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The association between the ratio of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol and serum uric acid levels and risk of hyperuricemia in different sex groups

A cross-sectional study

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Abstract

Dyslipidemia and hyperuricemia are recognized as significant risk factors for cardiovascular and metabolic diseases. However, the relationship between the novel lipid metabolism marker, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), and serum uric acid levels or hyperuricemia remains unclear. This study aimed to analyze these associations using data from a nationally representative population, with an emphasis on sex-specific differences and nonlinear relationships. Data from the National Health and Nutrition Examination Survey conducted from 2005 to 2018 were examined, involving 9439 adults, following the application of exclusion criteria. Weighted linear and logistic regression models categorized by sex were used to investigate the relationships between NHHR, uric acid concentrations, and hyperuricemia. Nonlinear relationships were assessed using restricted cubic splines, and threshold effects were explored using 2-part regression models. Subgroup analyses were conducted to evaluate potential modifiers of the relationship between NHHR and hyperuricemia. NHHR was significantly associated with serum uric acid levels and hyperuricemia in the general population with notable sex-specific differences. In females, NHHR was found to have a very significant positive correlation with hyperuricemia (OR 1.44, 95% confidence interval [CI]: 1.31–1.58, $P < .001$); however, this correlation was not as strong in males (OR = 1.07, 95% CI: 0.95–1.20, $P = .20$). Repeated analyses with nonlinear models showed that NHHR had a threshold relationship with hyperuricemia concentration which reached its highest level of 3.91 for the general population, with male and female inflection points at 4.637 and 4.452, respectively. Subgroup analyses demonstrated significant interactions with body mass index (BMI), smoking status, and stroke, further highlighting the heterogeneity of the NHHR-hyperuricemia relationship. NHHR is independently associated with serum uric acid levels and hyperuricemia, with significant sex-specific and nonlinear patterns. These findings suggest that the NHHR may serve as a valuable biomarker for assessing hyperuricemia risk, particularly in females. Further research is warranted to explore the underlying mechanisms and the clinical implications of these associations.

Abbreviations: BMI = body mass index, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, non-HDL-C = non-high-density lipoprotein cholesterol, OR = odds ratio, TC = total cholesterol, TG = triglyceride.

Keywords: cross-sectional study, female, hyperuricemia, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), ric acid

1. Introduction

Hyperuricemia, characterized by abnormally elevated serum uric acid levels, has been widely recognized as closely associated with various metabolic and cardiovascular diseases.[1–3] By 2016, the global prevalence of hyperuricemia had risen to 21%,[4] with rates in the United States ranging from 14.6 to 20%.[5] In recent years, numerous studies have focused on the role of lipid metabolism abnormalities in hyperuricemia

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The datasets generated during and/or analyzed during the current study are publicly available.

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and gout, exploring the predictive capability of different lipid indicators for hyperuricemia risk.[6,7] However, these studies typically investigated the relationship between single lipid indicators, such as total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and uric acid. The ratio of non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) (NHHR) has emerged as a novel metabolic marker that provides a more comprehensive assessment of lipid metabolic status by including HDL-C, LDL-C, very-low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein, and apolipoprotein A.[8] NHHR has been preliminarily proven to be an important independent risk factor for cardiovascular diseases,[9] chronic kidney disease,[10] kidney stones,[11] and nonalcoholic fatty liver disease.[12] NHHR provides a more accurate prediction of metabolic syndrome and insulin resistance than the apolipoprotein B/apolipoprotein A1 ratio.[13] The association between NHHR and serum uric acid levels has been well of studied in hyperuricemia, and the analysis of nonlinear relationships and sex differences is also inadequate. Therefore, the present study aimed to examine the relationship between NHHR and serum uric acid levels as well as the risk of hyperuricemia by analyzing data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2007 and 2018. As uric acid levels are highly correlated with various chronic diseases, a detailed analysis of the relationship between NHHR, serum uric acid levels and hyperuricemia risk will be of high relevance to the understanding of the etiology of hyperuricemia and the design of prevention strategies. It is against this background that, through this research, we want not only to increase the knowledge on hyperuricemia but also to contribute with new information for the clinical practice and prevention of hyperuricemia related diseases.

2. Materials and methods

The dataset utilized for this study was obtained from a publicly accessible NHANES database in the United States. Prior to their involvement, written informed consent was obtained from all participants. The NHANES maintains a specialized management system tasked with data collection and regular updates. The survey data and details pertaining to the project were periodically released on their website for public availability. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Ethics approval number: 2024-E425-01).

2.1. Participants

We utilized data extracted from the NHANES database, including HDL-C, non-HDL-C, total cholesterol (TC), serum uric acid, serum creatinine, glycated hemoglobin, urinary protein, urinary albumin, urinary creatinine, and relevant demographic information. Informed consent was obtained from all the participants or their guardians. Our analysis focused on participants from NHANES surveys conducted between 2005 and 2018. The first data set included 70,190 participants of whom 28,047 were children under the age of 18 years were removed. Of the total 42,143 participants, 27,196 were excluded because they had missing data on uric acid, TC, or HDL cholesterol, and 5508 participants were excluded due to missing important confounding variables. Thus, the final analysis was performed on 9439 participants (Fig. 1).

2.2. Covariates

The methodological approach involved a comprehensive assessment of participants' characteristics, with particular attention paid to sociodemographic attributes, including age, sex, race, and educational background. Medical history documentation encompassed several chronic conditions, notably hypertension, diabetes, coronary artery disease, heart failure, and previous stroke. Anthropometric measurements were obtained using standard protocols, with a focus on body mass index calculations and waist circumference measurements. Laboratory evaluations included key biochemical parameters, specifically serum creatinine, glycated hemoglobin, and various urinary markers including creatinine levels and albumin-to-creatinine ratio. In terms of behavioral factors, we assessed participants' lifestyle patterns using specific criteria established for categorization. Notably, individuals reporting the consumption of 12 or more alcoholic beverages within the previous year were classified as having regular drinking patterns. The smoking assessment protocol defines smokers as those with a lifetime history of consuming more than 100 cigarettes. Socioeconomic status evaluation utilized the poverty-to-income ratio framework, where values below unity indicate relative poverty conditions. Additionally, sedentary behavior patterns were documented to provide a comprehensive lifestyle profile of the study population.

