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Association between the uric acid-to-HDL-cholesterol ratio (UHR) and the risk of cardiovascular disease and dyslipidemia: a population-based study

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Abstract

Background and aims The uric acid-to-HDL-cholesterol ratio (UHR), a novel marker of metabolism and inflammation, has been investigated in various diseases. However, its potential associations with the incidence of cardiovascular disease (CVD) and dyslipidemia remain unclear. This study aimed to examine the relationships between the UHR and the incidence of CVD and dyslipidemia. The primary objective was to evaluate the role of the UHR in predicting CVD and dyslipidemia, whereas the secondary objective was to analyze the predictive effects of the UHR in different subgroups.

Methods We conducted a cross-sectional analysis using data from the 2001–2018 National Health and Nutrition Examination Survey (NHANES), which included 6,370 adults aged 18–80 years. Weighted binary logistic regression and subgroup analyses were performed to evaluate the independent associations between the UHR and the risk of various cardiovascular conditions, including overall CVD, congestive heart failure, myocardial infarction, angina, coronary heart disease, and dyslipidemia. To investigate potential nonlinear relationships between the UHR and these outcomes, restricted cubic spline modeling was applied to further elucidate the associations.

Results Among the 6,370 participants included in the study, 559 were diagnosed with CVD. Elevated UHR values were strongly associated with a greater incidence of CVD and its subtypes, including congestive heart failure, myocardial infarction, angina, and coronary heart disease (all $P < 0.001$). After accounting for weighted factors, participants in the higher UHR quartiles presented progressively higher rates of CVD: Quartile 1 (4.7%), Quartile 2 (6.3%), Quartile 3 (7.4%), and Quartile 4 (11%). A nonlinear relationship between the UHR and the risk of developing CVD was identified through restricted cubic spline (RCS) analysis. Among the subgroup of 4,117 participants with dyslipidemia, multivariable linear regression analysis demonstrated a significant positive association between the UHR and dyslipidemia (OR 17.38, 95% CI 16.24–18.60). This association remained robust even after adjusting for covariates (OR 11.65, 95% CI 8.995–15.17). RCS analysis further confirmed the nonlinear nature of this relationship. Subgroup analysis revealed

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no significant interaction between the UHR and overall CVD or CVD-related variables, such as congestive heart failure, myocardial infarction, angina, or coronary heart disease. However, for dyslipidemia, BMI showed a significant interaction, indicating that the positive association between the UHR and dyslipidemia risk is influenced by participants' BMI.

Conclusion A high UHR is associated with an increased risk of various cardiovascular conditions and dyslipidemia. The incorporation of routine UHR monitoring into clinical practice can support the early identification of high-risk individuals, facilitate timely interventions, and reduce the burden of cardiovascular and metabolic diseases.

Keywords Cross-sectional study, NHANES, HDL cholesterol, Uric acid, Cardiovascular diseases, Hyperlipidemias

Introduction

Cardiovascular disease (CVD) has become a leading cause of complications and mortality worldwide [1]. Over the past decade, the number of deaths attributable to CVD has increased by 12.5% globally [2]. The 2019 Global Burden of Disease (GBD) study reported a near doubling of CVD cases, increasing from 271 million in 1990 to 523 million in 2019 [3]. Early detection of CVD is crucial for preventing premature deaths and promoting long-term health benefits.

Uric acid (UA), the final product of purine metabolism, is primarily determined by the rate of purine metabolism and kidney function [4]. Numerous studies have demonstrated a correlation between serum uric acid levels and the risk of CVD [5–7], often linking it to factors such as fatty acid metabolism, chronic kidney disease (CKD), lipid levels, and diabetes [8–10]. High-density lipoprotein (HDL) is widely recognized for its antiatherosclerotic properties [11]. HDL not only facilitates cholesterol transport back to the liver but also has anti-inflammatory, antioxidant, and cytoprotective functions [12].

The serum uric acid-to-HDL-cholesterol ratio (SUA-to-HDL-C ratio, UHR) is an emerging metabolic marker with substantial clinical implications. The UHR reflects both the metabolic state of uric acid and the protective role of HDL. An elevated UHR may indicate an increased risk of metabolic syndrome [13], peripheral vascular disease [14], and diabetes [15]. Patients with higher UHR levels often exhibit fat accumulation [16, 17], impaired renal function [18], and an elevated risk of mortality [19]. Additionally, the UHR has been identified as a potential biomarker of increased inflammation [20].

Despite numerous studies highlighting the significance of UHR, its role in the cardiovascular clinical field remains largely underexplored. Most existing research has focused on specific populations, such as patients with diabetes, nonalcoholic fatty liver disease (NAFLD), or those undergoing peritoneal dialysis. For example, the UHR has been shown to predict cardiovascular and all-cause mortality in diabetic patients [19], correlate with atrial fibrillation in patients with NAFLD [21], and serve as a predictor of cardiovascular mortality in patients on peritoneal dialysis [22]. However, these findings are population-specific and do not address the potential broader applicability of UHR in the general population. Consequently, we hypothesize that elevated UHR levels are independently associated with the incidence of CVD and dyslipidemia in the general population. Testing this hypothesis could provide valuable insights into the utility of the UHR as a noninvasive tool for early risk stratification and preventive management across diverse clinical and demographic contexts.

Materials and methods

Data source and study population

The National Center for Health Statistics (NCHS) in Hyattsville, Maryland, conducts NHANES, a comprehensive, multistage, and complex survey aimed at the noninstitutionalized civilian population of the United States. It is designed to gather data from a nationally representative sample. The survey uses a stratified, multistage cluster sampling approach to ensure that the selection of participants accurately reflects the U.S. population.

For this analysis, data from nine NHANES cycles (2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018) were used, combining independent samples to ensure a sufficient sample size. This cross-sectional study included 6,370 participants aged 18–80 years from the 2001–2018 NHANES. The inclusion and exclusion criteria are summarized in the flowchart (Fig. 1). Participants under 18 or over 80 years of age were excluded, along with those lacking CVD data or with incomplete covariate information.

Definition of UHR

UA and HDL-C were measured in fasting blood samples collected from participants in the early morning. Different analyzers were used across various NHANES survey cycles [23, 24]. This study included HDL-C data from 2001–2018 [25]. Throughout the 2001–2018 period, contract laboratories adhered strictly to Westgard rules [26] and adhered to NHANES quality assurance and quality control (QA/QC) protocols, aligning with the standards set by the 1988 Clinical Laboratory Improvement Amendments to ensure data accuracy and consistency.

