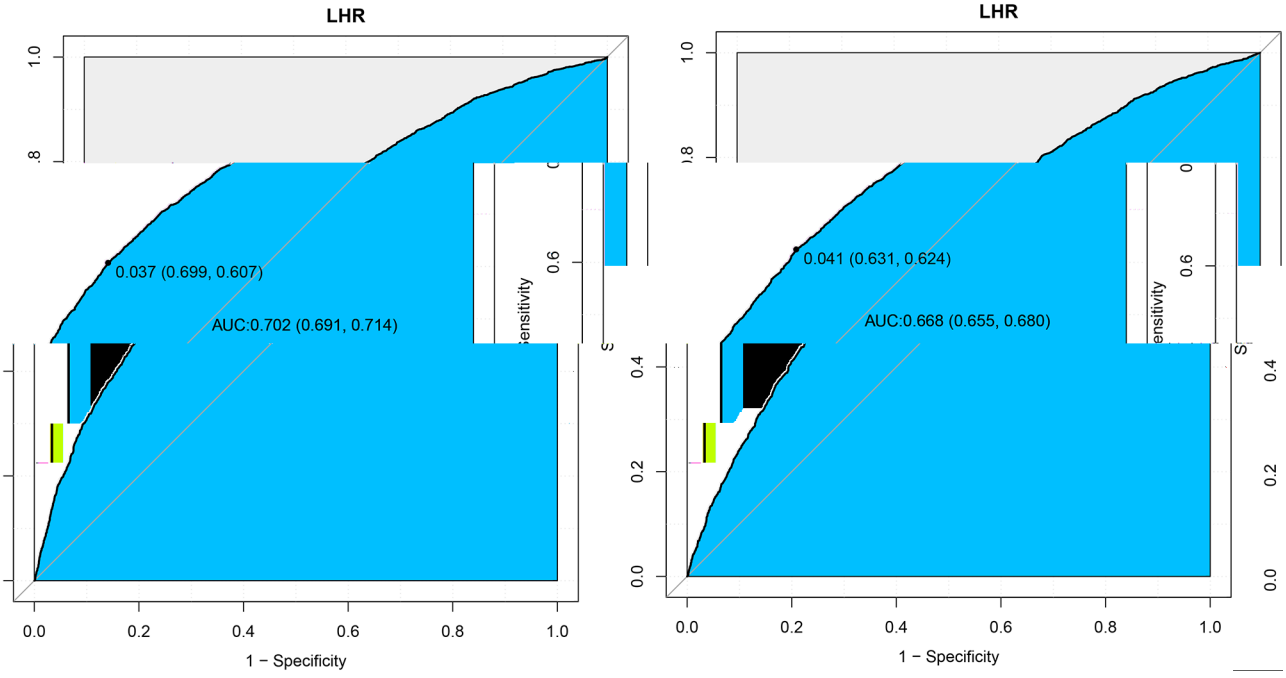

Fig. 4 ROC curve analysis of LHR for predicting IR in the female (**A**) and male (**B**) population. *Note*: ROC: receiver operating characteristic; LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance

reduces the expression of pro-inflammatory cytokines that lead to β-cell apoptosis [43–45]. IR is a pivotal factor in the pathogenesis of MetS [46]. IR directly affects glucose metabolism, leading to impaired fasting glucose or diabetes mellitu [47]. Furthermore, impaired insulin-mediated suppression of lipolysis results in elevated circulating free fatty acids (FFAs) [48]. High FFA concentrations promote LDL-C synthesis and reduce HDL-C levels [48]. In addition, the progression of hypertension is accelerated by IR through various mechanisms,

Table 9 ROC curve analysis of LHR for predicting IR

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Female				
LHR	0.037	0.607	0.699	0.702 (0.691–0.714)
Male				
LHR	0.041	0.624	0.631	0.668 (0.655–0.680)

Note ROC: receiver operating characteristic; LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; AUC: area under the curve; 95% CI: 95% confidence interval

Table 10 ROC curve analysis of LHR for predicting MetS

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Female				
LHR	0.038	0.634	0.687	0.709 (0.697–0.721)
Male				
LHR	0.043	0.614	0.642	0.673 (0.660–0.686)

Note ROC: receiver operating characteristic; LHR: lymphocyte to high-density lipoprotein cholesterol ratio; MetS: metabolic syndrome; AUC: area under the curve; 95% CI: 95% confidence interval

including increased sodium reabsorption and sympathetic nervous system activation [49].