2.3. Statistical analysis

Statistical analyses were conducted using the R software (version 4.4.0). A P value of .05 or less was set at $P < .05$. A weight adjustment method was used to handle the variability within the dataset. Participant demographics were analyzed using chi-square tests and t tests stratified by uric acid level and hyperuricemia status. Weighted linear and logistic regression models were used to examined the relationship between NHHR and uric acid levels and hyperuricemia status. The NHHR was divided into quartiles for categorical analysis. Trend tests were applied to evaluate linear trends between NHHR and uric acid levels as well as hyperuricemia status. Model 1 was univariable; Model 2 included adjustments for age, sex, and race. Model 3 was fully adjusted for variables including age, sex, race, family poverty income ratio, body mass index (BMI), waist circumference, educational attainment, alcohol use, smoking habits, marital status, diabetes, high blood pressure, serum creatinine, coronary heart disease, heart failure, stroke history, sedentary lifestyle, glycated hemoglobin levels, urinary albumin-to-creatinine ratio, urinary creatinine, and urinary albumin levels.

3. Results

3.1. Participants characteristics

Figure 1 shows the inclusion and exclusion flow for this study from the NHANES 2005 to 2018 dataset. Table 1 presents the characteristics of the study population stratified by NHHR quartiles. The median age was similar across quartiles ($P = .8$), although the age distribution differed significantly ($P < .001$). Sex distribution also varied across quartiles, with the percentage of males increasing from 34% in Q1 to 66% in Q4 ($P < .001$). The family poverty income ratio showed a decreasing trend from Q1 to Q4 ($P = .001$). Racial distribution differed significantly ($P < .001$) with Mexican American and other Hispanic participants increasing from Q1 to Q4, while non-Hispanic Black participants decreased. The BMI categories showed marked differences ($P < .001$); the proportion of obese individuals increased from 20% in Q1 to 52% in Q4, and waist circumference increased progressively across quartiles ($P < .001$). Educational attainment varied significantly ($P < .001$), with a higher proportion of individuals with education beyond high school in Q1 (67%) than in Q4 (58%). Significant differences were also observed in smoking status, marital status, diabetes prevalence, hypertension, serum creatinine level, HbA1c level, urinary biomarkers, lipid profiles, uric acid levels, and hyperuricemia prevalence. As shown in Figure 2, the median level

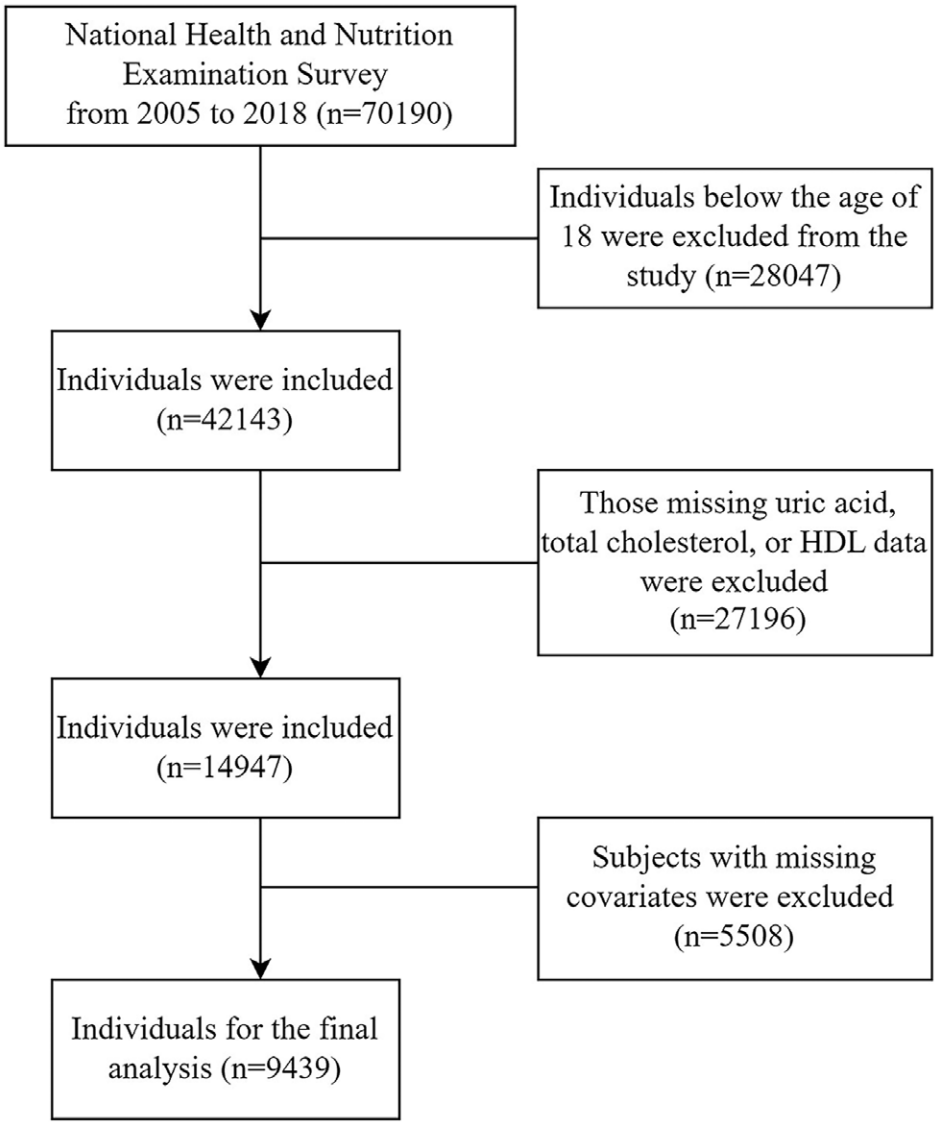

Figure 1. Flowchart illustrating the sample selection procedure from NHANES between 2005 and 2018. HDL = high-density lipoprotein.

of NHHR in individuals with hyperuricemia was significantly lower than that in individuals without hyperuricemia (2.41, IQR 1.77–3.27 vs 2.9, IQR 2.17–3.83, $P < .01$).