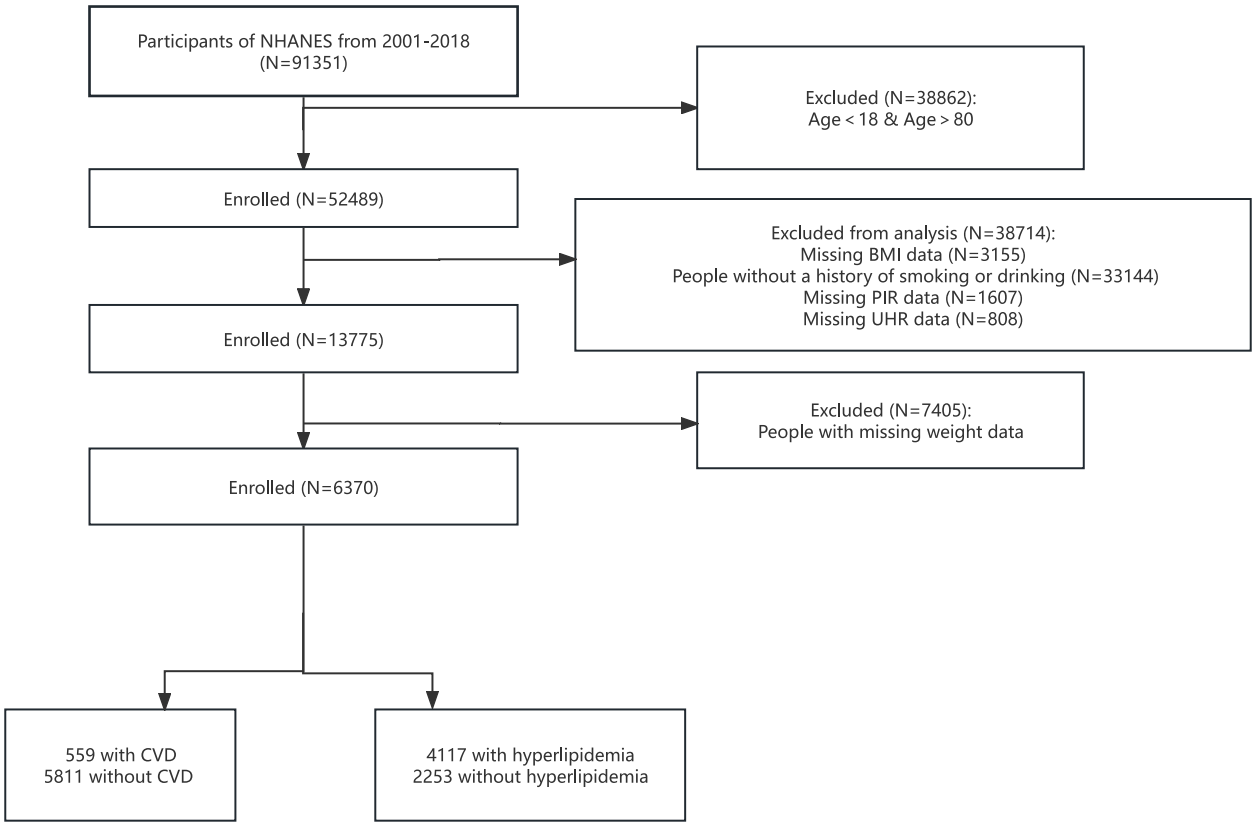

Fig. 1 Flowsheet

The UHR was calculated as defined, using the formula: UHR (%) = (UA [mg/dL] ÷ HDL [mg/dL]) × 100 [27, 28].

Total CVD, congestive heart failure, myocardial infarction, angina pectoris, coronary heart disease and hyperlipidemia assessment

The diagnosis of CVD was based on self-reported physician diagnoses obtained during standardized individual interviews via a medical conditions questionnaire. Participants were asked "Has a doctor or other health professional ever told you that you have congestive heart failure, coronary heart disease, angina, or a heart attack (myocardial infarction)?" If a participant answered "yes" to any of these questions, they were classified as having CVD. Similarly, diagnoses of congestive heart failure, myocardial infarction, angina, and coronary heart disease were determined on the basis of the corresponding questions.

Dyslipidemia was identified according to the criteria outlined in the 2002 Adult Treatment Panel III guidelines of the National Cholesterol Education Program. Participants meeting any of the following criteria were classified as having dyslipidemia: (1) total cholesterol (TC) ≥ 200 mg/dL; (2) triglyceride (TG) ≥ 150 mg/dL; (3) low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL; or (4) high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL for men or ≤ 50 mg/dL for women.

Covariate extraction

The following information was collected through a standardized interview questionnaire: age, sex, race or ethnicity, educational level, household income, smoking status, drinking habits, and physical activity. Race or ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Mexican American, Hispanic, or other. Educational level was classified as high school graduate or below and college or above. Household income was divided into three categories on the basis of the poverty-income ratio: ≤ 1.30, 1.31–3.50, and ≥ 3.50. Smoking status was classified on the basis of participants' self-reports of smoking more than 100 cigarettes in their lifetime and their current smoking habits, categorizing them as never smokers, former smokers, or current smokers. Alcohol consumption was classified into never drinkers, former drinkers, and current drinkers, determined by whether participants had consumed at least 12 alcoholic drinks in their lifetime and their drinking frequency within the past 12 months.

Diabetes was diagnosed on the basis of the following criteria: self-reported diabetes, use of insulin therapy, HbA1c ≥ 6.5%, or fasting blood glucose ≥ 126 mg/dL. Participants meeting any of these criteria were classified as having diabetes; otherwise, they were considered nondiabetic. Hypertension was diagnosed if participants were taking antihypertensive medications, had been diagnosed with hypertension, or had a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on three consecutive measurements.

Statistical analyses

All the statistical analyses were performed via R software (version 4.4.2). The complex, multistage, stratified cluster sampling design of the NHANES, including oversampling of specific subgroups, was accounted for in all analyses. Sample weights, stratification information, and primary sampling units embedded in the data were applied to ensure that the results reflected nationally representative estimates. The study population characteristics were divided into four groups based on UHR quartiles (Q1–Q4). The baseline characteristics of the participants are presented as medians (25 th–75 th percentiles) for continuous variables and counts (percentages) for categorical variables. Comparisons among the four groups were conducted via analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and the chi–square (χ^2) test for categorical variables.

Multivariate logistic regression was used to analyze the associations between the UHR and the risk of various cardiovascular conditions, including congestive heart failure, myocardial infarction, angina, coronary heart disease, and dyslipidemia, and three models were employed for statistical inference. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and race; and Model 3 was further adjusted for age, sex, race, educational level, poverty-income ratio (PIR), body mass index (BMI), smoking status, and drinking status.

The UHR was divided into quartiles (Q1–Q4) for stratification to ensure balanced and interpretable subgroups across the study population. Quartile-based stratification is widely used in epidemiological research because it provides sufficient granularity to detect dose–response relationships while maintaining statistical power within each group. Alternative stratification methods (e.g., tertiles and quintiles) were also tested during sensitivity analyses, yielding consistent results.

Rigorous data validation procedures were implemented, including the exclusion of participants with missing data or outliers identified on the basis of interquartile range (IQR) criteria. Furthermore, restricted cubic spline (RCS) analyses with five knots were utilized to investigate potential nonlinear associations between the UHR and the risks of various cardiovascular conditions.