In addition to IR, elevated LHR levels contribute to the progression of MetS via multiple alternative pathways. Winer et al. used murine models to demonstrate that CD8 + T cells infiltrate the adipose tissue, promoting local inflammatory responses and disrupting lipid metabolism [39]. Harrison et al. demonstrated that activated T lymphocytes generate reactive oxygen species (ROS) [50]. ROS trigger vasoconstriction, leading to sodium and water retention. Excess reactive oxygen species also activate the NF-κB pathway, enhancing angiotensin II (Ang II) expression [51]. Accumulating evidence demonstrates that reduced HDL-C levels compromise the cellular cholesterol efflux capacity and impair the functionality of the reverse cholesterol transport system, resulting in disturbances in lipid metabolic homeostasis [52, 53]. Furthermore, reduced HDL-C levels compromise the reverse cholesterol transport mechanism, facilitating cholesterol deposition in the vascular walls, thereby promoting arterial stiffness and consequent elevation in blood pressure [54]. Moreover, reduced HDL-C levels compromise nitric oxide (NO) bioavailability by attenuating HDL-C-dependent endothelial NO synthase (eNOS) activation [55]. This impairment of the NO signaling pathway subsequently leads to diminished vasodilatory capacity and increased vascular resistance [56]. Research demonstrates that declining HDL-C concentrations impair both their protective properties and the activities of essential enzymes such as paraoxonase-1 (PON1) and platelet-activating factor-acetyl hydrolase (PAF-AH) [57]. This dysfunction facilitates oxidized low-density lipoprotein and foam cell formations, ultimately contributing to atherogenesis [52].