3.2. Weighted regression association of NHHR with uric acid and hyperuricemia among all participants and sex-specific groups

Weighted regression analysis revealed significant associations between NHHR and both uric acid levels and hyperuricemia in the overall study population and different sex groups (Table 2). When examining continuous NHHR, each unit increase was associated with a 0.13 mg/dL elevation in uric acid levels (95% confidence interval [CI]: 0.09–0.18; $P < .001$) across all participants. However, notable sex-specific differences were observed in the relationship between NHHR and hyperuricemia. Although continuous NHHR was not significantly associated with hyperuricemia in males (odds ratio [OR] = 1.07; 95% CI: 0.95–1.20; $P = .2$), females demonstrated a strong positive association (OR = 1.44; 95% CI: 1.31–1.58; $P < .001$).

In the quartile analysis, the association patterns further emphasized these sex-specific differences. Among males, the relationships between NHHR quartiles and hyperuricemia were relatively modest, with only the highest quartile reaching statistical significance (OR = 2.16; 95% CI: 1.21–3.83; $P = .012$). The second and third quartiles showed marginally increased odds but failed to achieve statistical significance (Q2: OR = 1.54, $P = .078$; Q3: OR = 1.67, $P = .052$). In contrast, females exhibited a more pronounced dose-response relationship, with the highest NHHR quartile associated with substantially increased odds of hyperuricemia (OR = 3.49; 95% CI: 2.45–4.96; $P < .001$) compared to the lowest quartile. The sex-dependent nature of these associations was further supported by a significant interaction term (P for interaction < .001), suggesting that the relationship between NHHR and hyperuricemia differs fundamentally between males and females. Despite the overall positive trend observed across quartiles in both sexes (P for trend < .001), the magnitude and significance of the associations were consistently more robust in the female subgroup.

3.3. Nonlinear association between NHHR with uric acid and hyperuricemia

A nonlinear association between NHHR and uric acid levels was observed in the general population (Fig. 3A). Similarly, a nonlinear trend was observed between NHHR and hyperuricemia in

Table 1

Characteristics of the population stratified by NHHR from NHANES 2005 to 2018.

Characteristics	Q1, N = 2387	Q2, N = 2415	Q3, N = 2276	Q4, N = 2361	*P*
Age (yr)	48 (30, 65)	48 (33, 62)	49 (34, 61)	47 (37, 59)	.8
Sex					<.001
Female	1550 (66%)	1382 (57%)	1103 (47%)	835 (34%)	
Male	837 (34%)	1033 (43%)	1173 (53%)	1526 (66%)	
Family poverty income ratio	3.13 (1.53, 5.00)	3.06 (1.47, 5.00)	2.86 (1.45, 5.00)	2.55 (1.27, 4.67)	.001
Race					<.001
Mexican American	234 (6.3%)	317 (8.4%)	341 (9.0%)	380 (11%)	
Other Hispanic	190 (5.3%)	234 (5.7%)	266 (6.3%)	314 (8.1%)	
Non-Hispanic White	891 (66%)	895 (65%)	884 (67%)	934 (66%)	
Non-Hispanic Black	653 (13%)	564 (12%)	434 (8.9%)	343 (7.1%)	
Other/multiracial	419 (9.0%)	405 (9.4%)	351 (8.5%)	390 (8.3%)	
BMI group					<.001
Normal or less (<25)	1151 (52%)	782 (32%)	470 (19%)	332 (13%)	
Obese (30 or greater)	553 (20%)	845 (35%)	1029 (46%)	1165 (52%)	
Overweight (25–30)	661 (28%)	755 (33%)	755 (35%)	839 (35%)	
Education level					<.001
<High school	178 (4.3%)	225 (5.1%)	220 (4.7%)	249 (6.3%)	
=High school	772 (28%)	786 (30%)	848 (35%)	888 (36%)	
>High school	1437 (67%)	1404 (65%)	1208 (60%)	1224 (58%)	
Alcohol group					.15
Drinker	1148 (78%)	1168 (76%)	1075 (76%)	1243 (79%)	
Nondrinker	448 (22%)	484 (24%)	481 (24%)	421 (21%)	
Smoke group					<.001
Current smoker	389 (15%)	414 (17%)	414 (17%)	604 (26%)	
Former smoker	533 (24%)	581 (25%)	579 (27%)	567 (25%)	
Never smoker	1465 (61%)	1420 (58%)	1283 (56%)	1190 (49%)	
Marriage group					<.001
Married/living with partner	1293 (61%)	1436 (62%)	1402 (65%)	1540 (68%)	
Widowed/divorced/separate	523 (17%)	538 (19%)	481 (19%)	480 (18%)	
Never married	571 (22%)	441 (18%)	393 (16%)	341 (15%)	
Diabetes					.026
Yes	323 (9.3%)	312 (9.6%)	338 (11%)	353 (13%)	
No	2004 (89%)	2043 (88%)	1873 (87%)	1939 (84%)	
Borderline	60 (2.0%)	60 (1.9%)	65 (2.8%)	69 (2.7%)	
Hypertension	857 (30%)	874 (32%)	882 (36%)	914 (38%)	<.001
Coronary heart disease	130 (4.8%)	90 (3.2%)	88 (2.9%)	83 (3.7%)	.052
Heart failure	96 (2.7%)	68 (2.2%)	82 (2.8%)	86 (3.2%)	.4
Stroke	114 (3.7%)	86 (3.1%)	83 (2.5%)	75 (2.7%)	.2
Sedentary time (h)	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	6.0 (4.0, 9.0)	6.0 (4.0, 8.8)	.093
Sedentary group					.4
<3 h	343 (12%)	325 (11%)	290 (10%)	327 (11%)	
>6 h	936 (42%)	989 (43%)	960 (46%)	954 (42%)	
3–6 h	1108 (46%)	1101 (46%)	1026 (43%)	1080 (46%)	
Serum creatinine (mg/dL)	71 (61, 83)	73 (62, 85)	75 (64, 88)	78 (66, 89)	<.001
HbA1c (%)	5.40 (5.10, 5.70)	5.40 (5.20, 5.80)	5.50 (5.20, 5.80)	5.60 (5.30, 5.90)	<.001
uACR (mg/g)	7 (5, 13)	7 (4, 12)	6 (4, 11)	7 (4, 13)	.001
Urinary creatinine (mg/dL)	102 (55, 159)	107 (62, 164)	115 (72, 169)	124 (74, 179)	<.001
Urinary albumin (μg/mL)	7 (4, 15)	8 (4, 15)	8 (4, 14)	9 (5, 19)	<.001
TC (mmol/L)	4.29 (3.75,4.94)	4.63 (4.06, 5.22)	4.92 (4.40, 5.53)	5.59 (4.94, 6.31)	<.001
TG (mmol/L)	0.69 (0.52, 0.93)	0.95 (0.71, 1.23)	1.23 (0.95, 1.64)	1.91 (1.40, 2.65)	<.001
LDL-C (mmol/L)	2.17 (1.76, 2.56)	2.72 (2.30, 3.13)	3.08 (2.61, 3.55)	3.60 (3.05, 4.24)	<.001
HDL-C (mmol/L)	1.78 (1.53, 2.04)	1.45 (1.27, 1.66)	1.24 (1.11, 1.40)	1.03 (0.91, 1.19)	<.001
Non-HDL-C	2.49 (2.12, 2.92)	3.18 (2.77, 3.57)	3.67 (3.25, 4.11)	4.50 (3.96, 5.12)	<.001
NHHR	1.48 (1.21, 1.67)	2.17 (2.01, 2.35)	2.94 (2.74, 3.13)	4.20 (3.73, 4.91)	<.001
Uric acid (mg/dL)	4.80 (4.00, 5.70)	5.10 (4.30, 6.00)	5.60 (4.70, 6.50)	6.00 (5.10, 6.90)	<.001
Hyperuricemia	345 (13%)	440 (17%)	578 (24%)	723 (31%)	<.001