For subgroup analyses of the associations between the UHR and the risk of CVD and dyslipidemia, the data were stratified by sex (male/female), BMI (normal weight/overweight/obese), alcohol use (never/former/current), smoking status (never/former/current), diabetes status (yes/no), and hypertension status (yes/no). Statistical significance was defined as a two-sided P value < 0.05.

Results

Baseline characteristics of the study participants

Table 1 presents the baseline characteristics of the 6,370 participants. Among these patients, 37% were male, 63% were female, and the average age was 49 years. Additionally, 56% had an education level above high school, 16% had diabetes, 41% had hypertension, the prevalence of CVD was 7.3%, and the prevalence of dyslipidemia was 64%. Compared with participants in the lowest UHR quartile, those in higher UHR quartiles presented a greater prevalence of both CVD and dyslipidemia. Furthermore, participants with higher UHR levels were more likely to be older, male, non-Hispanic White, obese, smokers, and have diabetes and hypertension. Significant differences in triglyceride levels were also observed among participants with higher UHR levels.

The possible relationships among UHR, CVD, and hyperlipidemia

This study analyzed the relationship between the UHR and the risk of CVD (Table 2). The results revealed a significant positive correlation between the UHR and CVD risk, regardless of whether the UHR was treated as a continuous variable or categorized into quartiles. In the fully adjusted Model 3, each one-unit increase in UHR was associated with a significant increase in CVD risk (OR = 1.589, 95% CI: 1.029–2.454, P = 0.037). Compared with the lowest quartile, the second, third, and fourth quartiles had 5.2%, 17.8%, and 69.6% higher risks of CVD, respectively, with a significant linear trend (P < 0.001).

For congestive heart failure (CHF), we found a strong association between the UHR and the likelihood of CHF (Model 3: OR = 4.146, 95% CI: 2.496–6.887, P < 0.001) (Table 3). In subsequent sensitivity analyses, the adjusted OR for CHF in the highest UHR quartile compared with the lowest quartile was 4.402 (95% CI: 1.923–8.494, P < 0.001), further confirming a robust and statistically significant positive association between elevated UHR and increased risk of CHF.

With respect to atherosclerotic cardiovascular disease (ASCVD) and angina, Model 2 (adjusted for age, sex, and race) revealed that an elevated UHR was significantly

Table 1 Weighted baseline characteristics of the study population

Characteristic	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
Gender (%)						**< 0.001**
Male	2256 (37)	153 (8)	380 (27)	673 (42)	1050 (69)	
Female	4114 (63)	1438 (92)	1152 (73)	981 (58)	543 (31)	
Age (years)	49 (34,63)	47 (33,61)	49 (34,63)	50 (35,64)	49 (35,63)	0.165
Ethnic (%)						0.07
Mexican American	1142 (9.6)	324 (10)	284 (10)	281 (8.8)	253 (9.2)	
Other Hispanic	540 (5.6)	140 (6.2)	128 (5.5)	143 (5.3)	129 (5.4)	
Non-Hispanic White	2365 (62)	542 (60)	525 (58)	612 (62)	686 (65)	
Non-Hispanic Black	1476 (14)	366 (14)	396 (16)	405 (14)	309 (11)	
Other Race	847 (9.7)	219 (9.8)	199 (10)	213 (9.7)	216 (9.4)	
Educational level, (%)						**0.043**
High school or lower	3230 (44)	769 (39)	783 (45)	852 (45)	826 (46)	
Above high school	3140 (56)	822 (61)	749 (55)	802 (55)	767 (54)	
Family income to poverty ratio, *n* (%)						0.499
≤ 1.3	2116 (24)	529 (23)	522 (26)	517 (23)	548 (26)	
1.3 to 3.5	2587 (39)	644 (38)	606 (38)	709 (40)	628 (40)	
≥ 3.5	1667 (37)	418 (39)	404 (36)	428 (37)	417 (35)	
Total Cholesterol, mg/dl	188 (163,217)	193 (167,220)	190 (167,217)	185 (158,215)	185 (160,214)	**0.001**
Triglycerides, mg/dl	105 (73,155)	78 (58,107)	94 (68,130)	114 (80,160)	152 (107,213)	**< 0.001**
HDL-C, mg/dl	51 (42,62)	69 (60,78)	56 (50,63)	48 (43,54)	39 (35,44)	**< 0.001**
LDL-C, mg/dl	110 (88,135)	105 (85,130)	113 (91,137)	112 (87,138)	110 (88,135)	**< 0.001**
BMI, kg/m^2	28 (24,34)	25 (22,29)	28 (24,33)	30 (25,35)	31 (28,37)	**< 0.001**
Drink, *n* (%)						**0.038**
Never	2345 (32)	665 (35)	574 (34)	592 (30)	514 (31)	
Former	1615 (23)	346 (19)	386 (23)	420 (24)	463 (26)	
Now	2410 (45)	580 (46)	572 (44)	642 (46)	616 (43)	
Smoke, *n* (%)						**< 0.001**
Never	4399 (68)	1245 (77)	1078 (68%)	1090 (64)	986 (63)	
Former	1166 (19)	203 (14)	257 (19)	314 (20)	392 (23)	
Now	805 (13)	143 (9.0)	197 (13)	250 (16)	215 (14)	
Diabetes, *n* (%)	1369 (16)	178 (7.5)	274 (13)	412 (19)	505 (26)	**< 0.001**
Hypertension, *n* (%)	2938 (41)	538 (29)	676 (39)	838 (43)	886 (53)	**< 0.001**
Serum uric acid, mg/dl	5.20(4.30,6.20)	3.90(3.40,4.50)	4,80(4.30,5.40)	5.50(5.00,6.10)	6.70(6.00,7.40)	**< 0.001**
CVD, *n* (%)	559 (7.3)	77 (4.7)	125 (6.3)	144 (7.4)	213 (11)	**< 0.001**
CHF, *n* (%)	216 (2.5)	24 (1.0)	41 (2.0)	58 (2.5)	93 (4.5)	**< 0.001**
ASCVD, *n* (%)	264 (3.3)	33 (1.8)	60 (2.8)	67 (3.0)	104 (5.4)	**< 0.001**
Angina, *n* (%)	171 (2.7)	29 (1.9)	34 (1.6)	42 (2.5)	66 (4.5)	**< 0.001**
CHD, *n* (%)	269 (3.7)	32 (1.9)	60 (3.1)	75 (4.0)	102 (5.6)	**< 0.001**
Hyperlipidemia, *n* (%)	4117 (64)	804 (47)	893 (57)	1095 (67)	1325 (84)	**< 0.001**
UHR	10.2 (7.4,13.6)	5.8 (5.0,6.6)	8.6 (7.9,9.2)	11.5(10.7,12.4)	16.5(14.9,19.0)	**< 0.001**