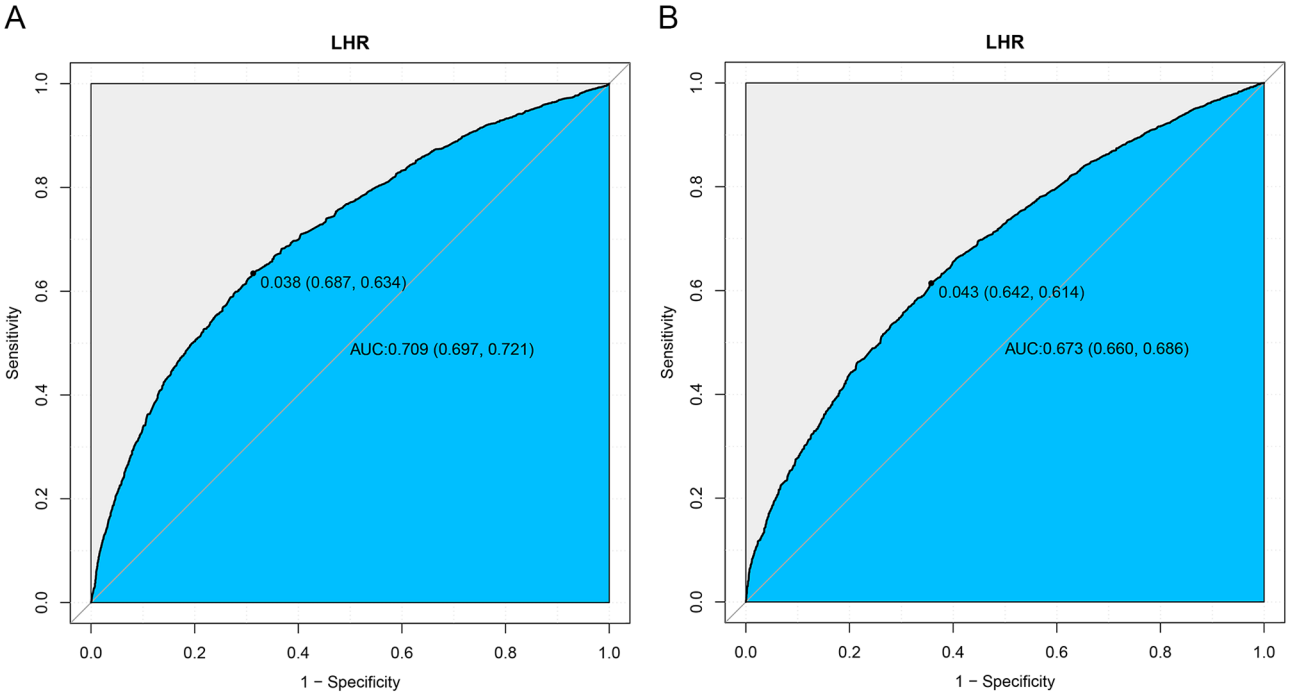

Fig. 5 ROC curve analysis of LHR for predicting MetS in the female (**A**) and male (**B**) population. *Note*: ROC: receiver operating characteristic; LHR: lymphocyte to high-density lipoprotein cholesterol ratio; MetS: metabolic syndrome

Our study findings revealed that in populations with low LHR, there was a stronger association between LHR and the risk of IR and MetS. Our previous baseline analysis indicated that the inflection point of 0.055 lay within the fourth quartile of LHR, suggesting that at this level, the body is undergoing a heightened inflammatory response. This might be attributed to a functional shift of HDL-C from anti-inflammatory to pro-inflammatory when the body was experiencing a heightened inflammatory response [58]. Under these conditions, higher HDL-C levels might have led to a stronger inflammatory response, thereby increasing the risk of IR and MetS, while paradoxically resulting in lower LHR values. The precise mechanisms underlying the transition of HDL-C to a pro-inflammatory state during heightened inflammation remain not fully elucidated. However, previous studies have suggested that acute inflammatory responses are associated with increased levels of serum amyloid A (SAA), which can displace the major apolipoprotein of HDL-C, apolipoprotein A-I (apoA-I) [58, 59]. This displacement may alter HDL-C functionality, causing it to lose its anti-inflammatory properties and instead promote inflammation [60]. In addition, during acute infections, plasma levels of certain proteins involved in HDL-C-mediated reverse cholesterol transport, such as lecithin–cholesterol acyltransferase (LCAT), are reportedly reduced [60, 61]. This disruption in cholesterol efflux may lead to the accumulation of intracellular inflammatory mediators, thereby further exacerbating the inflammatory response [62]. Although we have proposed potential explanations for the observed phenomenon, further research is required to elucidate the precise biological mechanisms.

Study strengths and limitations

This study had several strengths. Firstly, this study provides the first systematic analysis of the association between LHR and both IR and MetS in Americans. Secondly, the study utilized the NHANES database, a large-scale national survey including 14,779 adult participants, ensuring strong representativeness. Thirdly, by incorporating extensive confounding variables across demographics, lifestyle factors, comorbidities, and laboratory indicators, we significantly improved the validity of our research outcomes. Finally, we pioneered the application of RCS and threshold effect analyses to explore the nonlinear associations between LHR and both IR and MetS.

The present study has some notable limitations. First, in the multivariable logistic regression analysis, we adjusted for a wide range of potential confounders, including demographic characteristics, lifestyle factors, comorbidities, and laboratory indicators. However, there may still be unidentified or unmeasured residual confounders that could introduce bias into the results. Second, this study utilized cross-sectional data, and even after multivariable adjustments, logistic regression analysis can only reflect associations between variables rather than causal relationships. Third, our conclusions mainly represent U.S. population patterns, warranting caution when applying them to populations in other regions. Future research should prioritize longitudinal cohort studies in diverse regional populations to provide a more comprehensive understanding of its potential as a biomarker for chronic disease prediction. Fourth, studies have demonstrated that various foods and medications can affect lymphocyte counts and HDL-C levels, including foods such as fruits, vegetables, and fish oil, as well as medications such as immunosuppressants, chemotherapeutic agents, and lipid-lowering drugs [63–68]. Considering the aforementioned influencing factors, a single blood measurement of LHR may not fully reflect the body's long-term inflammatory and metabolic status. Although we excluded individuals taking lipid-lowering medications in our multiple imputation analysis, current methodologies are unable to account for all other potential medications that may affect LHR. In the future, we recommend conducting cohort studies and employing multiple time-point blood measurements to capture the dynamic changes in LHR, thereby offering a more comprehensive evaluation of its value as a metabolic health indicator. Additionally, future research should consider integrating other potential influencing factors, such as dietary records and medication use, to better account for the impact of short-term fluctuations on study outcomes. With such a design, we believe it will be possible to more accurately elucidate the long-term associations between LHR and IR or MetS. Moreover, the observed nonlinear relationships and sex-specific differences suggested that LHR may be regulated by complex biological mechanisms. Future research should focus on exploring the potential underlying biological mechanisms to further elucidate its role in metabolic disorders.