BMI = body mass index, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, LDL-C = low-density lipoprotein-cholesterol, NHANES = National Health and Nutrition Examination Survey, NHHR = non-HDL-C/HDL-C, TC = total cholesterol, TG = triglyceride, uACR = urine albumin/urine creatinine, OR = odds ratio.

the general population (Fig. 3B). In males, the nonlinear association between NHHR and uric acid was consistent with findings in the general population (Fig. 3C). The relationship between NHHR and hyperuricemia in males also displayed a nonlinear pattern (Fig. 3D). In females, the association between NHHR and uric acid followed a nonlinear pattern (Fig. 3E). The relationship between NHHR and hyperuricemia in females was nonlinear (Fig. 3F). The threshold effect analysis of NHHR on uric acid and hyperuricemia was conducted using a 2-part regression model for all participants and stratified by sex (Table 3). For uric acid, the inflection points of NHHR were identified as 4.33 for all participants, 6.234 for males, and 5.226 for females. Below the inflection point (<*K*), NHHR was positively associated with uric acid levels in all participants (β = 0.28, 95% CI: 0.24–0.33, *P* < .001) and in females (β = 0.204, 95% CI: 0.159–0.249, *P* < .001), but no significant association was observed in males (β = 0.201, 95% CI: −0.193, 0.242, *P* = .303). Above the inflection point (>*K*), NHHR was negatively associated with

uric acid levels in all participants (β = −0.10, 95% CI: −0.17, −0.03, P = .004) and in males (β = −0.101, 95% CI: −0.176, 0.009, P = .057), though the association in males did not reach statistical significance. In females, no significant association was observed above the inflection point (β = 0.015, 95% CI: −0.578, 0.609, P = .959). The log-likelihood ratio test indicated a significant threshold effect in all participants (P < .001) and females (P = .033), but not in males (P = .104). For hyperuricemia, the inflection points of NHHR were 3.91 for all participants, 4.637 for males, and 4.452 for females. Below the inflection point (<K), NHHR was strongly associated with an increased risk of hyperuricemia in all participants (OR = 1.711, 95% CI: 1.710–1.712, P < .001), males (OR = 1.287, 95% CI: 1.141–1.452, P < .001), and females (OR = 1.625, 95% CI: 1.435–1.840, P < .001). Above the inflection point (>K), NHHR remained significantly associated with hyperuricemia in all participants (OR = 0.85, 95% CI: 0.84–0.86, P < .001), but no significant association was observed in males (OR = 0.918, 95% CI: 0.712–1.184, P = .511) or females (OR = 1.609, 95% CI: 0.912–2.838, P = .1003). The log-likelihood ratio test confirmed a significant threshold effect in all participants (P < .001) and males (P = .011), but not in females (P = .229). These findings highlight sex-specific differences in the relationship between NHHR and both uric acid levels and hyperuricemia.

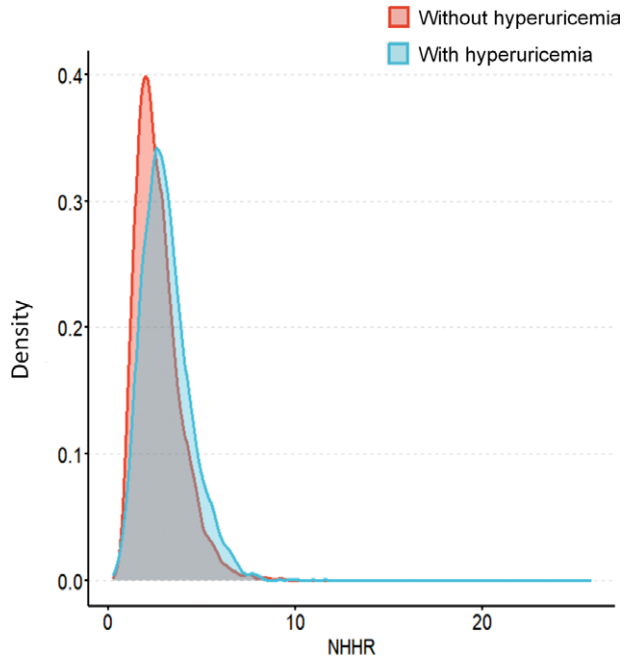

Figure 2. The distribution of NHHR in individuals without hyperuricemia and with hyperuricemia. NHHR = non-high density lipoprotein to high density lipoprotein ratio.