Median (IQR) for continuous; n() for categorical, and all estimates accounted for complex survey designs in NHANES

Bold indicates statistical significance

LDL-C Low-density lipoprotein cholesterol, *HDL-C* High-density lipoprotein cholesterol, *BMI* Body mass index, *CVD* Cardiovascular disease, *CHF* Congestive heart failure, *ASCVD* Atherosclerotic cardiovascular disease, *CHD* Congestive heart disease

associated with an increased risk of both conditions. Specifically, each one-unit increase in the UHR was associated with increased risks of ASCVD (OR = 1.900, 95% CI: 1.095–3.296, P = 0.023) and angina (OR = 2.236, 95% CI: 1.011–4.043, P = 0.047) (Tables 4 and 5). Importantly, even after adjusting for all covariates in Model 3, the UHR in the fourth quartile remained significantly associated with the risk of ASCVD compared with that in the

Table 2 The association between UHR and the risk of CVD

CVD	OR(95%CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
UHR(continuous)	2.277(1.588,3.266), **$p < 0.001$**	2.034(1.340,3.087), **$p = 0.001$**	1.589(1.029,2.454), **$p = 0.037$**	1.343(1.190,1.516), **$p < 0.001$**
UHR(quartiles)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.384(0.918,2.087), $p = 0.12$	1.252(0.801,1.956), $p = 0.321$	1.052(0.682,1.625), $p = 0.817$	1.050(0.684,1.612), $p = 0.823$
Quartile 3	1.627(1.083,2.444), **$p = 0.02$**	1.450(0.938,2.243), $p = 0.094$	1.178(0.761,1.823), $p = 0.459$	1.175(0.717,1.925), $p = 0.518$
Quartile 4	2.479(1.704,3.607), **$p < 0.001$**	2.224(1.447,3.416), **$p < 0.001$**	1.696(1.113,2.585), **$p = 0.014$**	1.655(0.884,3.098), $p = 0.114$
P for trend	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**

95%CI: 95% Confidence Interval

Model 1 was unadjusted;

Model 2 was adjusted for age, gender and race;

Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake

Model 4 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes, hypertension and serum uric acid levels

Table 3 The association between UHR and the risk of CHF

CHF	OR(95%CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
UHR(continuous)	4.457 (2.861,6.943), **$p < 0.001$**	5.811(3.519,4.159), **$p < 0.001$**	4.146(2.496,6.887), **$p < 0.001$**	1.628(1.344,1.971), **$p < 0.001$**
UHR(quartiles)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	2.043(1.014,4.114), **$p = 0.446$**	2.044(1.005,4.159), **$p = 0.049$**	1.639(0.803,3.346), $p = 0.173$	1.423(0.871,2.808), $p = 0.306$
Quartile 3	2.630(1.282,5.393), **$p = 0.009$**	2.825(1.322,6.037), **$p = 0.008$**	2.162(1.009,4.634), $p = 0.047$	1.700(0.834,3.465), $p = 0.143$
Quartile 4	4.769(2.389,9.520), **$p < 0.001$**	6.036(2.909,12.52), **$p < 0.001$**	4.402(1.923,8.494), **$p < 0.001$**	2.598(1.081,6.242), **$p = 0.033$**
P for trend	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**

95%CI: 95% Confidence Interval

Model 1 was unadjusted;

Model 2 was adjusted for age, gender and race;

Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake;

Model 4 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes, hypertension and serum uric acid levels

Table 4 The association between UHR and the risk of ASCVD

ASCVD	OR(95%CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
UHR(continuous)	2.753(1.642,4.617), **$p < 0.001$**	1.900(1.095,3.296), **$p = 0.023$**	1.500(0.875,2.569), $p = 0.139$	1.442(1.181,1.760), **$p < 0.001$**
UHR(quartiles)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.604(0.918,2.802), $p = 0.097$	1.322(0.745,2.382), $p = 0.331$	1.141(0.803,3.346), $p = 0.173$	1.124(0.624,2.024), $p = 0.694$
Quartile 3	1.708(0.964,3.025), **$p = 0.009$**	1.297(0.722,2.331), $p = 0.381$	1.080(1.009,4.634), $p = 0.047$	1.045(0.550,1.984), $p = 0.892$
Quartile 4	3.157(1.735,5.744), **$p < 0.001$**	2.138(1.157,3.951), **$p = 0.016$**	1.660(1.923,8.494), **$p < 0.001$**	1.551(0.714,3.369), $p = 0.264$
P for trend	**$p < 0.001$**	**$p = 0.018$**	**$p = 0.029$**	**$p = 0.043$**

95%CI: 95% Confidence Interval

Model 1 was unadjusted;

Model 2 was adjusted for age, gender and race;

Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake

Model 4 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes, hypertension and serum uric acid levels

Table 5 The association between UHR and the risk of Angina

Angina	OR(95%CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
UHR(continuous)	2.608(1.291,5.267), **$p = 0.008$**	2.236(1.011,4.043), **$p = 0.047$**	1.757(0.765,4.033), $p = 0.182$	1.434(1.172,1.755), **$p < 0.001$**
UHR(quartiles)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	0.875(0.485,1.579), $p = 0.655$	0.784(0.420,1.464), $p = 0.442$	0.655(0.352,1.216), $p = 0.178$	0.694(0.357,1.352), $p = 0.281$
Quartile 3	1.362(0.670,2.770), $p = 0.390$	1.199(0.595,2.416), $p = 0.610$	0.974(0.484,1.962), $p = 0.941$	1.102(0.440,2.759), $p = 0.835$
Quartile 4	2.518(1.454,4.361), **$p < 0.001$**	2.170(1.161,4.057), **$p = 0.016$**	1.647(0.874,3.103), **$p = 0.122$**	1.953(0.747,5.107), **$p = 0.170$**
P for trend	**$p < 0.001$**	**$p = 0.006$**	**$p = 0.013$**	**$p = 0.024$**

95%CI: 95% Confidence Interval

Model 1 was unadjusted;

Model 2 was adjusted for age, gender and race;

Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake

Model 4 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes, hypertension and serum uric acid levels

lowest quartile (OR = 1.660, 95% CI: 1.923–8.494; $P < 0.001$).

The associations between UHR, coronary heart disease (CHD), and dyslipidemia are shown in Tables 6 and 7. As evidenced by the data, higher UHR levels were strongly associated with an increased risk of CHD and dyslipidemia. According to the fully adjusted model, each one-unit increase in the UHR was linked to a greater likelihood of CHD (OR = 1.837, 95% CI: 1.100–3.069, $P = 0.021$) and dyslipidemia (OR = 11.65, 95% CI: 8.955–15.17, $P < 0.001$). Sensitivity analysis revealed that participants in the highest UHR quartile had an adjusted OR of 12.55 (95% CI: 9.391–16.76) for dyslipidemia compared with those in the lowest quartile. These findings further confirm a significant positive association between elevated UHR and increased risk of dyslipidemia.