Conclusion

We found that higher levels of LHR, a composite indicator reflecting both inflammatory and lipid metabolic status, were positively associated with IR and MetS in the adult U.S. population. Our findings indicate that LHR could serve as a convenient and reliable biomarker for screening metabolic disorders. Nevertheless, further prospective investigations are warranted to establish the causality and elucidate the precise biological mechanisms involved.

Abbreviations

IR	Insulin Resistance
MetS	Metabolic Syndrome
LHR	Lymphocyte-to-High-Density Lipoprotein Cholesterol Ratio
NHANES	National Health And Nutrition Examination Survey

HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel III
HDL-C	High-Density Lipoprotein Cholesterol
PIR	Poverty Income Ratio
DM	Diabetes Mellitus
CVD	Cardiovascular Disease
BMI	Body Mass Index
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CR	Creatinine
UA	Uric Acid
BUN	Blood Urea Nitrogen
TC	Total Cholesterol
LDL-C	Low-Density Lipoprotein Cholesterol
MET	Metabolic Equivalent
FPG	Fasting Plasma Glucose
OR	Odds Ratios
95% CI	95% Confidence Intervals
VIF	Variance Inflation Factor
RCS	Restricted Cubic Spline
SD	Standard Deviation
IQR	Interquartile Range
ROC	Receiver Operating Characteristic
AUC	Area Under the Curve
TG	Increased Triglycerides
SII	Systemic Immune-Inflammation
TNF-α	Tumor Necrosis Factor-alpha
IL-6	Interleukin-6
IL-1β	Interleukin-1beta
IgG	Immunoglobulin G
SR-BI	Scavenger Receptor type I
AMPK	AMP-Activated Protein Kinase
GLUT4	Glucose Transporter 4
NF-κB	Nuclear Factor κB
FFAs	Free Fatty Acids
ROS	Reactive Oxygen Species
Ang II	Angiotensin II
NO	Nitric Oxide
eNOS	endothelial NO Synthase
PON1	Paraoxonase-1
PAF-AH	Platelet-Activating Factor-Acetyl Hydrolase
SAA	Serum Amyloid A
apoA-I	apolipoprotein A-I
LCAT	Lecithin–Cholesterol Acyltransferase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02411-7.

Supplementary Material 1: Additional File 1.xlsx. Subgroup analysis for the association between LHR and MetS. Note: LHR: lymphocyte to high-density lipoprotein cholesterol ratio; IR: insulin resistance; BMI: body mass index; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4.

Supplementary Material 2: Additional File 2.xlsx. Subgroup analysis for the association between LHR and MetS. Note LHR: lymphocyte to high-density lipoprotein cholesterol ratio; MetS: metabolic syndrome; BMI: body mass index; OR: odds ratio; 95% CI: 95% confidence interval; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4.

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Author contributions
JWG and KM made significant contributions to the conception, design, data acquisition, analysis and interpretation of the work, as well as drafted the work and made substantial modifications. XW made significant contributions to the drafting of the work. JJY made significant contributions to the drafting of the manuscript. HY made significant contributions to the drafting of the work. SQ made significant contributions to the drafting of the work. HBC made significant contributions to the drafting of the work. LB made significant contributions to drafting the work and made substantial modifications to it. All the authors read and approved the final manuscript. JWG and KM have contributed equally to this work.

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Data availability
The NHANES dataset incorporated into this investigation is available via the official website. Comprehensive details concerning the dataset and access protocols are provided on the NHANES official website: https://www.cdc.gov/nchs/nhanes.

Declarations

Ethics approval and consent to participate
The NHANES protocol was reviewed and approved by the Ethics Review Board of the National Center for Health Statistics, and all participants provided informed consent. As a secondary analysis of publicly available de-identified data, the present study did not require additional ethical review.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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