3.4. Subgroup analyses

Subgroup analyses were performed to assess the relationship between the NHHR and hyperuricemia (Fig. 4). The total odds ratio (OR) for hyperuricemia was 1.32 (95% CI: 1.23–1.41, P < .001), demonstrating a notable positive correlation. Age-stratified analysis demonstrated consistent relationships across all age categories, with odds ratios spanning from 1.23 (95% CI: 1.08–1.41) in individuals aged 20 to 39 years to 1.36 (95% CI: 1.24–1.58) in participants aged 60 years and above (P for interaction = .644). Regarding race, the correlation was most pronounced in non-Hispanic Black individuals (OR: 1.54, 95% CI: 1.29–1.84, P < .001), followed by non-Hispanic Whites (OR: 1.32, 95% CI: 1.18–1.46, P < .001), with no notable interaction among racial categories (P for interaction = .754). Regarding sedentary time, individuals with more than 6 hours of daily sedentary activity displayed a greater OR (1.39, 95% CI: 1.26–1.53, P < .001) than those with less 3 hours per day (OR: 1.13, 95% CI: 0.97–1.56, P = .09), although the interaction was not statistically significant (P for interaction = 0.141). BMI notably altered the relationship (P for interaction = .03), with the most pronounced effect observed in individuals with BMI < 25 (OR: 1.73, 95% CI: 1.41–2.11, P < .001). The smoking status also demonstrated significant differences (P for interaction = .045). Current smokers had the highest OR (1.28, 95% CI: 1.11–1.49, P = .001), followed by former smokers (OR: 1.21, 95% CI: 1.05–1.36, P = .006), and never smokers (OR: 1.41, 95% CI: 1.28–1.56, P < .001). Among participants with diabetes, the association was most pronounced in those with

Table 2

Weighted regression association of NHHR with uric acid and hyperuricemia in all participants and different sex groups.

	All participants		Male		Female	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Uric acid						
NHHR, continues	0.13 (0.09, 0.18)	<.001	0.08 (0.03, 0.13)	.005	0.19 (0.13, 0.24)	<.001
NHHR, Quartile						
Quartile 1	Reference		Reference		Reference	
Quartile 2	0.14 (0.04, 0.23)	.009	0.18 (0.02, 0.33)	.030	0.10 (−0.03, 0.23)	.13
Quartile 3	0.23 (0.11, 0.36)	<.001	0.28 (0.11, 0.46)	.004	0.17 (0.02, 0.32)	.027
Quartile 4	0.58 (0.44, 0.71)	<.001	0.48 (0.30, 0.67)	<.001	0.68 (0.51, 0.85)	<.001
P for trend		<.001		<.001		<.001
Hyperuricemia						
NHHR, continues	1.20 (1.09, 1.33)	<.001	1.07 (0.95, 1.20)	.2	1.44 (1.31, 1.58)	<.001
NHHR, Quartile						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.42 (1.11, 1.82)	.008	1.54 (0.95, 2.49)	.078	1.27 (0.87, 1.85)	.2
Quartile 3	1.70 (1.16, 2.48)	.01	1.67 (0.99, 2.81)	.052	1.72 (1.17, 2.52)	.009
Quartile 4	2.69 (1.89, 3.82)	<.001	2.16 (1.21, 3.83)	.012	3.49 (2.45, 4.96)	<.001
P for trend		<.001		<.001		<.001
P for interaction	<.001					

Adjusted in Model 3: age, sex, race, family poverty income ratio, BMI, waist circumference, education level, alcohol consumption status, smoking status, marital status, diabetes, HTN, serum creatinine, coronary heart disease, heart failure, stroke, sedentary time, glycohemoglobin, urine albumin/urine creatinine, urinary creatinine, urinary albumin.

BMI = body mass index, HTN = hypertension, NHHR = non-high density lipoprotein to high density lipoprotein ratio, OR = odds ratio.