Interestingly, after adjusting for diabetes, hypertension, and serum uric acid in Model 4, the associations between the UHR and several cardiovascular diseases (such as angina, ASCVD, and CHD) significantly weakened, and in most cases, they were no longer statistically significant. This is likely because factors such as diabetes, hypertension, and serum uric acid are major risk factors for cardiovascular disease, which may partially obscure the independent effect of the UHR. However, the relationship between UHR and hyperlipidemia remained significant, suggesting that UHR plays a strong predictive role in lipid metabolism disorders. Even after adjusting for other metabolic factors, the UHR still effectively predicts hyperlipidemia risk, highlighting its potential value in predicting metabolic dysregulation and lipid abnormalities. Finally, we constructed an adjusted model incorporating the use of statins and antihypertensives and compared its Akaike information criterion (AIC) to that of our baseline model. Although the overall nonlinear trend remained similar, the reduced AIC (a difference

Table 6 The association between UHR and the risk of CHD

CHD	OR(95%CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
UHR(continuous)	2.975(1.890,4.681), **$p < 0.001$**	2.013(1.244,3.258), **$p = 0.005$**	1.837(1.100,3.069), **$p = 0.021$**	1.422(1.187,1.703), **$p < 0.001$**
UHR(quartiles)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.650(0.873,3.119), $p = 0.122$	1.343(0.694,2.600), $p = 0.442$	1.213(0.634,2.318), $p = 0.557$	1.132(0.601,2.130), $p = 0.699$
Quartile 3	2.165(1.119,4.118), **$p = 0.022$**	1.615(0.807,3.230), $p = 0.174$	1.450(0.714,2.943), $p = 0.301$	1.275(0.551,2.946), $p = 0.568$
Quartile 4	3.052(1.660,5.613), **$p < 0.001$**	1.968(1.054,3.674), **$p = 0.034$**	1.716(0.937,3.141), $p = 0.080$	1.396(0.555,3.512), $p = 0.476$
P for trend	**$p < 0.001$**	**$p = 0.025$**	**$p = 0.013$**	**$p = 0.019$**

95%CI: 95% Confidence Interval

Model 1 was unadjusted;

Model 2 was adjusted for age, gender and race;

Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake

Model 4 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes, hypertension and serum uric acid levels

Table 7 The association between UHR and the risk of Hyperlipidemia

Hyperlipidemia	OR(95%CI)			
	Model 1	Model 2	Model 3	Model 4
UHR(continuous)	17.38(16.24,18.60), ***p* < 0.001**	13.44(10.33,17.49), ***p* < 0.001**	11.65(8.955,15.17), ***p* < 0.001**	1.738(1.624,1.860), ***p* < 0.001**
UHR(quartiles)				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.489(1.223,1.813), ***p* < 0.001**	1.925(1.581,2.343), ***p* < 0.001**	1.732(1.416,2.120), ***p* < 0.001**	2.415(1.973,2.956), ***p* < 0.001**
Quartile 3	2.341(1.912,2.866), ***p* < 0.001**	4.015(3.226,4.998), ***p* < 0.001**	3.453(2.755,4.329), ***p* < 0.001**	6.155(4.767,7.949), ***p* < 0.001**
Quartile 4	5.865(4.708,7.305), ***p* < 0.001**	15.30(11.53,20.29), ***p* < 0.001**	12.55(9.391,16.76), ***p* < 0.001**	35.36(22.89,54.63), ***p* < 0.001**
P for trend	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**

95%CI: 95% Confidence Interval

Model 1 was unadjusted;

Model 2 was adjusted for age, gender and race;

Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake

Model 4 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes, hypertension and serum uric acid levels

of 13.303) demonstrated that medication use served as a moderating factor in the UHR–hyperlipidemia association (Supplementary material 1).

RCS analysis

We used RCS curves to analyze the nonlinear characteristics of the relationships between UHR and the likelihood of developing CVD, CHF, ASCVD, angina, CHD, or dyslipidemia. Our findings indicate an approximately linear relationship between UHR and CVD (*P* for nonlinearity = 0.4932). Additionally, the results suggest that UHR has an approximately linear relationship with CHF (*P* for nonlinearity = 0.5640), ASCVD (*P* for nonlinearity = 0.1907), angina (*P* for nonlinearity = 0.1501), and CHD (*P* for nonlinearity = 0.9520). However, a significant nonlinear relationship was observed between the UHR and dyslipidemia (*P* for nonlinearity < 0.0001) (Fig. 2).

To explore the nonlinear relationship between the UHR and dyslipidemia, we conducted a sex-stratified analysis via the generalized additive model (GAM). The results revealed distinct patterns between males and females. In males, a clear threshold effect was observed, with a significant increase in the risk of dyslipidemia once the UHR exceeded a certain threshold. In contrast, the relationship in females was more gradual but still nonlinear (Supplementary materials 2). Notably, sex significantly modulated this relationship, with females having a greater risk of dyslipidemia than males at the same UHR (Supplementary materials 3). These findings underscore the importance of considering sex differences, which may be influenced by hormonal and metabolic factors. Moreover, although age also showed some relationship in the model, its impact on dyslipidemia was more gradual and less pronounced than the nonlinear relationship between UHR and dyslipidemia (Supplementary materials 4).

Subgroup analysis

We conducted subgroup analyses and interaction effect tests to evaluate the consistency of the associations between the UHR and the risk of developing CVD, CHF, ASCVD, angina, CHD, or dyslipidemia across different population subgroups. The subgroups analyzed included sex, BMI, smoking status, drinking status, diabetes status, and hypertension status.

The interaction P values for the risk of CVD (Fig. 3a), CHF (Fig. 3b), ASCVD (Fig. 3c), angina (Fig. 3d), and CHD (Fig. 3e) were not statistically significant. These findings indicate that these associations are not influenced by sex, BMI, hypertension, diabetes, smoking, or drinking status. The results suggest that the positive associations between UHR and the risks of CVD, CHF, ASCVD, angina, and CHD are consistent across various population subgroups, demonstrating broad applicability.

Subgroup analysis of UHR and dyslipidemia (Fig. 3f) revealed that BMI significantly influenced this relationship. Across all BMI categories, higher UHR levels were significantly linked to an increased risk of dyslipidemia. This underscores the importance of accounting for BMI as a potential moderating factor when examining the relationship between the UHR and dyslipidemia.