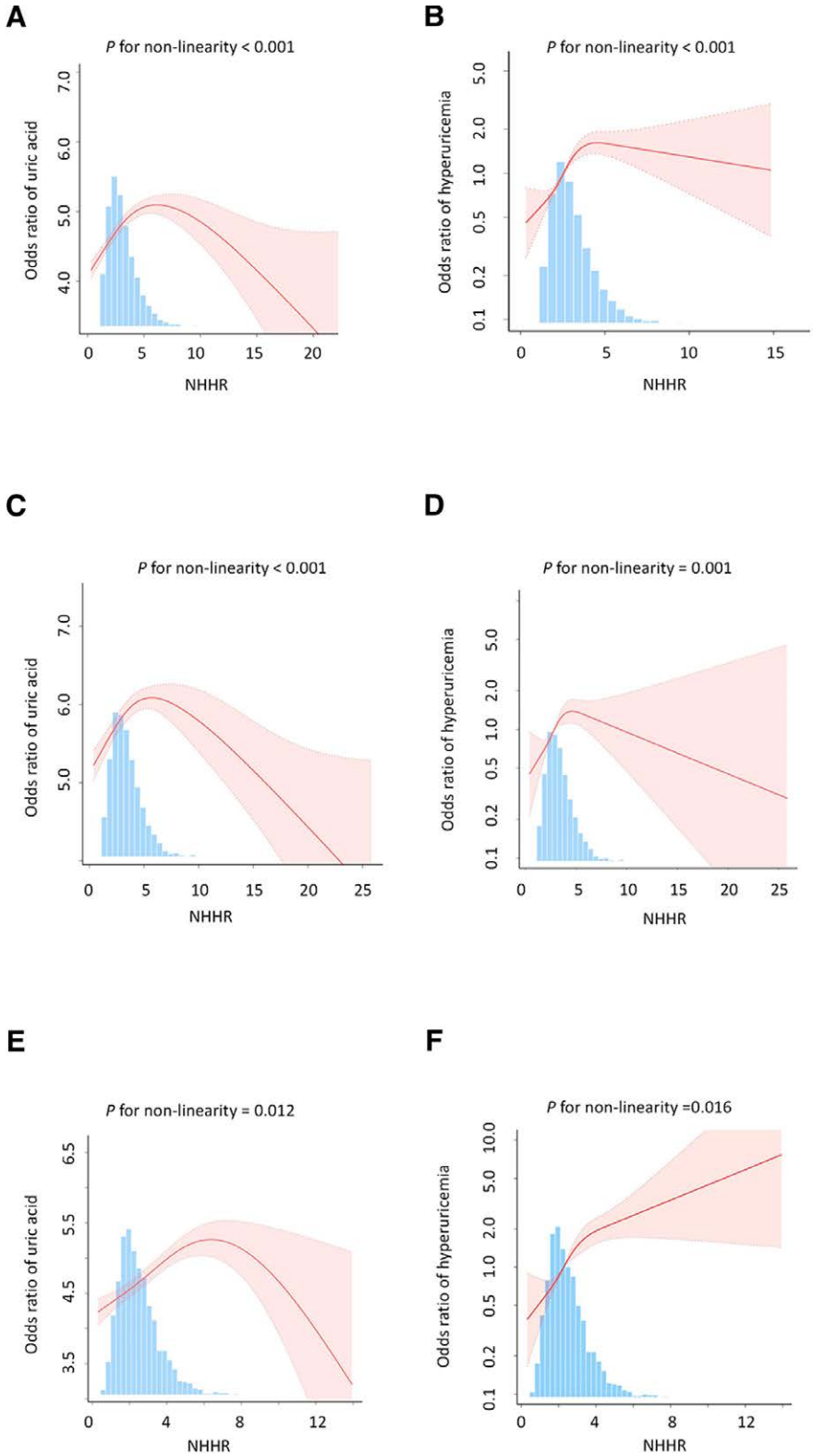

Figure 3. Nonlinear associations between neutrophil-to-high-density lipoprotein cholesterol ratio (NHHR) and uric acid/hyperuricemia. The relationship between NHHR and uric acid levels (A, C, E) and hyperuricemia (B, D, F) in the total participants (A, B), males (C, D), and females (E, F). Adjustments were made for various factors, including age, sex, race, family poverty income ratio, BMI, waist circumference, education level, alcohol consumption status, smoking status, marital status, diabetes, HTN, serum creatinine, coronary heart disease, heart failure, stroke, sedentary time, glycohemoglobin, urine albumin/urine creatinine, urinary creatinine, urinary albumin. BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, NHHR = non-high density lipoprotein to high density lipoprotein ratio, non-HDL-C = non-high-density lipoprotein cholesterol, OR = odds ratio.

borderline diabetes (OR: 2.25, 95% CI: 1.38–3.66, $P = .001$), while the association remained significant in participants without diabetes (OR: 1.31, 95% CI: 1.21–1.41, $P < .001$). As for the participants with CHD, the OR was significantly higher (1.97, 95% CI: 1.36–2.86, $P < .001$) than in those without CHD (OR 1.31, 95% CI: 1.22–1.40, $P < .001$) although the interaction

Table 3

Threshold effect analysis of NHHR on uric acid and hyperurcemia using a two-part regression model in all participants and different sex groups.

	All participants		Male		Female	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Uric acid						
Inflection point (*K*)	4.33		6.234		5.226	
<*K* effect size OR (95% CI)	0.28 (0.24, 0.33)	<.001	0.201 (–0.193, 0.242)	.303	0.204 (0.159, 0.249)	<.001
>*K* effect size OR (95% CI)	–0.10 (–0.17, –0.03)	.004	–0.101 (–0.176, 0.009)	.057	0.015 (–0.578, –0.609)	.959
P for log likelihood ratio test	<.001		.104		.033	
Hyperuricemia						
Inflection point (*K*)	3.91		4.637		4.452	
<*K* effect size OR (95% CI)	1.711 (1.710, 1.712)	<.001	1.287 (1.141, 1.452)	<.001	1.625 (1.435, 1.840)	<.001
>*K* effect size OR (95% CI)	0.85 (0.84, 0.86)	<.001	0.918 (0.712, 1.184)	.511	1.609 (0.912, 2.838)	.1003
P for log likelihood ratio test	<.001		.011		.229	

Adjusted in Model 3: age, sex, race, family poverty income ratio, BMI, waist circumference, education level, alcohol consumption status, smoking status, marital status, diabetes, HTN, serum creatinine, coronary heart disease, heart failure, stroke, sedentary time, glycohemoglobin, urine albumin/urine creatinine, urinary creatinine, urinary albumin.

BMI = body mass index, HTN = hypertension, NHHR = non-high density lipoprotein to high density lipoprotein ratio, OR = odds ratio.

was not statistically significant (*P* for interaction = .127). In addition, hypertension showed a higher effect (OR: 1.33, 95% CI: 1.11–1.36, *P* < .001) as compared to those without hypertension (OR: 1.25, 95% CI: 1.15–1.52, *P* < .001; *P* for interaction = .029). Lastly, alcohol consumption showed no significant interaction (*P* for interaction = .224); however, drinkers had a slightly higher OR (1.37, 95% CI: 1.27–1.49, *P* < .001) than nondrinkers (OR: 1.17, 95% CI: 1.03–1.33, *P* = .02).

4. Discussions

The objective of this study was to explore the potential relationship between NHHR and uric acid levels and hyperuricemia. The analysis of data from 9439 participants demonstrated a significant association; as NHHR increased, so did the levels of uric acid and the risk of hyperuricemia. This relationship holds true regardless of whether NHHR is treated as a continuous or categorical variable. Further analysis revealed a nonlinear relationship between NHHR, uric acid, and hyperuricemia, identifying turning points at 4.33 and 3.91, respectively. Below these thresholds, NHHR showed a positive correlation with blood uric acid levels and prevalence of hyperuricemia. The nonlinear relationship between NHHR and uric acid parameters may be explained by the saturation effect. Below the turning points, increased NHHR reflects an enhanced inflammatory status, leading to elevated uric acid production through increased xanthine oxidase activity and reduced renal excretion.[14,15] However, beyond these thresholds, several compensatory mechanisms may be activated: negative feedback regulation of inflammatory pathways to prevent excessive inflammation[14]; saturation of purine metabolism enzymes[16]; and activation of anti-inflammatory mechanisms mediated by regulatory T cells and anti-inflammatory cytokines.[17] These physiological adaptations may explain the plateau effect observed at higher NHHR values, suggesting a protective mechanism against unrestricted inflammatory responses.

Our results demonstrated that NHHR was positively associated with uric acid levels in both sexes, but the strength and pattern of these associations differed markedly. In males, no significant association was observed between the NHHR and hyperuricemia. However, the inflection point of NHHR for males was 4.637, below which NHHR was significantly associated with an increased risk of hyperuricemia. Beyond these thresholds, the correlation becomes negative. This nonlinear trend was statistically significant and aligns with prior studies that have reported sex-specific differences in lipid metabolism and its association with uric acid levels.[18] The association between NHHR and hyperuricemia observed in females may reflect a biological threshold beyond which additional increases in NHHR do not further exacerbate the risk of hyperuricemia, potentially due to compensatory mechanisms in uric acid clearance or hormonal regulation.[19] In contrast, males displayed with no significant saturation effect observed. This difference may be attributed to sex-specific variations in lipid metabolism, body fat distribution, and hormonal influences, particularly the protective effects of estrogen in females.[20] Estrogen enhances renal uric acid excretion, which may partially explain the plateau effect observed in females.[21]

The observed sex-based differences in the NHHR-uric acid connection can be linked to various biological mechanisms. Initially, females typically showed reduced NHHR levels and increased HDL-C concentrations relative to males, potentially providing a protective advantage against hyperuricemia.[22,23] HDL-C has been associated with the regulation of oxidative stress and inflammation, both of which are significant factors in hyperuricemia.[22] In males, decreased HDL-C levels and increased NHHR values can intensify oxidative stress and inflammatory processes, resulting in a stronger and more direct link with hyperuricemia.[24] Additionally, the effect of sex hormones on uric acid metabolism must not be ignored. Estrogen increases uric acid elimination by upregulating renal urate transporters, such as ABCG2, and downregulating URAT1.[25] This hormonal effect might play a role in the saturation phenomenon seen in females, as the kidney's ability to clear uric acid becomes less sensitive to additional rises in NHHR at elevated levels. On the other hand, the lack of estrogen in males could lead to a constant and straightforward correlation between NHHR and hyperuricemia.[26] Thirdly, variations in fat distribution and body fat may also be influential. Generally, females tend to show a greater amount of subcutaneous fat, while males possess more visceral fat, whereas is metabolically active and linked to heightened inflammation and uric acid levels.[27,28] This variation in fat distribution might enhance the NHHR-uric acid link in males, while reducing it in females at elevated NHHR levels.

The quartile analysis of NHHR revealed that despite similar median ages across the groups, there were significant differences in the age distribution.[29] Additionally, an increase in BMI indicated that obesity was more prevalent in the high NHHR group, and obesity is widely recognized as a significant risk factor for cardiovascular diseases.[30] In summary, high NHHR is associated with various adverse health conditions. Therefore, NHHR could serve as a significant indicator for assessing cardiovascular and metabolic health, and there is a need to strengthen early intervention for high-risk populations. The results of the weighted regression analysis indicated a significant association between NHHR and serum uric acid levels as well as hyperuricemia in adults. Whether analyzed as a continuous variable or in quartiles, NHHR is positively correlated