Discussion

In this cross-sectional study of 6,370 participants, we observed that elevated UHR levels were significantly and independently associated with increased risks of CVD, CHF, ASCVD, angina, CHD, and dyslipidemia. The relationship between the UHR and CVD risk appeared to be approximately linear, whereas the association with dyslipidemia was nonlinear. Subgroup and interaction analyses stratified by sex, BMI, smoking status, drinking status, diabetes status, and hypertension status revealed

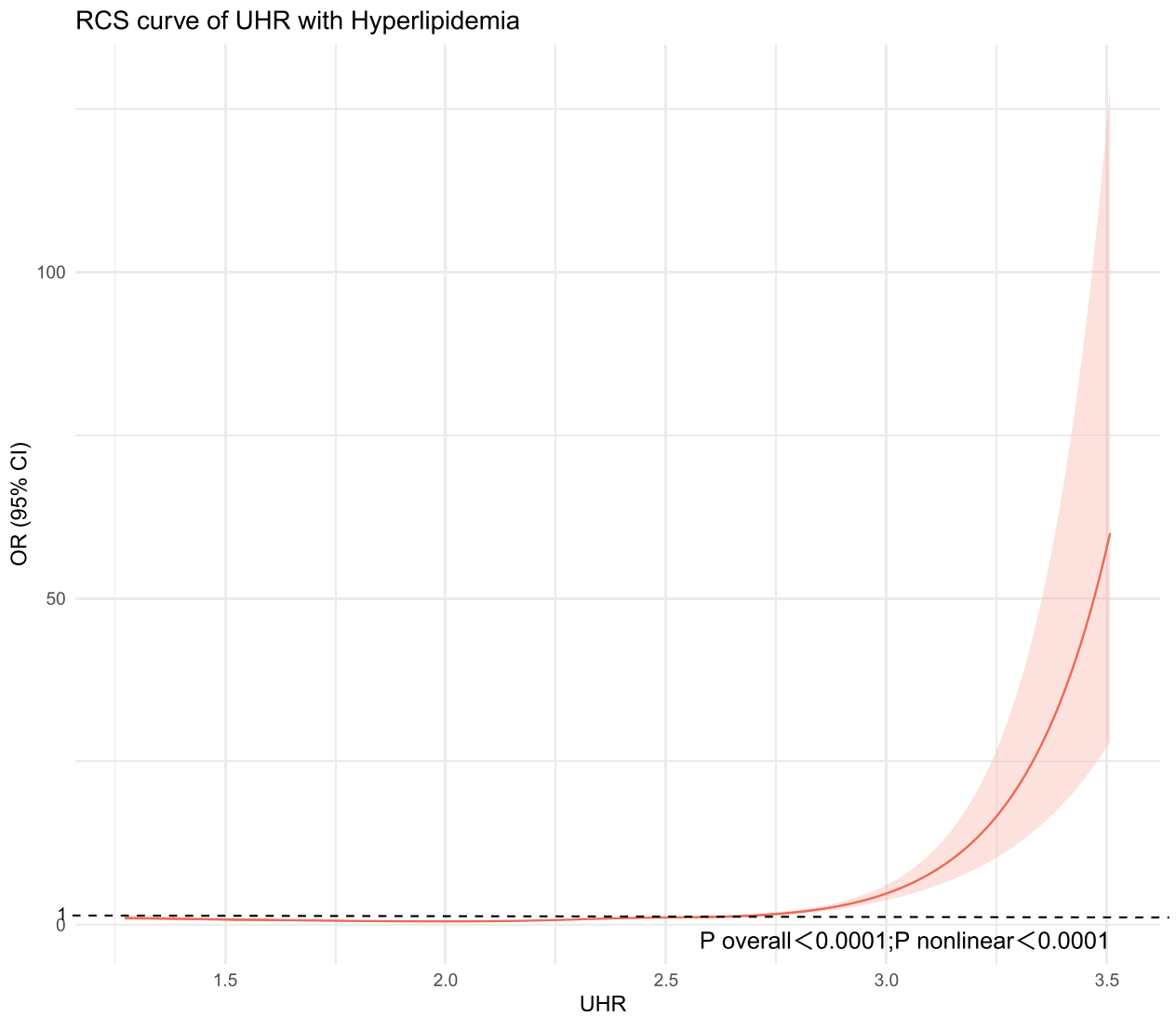

Fig. 2 RCS curve of UHR with hyperlipidemia

consistent associations between the UHR and the risks of CVD, CHF, ASCVD, angina, and CHD. However, the interaction analysis revealed that the positive association between UHR and dyslipidemia was influenced by participants' BMI status. Future research should explore whether interventions targeting the UHR can improve the clinical outcomes of these patients.

To date, whether serum uric acid (SUA) can be considered an independent risk factor for CVD remains a topic of debate. The associations between SUA and different types of CVD may be confounded by common factors in cardiac patients, such as hypertension, dyslipidemia, diabetes, alcohol consumption, hypothyroidism, and the use of diuretics [29]. This uncertainty may stem from the dual pro-oxidative and antioxidative properties of SUA. When SUA levels are either excessively low or high or exceed the body's regulatory capacity, the risk of CVD development may increase. For example, when the pro-oxidative effects of SUA outweigh its antioxidative properties, it may act as a risk factor and is closely linked to endothelial dysfunction [30], increased oxidative stress[31], and systemic inflammation[32], all of which contribute to the onset of CVD. Conversely, if SUA functions as an endogenous antioxidant, it may exert significant protective effects by reducing vascular damage and preventing the occurrence of CVD [33, 34]. Additionally, SUA is closely associated with dyslipidemia. Studies have shown that elevated SUA levels are significantly correlated with lipid abnormalities, such as increased triglycerides, elevated low-density lipoprotein cholesterol, and decreased