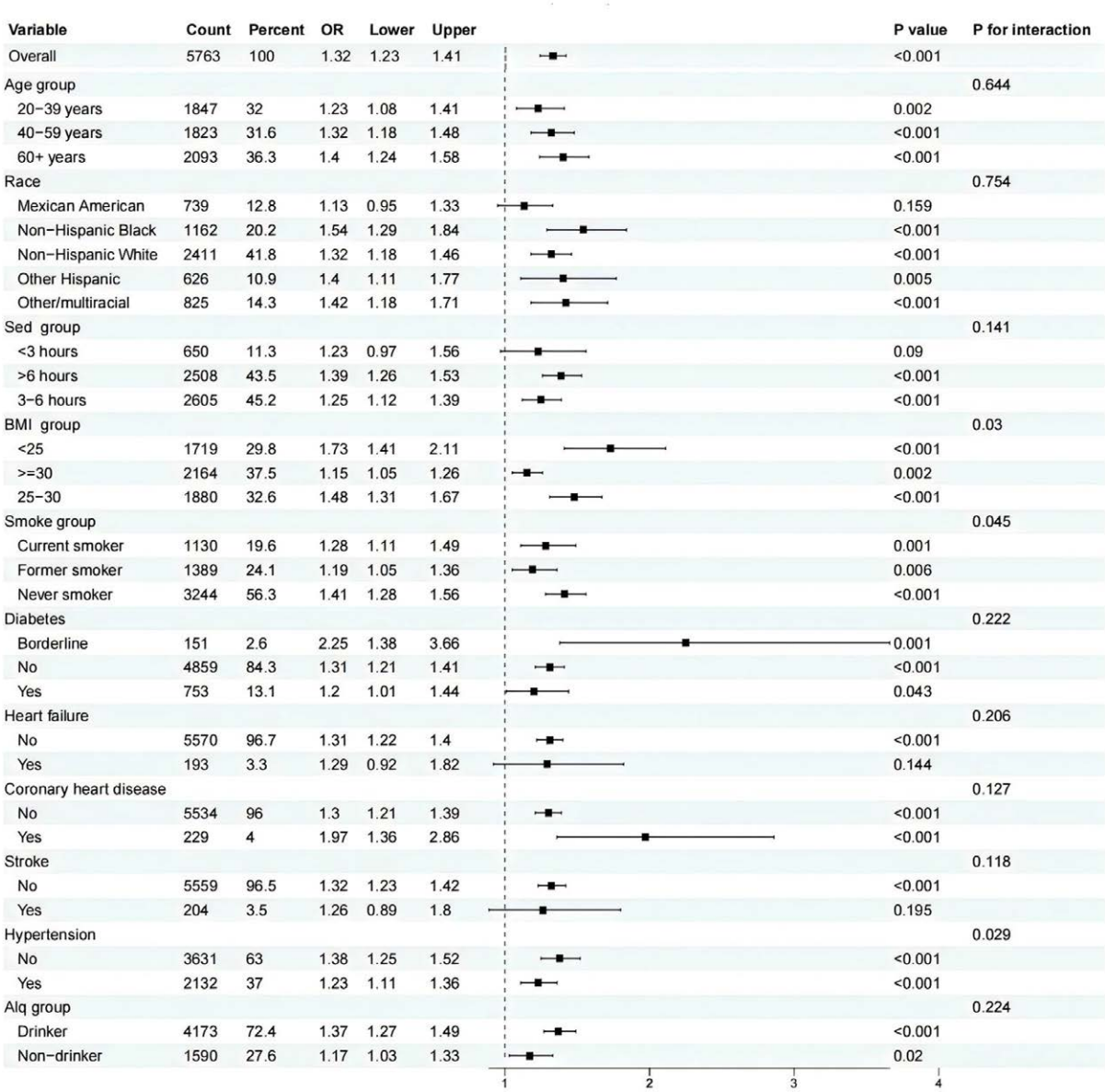

Figure 4. Subgroup analyses were performed to assess the impact of NHHR on hyperuricemia. Alq = alcohol-related questions, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, NHHR = non-high density lipoprotein to high density lipoprotein ratio, non-HDL-C = non-high-density lipoprotein cholesterol, OR = odds ratio, Sed = sedentary.

with serum uric acid levels and the risk of hyperuricemia. This finding supports the critical role of lipid metabolism disorders in the pathophysiology of hyperuricemia.[31] In previous studies, TC, TG, and LDL-C levels have been positively associated with hyperuricemia.[6,7] A small-sample cross-sectional study showed that HDL-C serves as a safeguard against elevated uric acid levels in individuals with gout.[32] Furthermore, another study demonstrated that the TG/HDL-C ratio is positively with hyperuricemia incidence.[33] It is noteworthy that NHHR incorporates a more comprehensive lipid profile compared to the aforementioned lipid components, potentially offering a more holistic reflection of the impact of lipid metabolism on uric acid levels and hyperuricemia. For example, non-HDL can indicate residual cholesterol levels, which have been shown to be significantly associated with hyperuricemia.[34] Our study results indicate a nonlinear relationship between NHHR and uric acid levels and hyperuricemia. This suggests that notable differences exist around the specific NHHR values. In the lower range of NHHR values, uric acid levels are positively correlated with NHHR; however, beyond a certain threshold, this correlation turns negative. Regarding hyperuricemia risk, there is a positive correlation with NHHR below a certain threshold, but this correlation weakens beyond this point. The log-likelihood ratio test confirmed this nonlinear threshold effect, demonstrating its robustness and scientific validity. These findings indicate that clinical practice should adopt differentiated intervention measures based on different NHHR levels to effectively control uric acid levels and prevent hyperuricemia. Further research is needed to investigate whether specific modulation of NHHR can effectively lower serum uric acid levels and the incidence of hyperuricemia in high-risk populations.

NHHR has recently emerged as an innovative lipid biomarker and is recognized as an independent risk factor for the development of atherosclerotic plaques.[35] Its critical role in impeding plaque progression highlights its importance, in addition to conventional lipid markers. NHHR has demonstrated considerable diagnostic value in predicting various metabolic disorders, including metabolic syndrome,[13] insulin resistance,[13]

diabetes,[11,36] and nonalcoholic fatty liver disease (NAFLD),[12,37] kidney stones,[38] affirming its utility in lipid management. Moreover, this study points to a potential positive correlation between NHHR and uric acid levels, as well as hyperuricemia. This suggests that NHHR could serve as a significant biomarker for exploring the relationship between lipid metabolism and hyperuricemia. Given the intricate relationships between lipid dysregulation, metabolic syndromes, and increased uric acid levels, NHHR may offer deeper insights into the underlying pathophysiological mechanisms. Future research should focus on validating these results among varied population groups and delving into the molecular pathways that connect NHHR with lipid irregularities and uric acid metabolism. Such investigations could pave the way for more precise and effective interventions targeting both cardiovascular and metabolic health.

4.1. Limitations

Despite providing strong evidence on the relationship between NHHR, serum uric acid levels, and hyperuricemia, this study had several limitations. First, because of the cross-sectional study design, we can only recognize connections between variables but cannot determine causal relationships. This cross-sectional study found a relationship between NHHR and hyperuricemia, but further research is needed to determine whether there is a causal relationship between the 2. This finding requires additional confirmation through longitudinal studies. Second, the study sample was obtained from the NHANES database covering 2005 to 2018, which, while nationally representative, might not be applicable to groups with varying demographic or socioeconomic traits. Moreover, even after accounting for various potential confounding factors, residual confounding factors (e.g., dietary patterns, medication consumption, and genetic predisposition) could still affect our understanding of the findings. In addition to antihypertensive and anti-diabetic medications, other prescribed drugs were excluded as confounding variables in the statistical analysis. Finally, some factors, including smoking habits and levels of physical activity, relied on self-reported information from participants, which might have led to recall or classification bias, possibly affecting the accuracy of the study results.

5. Conclusion

In conclusion, our study revealed significant sex-specific differences in the association between NHHR and hyperuricemia. NHHR was positively associated with uric acid levels and the risk of hyperuricemia in females, but this association was not significant in males. Future research should focus on elucidating the mechanisms underlying these disparities to enhance personalized medical approaches. Nevertheless, given the cross-sectional nature of our study, further longitudinal and interventional studies are necessary to clarify whether a causal relationship exists between NHHR and hyperuricemia.

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