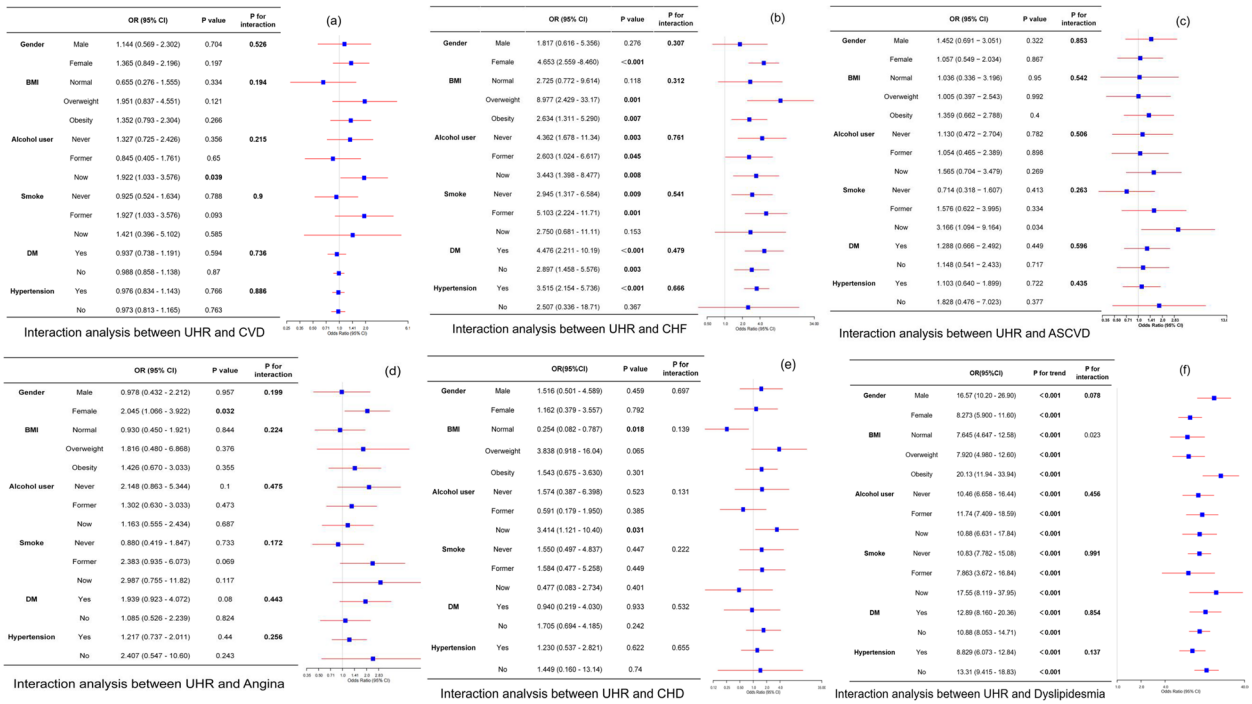

Fig. 3 UHR interaction analysis

high-density lipoprotein cholesterol [35, 36]. SUA may also disrupt lipid metabolism by promoting lipid synthesis in hepatocytes through endoplasmic reticulum stress, exacerbating intracellular fat accumulation and degeneration, and further contributing to lipid metabolic disorders [36–38].

Extensive epidemiological evidence has previously suggested a negative correlation between plasma HDL-C levels and the incidence of CVD [39]. However, recent studies have provided a more nuanced analysis of the relationship between HDL levels and CVD risk, revealing a "U-shaped" or "L-shaped" curve rather than a simple linear trend [39, 40]. In a study by Chen et al., findings indicated that cardiovascular risk ceased to decrease further when HDL-C levels exceeded 70 mg/dL. A significant negative correlation between HDL-C and CVD was observed when HDL-C levels were ≤ 50 mg/dL; however, no association was found when HDL-C levels exceeded 50 mg/dL. Thus, the relationship between HDL and CVD incidence may not follow a straightforward linear pattern.

The UHR, as a simple and accessible biomarker for assessing the risk of CVD and dyslipidemia, offers several advantages. It overcomes the limitations of evaluating risk with a single indicator, mitigating the impact of nonlinear relationships within specific ranges. By integrating the pro-oxidative effects of high uric acid with the diminished antioxidative capacity of low HDL, the UHR provides a more comprehensive reflection of an individual's metabolic balance. Currently, the Framingham risk score (FRS) remains a widely used predictor of CVD [41], incorporating factors such as age, smoking status, blood pressure, total cholesterol, and HDL-C levels [42]. However, the FRS does not account for emerging metabolic markers, such as serum uric acid levels. By integrating the UHR with the FRS or traditional lipid parameters, clinicians may achieve more comprehensive risk stratification, particularly in individuals with metabolic syndrome or insulin resistance. Evaluating whether incorporating the UHR into established risk models can increase the predictive accuracy for CVD and related metabolic disorders presents a promising avenue for future research. The UHR serves not only as a risk assessment tool but also as a target for preventive and individualized therapeutic interventions. As it reflects both uric acid burden and HDL-C status, interventions aimed at either component may help reduce cardiovascular and metabolic risks. Dietary modifications, such as reducing the intake of purine-rich foods, sugar-sweetened beverages, and alcohol while increasing the consumption of unsaturated fats, engaging in regular aerobic exercise, maintaining a healthy weight, and quitting smoking, may contribute to improved uric acid and HDL-C levels, thereby lowering the UHR and its associated risks. Additionally, uric acid-lowering medications, such as allopurinol and febuxostat, as well as lipid-lowering agents, including

statins and fibrates, may help improve lipid profiles, alleviate oxidative stress, and enhance endothelial function.

Chen et al. demonstrated a positive association between UHR and the incidence of CVD in individuals aged 50 years and above [43]. Our findings are consistent with existing evidence, further supporting the link between UHR levels and the prevalence of CVD in the general adult population. Furthermore, we established a similar association between the UHR and dyslipidemia. Previous studies have reported that elevated UHR levels are closely linked to an increased risk of adverse cardiovascular events and CVD-related mortality in patients with conditions such as acute myocardial infarction [44] and chronic total coronary occlusion [27]. In patients with heart failure, serum uric acid levels and dyslipidemia have become independent risk factors[45, 46]. Moreover, acute ischemic stroke (AIS) is associated with hyperuricemia and dyslipidemia, with no significant sex differences observed [47]. By employing advanced subgroup analyses and interaction effect testing, we verified the generalizability of our findings and explored potential mechanisms influencing the conclusions. These findings highlight the significance of the UHR as a valuable correlate for assessing the risk of CVD and dyslipidemia.

In light of these findings, the UHR could be integrated into routine clinical screening for CVD and dyslipidemia. Because uric acid and HDL-C are already commonly measured in standard health examinations, calculating the UHR would impose minimal additional cost or complexity. Incorporating UHR alongside established risk factors—such as blood pressure, lipid profiles, and body mass index—may enable earlier identification of individuals at elevated risk and potentially improve patient outcomes through timely interventions. However, to confirm its utility and establish any optimal UHR cutoff, further large-scale prospective studies or randomized controlled trials are essential. These should include cost-effectiveness evaluations, different demographic or ethnic groups, and clear definitions of UHR thresholds to determine whether routine UHR assessment can significantly enhance current risk stratification models in various clinical settings.

Moreover, although our cross-sectional results suggest robust associations between UHR and both CVD and dyslipidemia, prospective cohort studies are necessary to determine causal or temporal relationships. Such studies could track changes in UHR over time, capture the incidence of cardiovascular events or dyslipidemia onset, and assess how interventions targeting UHR might alter these outcomes. Randomized controlled trials could further elucidate whether lowering the UHR, either through lifestyle modification or pharmacological approaches, translates into reduced cardiovascular risk or improvements in lipid profiles. Mechanistic investigations examining the interplay between hyperuricemia, HDL-C, and metabolic pathways (e.g., insulin resistance, oxidative stress) would also help address unresolved biological questions raised in this study. By filling these gaps, future research could strengthen the evidence base for adopting UHR as part of routine clinical practice and better inform guidelines on personalized risk management.

Although the specific biological mechanisms by which the UHR influences CVD and dyslipidemia remain unclear, existing studies suggest that metabolic syndrome may be a key underlying pathway. As highlighted by Yu et al., hyperuricemia is an important marker of metabolic syndrome and is significantly associated with obesity, insulin resistance, and dyslipidemia [13]. Experimental studies have shown that uric acid may exacerbate insulin resistance and glucose regulation abnormalities by generating reactive oxygen species (ROS) through the activation of xanthine oxidase (XOR) [48]. These metabolic disturbances form the core of metabolic syndrome and create conditions conducive to the development of CVD.

In recent years, in addition to the UHR, several new biomarkers have been proposed for the risk assessment of cardiovascular and metabolic diseases. These indices include the triglyceride–glucose (TyG) index, neutrophil–lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR). The TyG index has been shown to be an effective tool for assessing insulin resistance and cardiovascular risk and better reflects insulin resistance and inflammatory responses, thus improving the accuracy of early warning of cardiovascular disease [49]. The NLR, an indicator of systemic inflammation, has been closely linked to various cardiovascular diseases and metabolic disorders, such as diabetes, hypertension, and obesity [50, 51]. In contrast, the NLR focuses more on systemic inflammatory responses in metabolic diseases. PLR, which reflects inflammation levels through the ratio of platelets to lymphocytes in peripheral blood, also has value in predicting cardiovascular risk [51]. Compared with the TyG index, the UHR may provide a comprehensive reflection of the overall risk of metabolic syndrome and cardiovascular diseases, whereas the NLR and PLR are more focused on the inflammatory response. Therefore, in studies of the inflammatory mechanisms involved in cardiovascular diseases, the UHR, NLR, and PLR may complement each other. By comparing these emerging biomarkers, future research can better assess their predictive value in clinical risk assessment, early screening, and preventive interventions and provide more accurate guidance for their combined application.

Study strengths and limitations

This study has several strengths. First, it is based on the NHANES database, which employs a complex multistage probability sampling design to represent the noninstitutionalized U.S. population. This ensures that our findings have broad generalizability and applicability. With a sample size of 6,370 participants, the study provides robust statistical power and contributes valuable data to this field. We utilized NHANES sample weights in our analyses to further enhance the reliability and applicability of the results. Additionally, by adjusting for multiple covariates, we effectively controlled for potential confounding bias, improving the credibility of the findings and their relevance to a broader population. Finally, we conducted sensitivity analyses and subgroup analyses to comprehensively assess the relationships between the UHR and the risks of CVD and dyslipidemia, thereby increasing the robustness and reliability of our study. Despite its strengths, this study has several limitations that should be noted. First, as a cross-sectional study, it cannot establish causal relationships but only reveals associations between UHR and the likelihood of CVD and dyslipidemia. To confirm these findings, prospective cohort studies are needed. Although we adjusted for multiple potential confounding variables, the influence of residual confounding and unknown variables cannot be completely ruled out, which may introduce bias in the interpretation of the results. Measurement errors and unmeasured variables might also contribute to confounding effects. Additionally, the data used in this study were derived from the NHANES database, which includes samples from the U.S. population. Owing to differences in living environments, dietary habits, and genetic backgrounds, the generalizability of our findings to global populations may be limited, and further validation in other ethnic groups and regions is necessary. Furthermore, the NHANES collected only baseline UHR values and lacked longitudinal data on UHR status during follow-up. This limitation could underestimate the association between the UHR and CVD risk. Although we attempted to include relevant covariates, such as antihypertensive and lipid-lowering treatments, to reduce bias, the lack of detailed data on serum uric acid-lowering medications (e.g., allopurinol, febuxostat, or probenecid) in the NHANES database may have overlooked important potential confounders. In conclusion, clinical information such as complete medical history or medication use may be missing or underreported. Further research is needed to validate the associations between the UHR and the risks of CVD and dyslipidemia. In addition to the limitations already mentioned, several other factors should be considered. The self-reported nature of certain variables, such as smoking, alcohol consumption, and dietary habits, introduces the potential for reporting bias, which could affect the accuracy of these data. The dataset lacks detailed genetic information and specific medication data, which could influence the associations between UHR and cardiovascular outcomes, particularly in terms of treatment effects and genetic predispositions. These factors may introduce confounding factors and reduce the generalizability of our findings.

Conclusion

Our study revealed positive correlations between elevated UHR levels and the occurrence of cardiovascular disease (CVD), congestive heart failure (CHF), atherosclerotic cardiovascular disease (ASCVD), angina, coronary heart disease (CHD), and dyslipidemia in the general adult population. Additionally, a nonlinear relationship was observed between the UHR and the likelihood of dyslipidemia. This research has significant implications, particularly for reducing screening costs. These findings highlight the potential of targeted interventions focusing on UHR to lower the risk of CVD and hyperlipidemia.

Abbreviations

CVD	Cardiovascular disease
NHANES	National Health and Nutrition Examination Survey
UA	Uric acid
HDL	High-density lipoprotein
UHR	Uric acid-to-HDL-cholesterol ratio
TC	Total cholesterol
TG	Triglycerides
LDL-C	Low-density lipoprotein cholesterol
HbA1c	Glycosylated hemoglobin A1c
ANOVA	Analysis of variance
PIR	Poverty-income ratio
BMI	Body mass index
IQR	Interquartile range
RCS	Restricted cubic spline
CHF	Congestive heart failure
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
AIC	Akaike information criterion
GAM	Generalized additive model
AIS	Acute ischemic stroke
TyG	Triglyceride-glucose
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
ROS	Reactive oxygen species
XOR	Xanthine oxidase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02551-4.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions
Z Fang, F Luo, and Y Yi conceived the idea; Y Yi wrote the manuscript; Yi Y, Q Luo, J Chen, Ze Chen, HAA and P Chen collected and read the literature; and J Tang, F Luo and Z Fang read through and corrected the manuscript. All the authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
The protocol for NHANES was approved by the National Center for Health Statistics Ethics Review Board in the United States, and all participants provided written informed consent. The authors have disclosed no conflicts of interest.

Competing interests
The authors declare no competing interests.

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References

1. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1151–1210.
2. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459–1544.
3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76:2982–3021.
4. Wen S, Arakawa H, Tamai I. Uric acid in health and disease: From physiological functions to pathogenic mechanisms. Pharmacol Ther. 2024;256:108615.
5. Kuwabara M, Ae R, Kosami K, Kanbay M, Andres-Hernando A, Hisatome I, Lanaspa MA. Current updates and future perspectives in uric acid research, 2024. Hypertens Res. 2025;48:867–73.
6. Chang DY, Wang JW, Chen M, Zhang LX, Zhao MH. Association between serum uric acid level and mortality in China. Chin Med J (Engl). 2021;134:2073–80.
7. Li N, Cui L, Shu R, Song H, Wang J, Chen S, Han Y, Yu P, Yuan W, Wang J, et al. Associations of uric acid with the risk of cardiovascular disease and all-cause mortality among individuals with chronic kidney disease: the Kailuan Study. Eur J Prev Cardiol. 2024;31:2058–66.
8. Lou B, Wu H, Ott H, Bennewitz K, Wang C, Poschet G, Liu H, Yuan Z, Kroll J, She J. Increased circulating uric acid aggravates heart failure via impaired fatty acid metabolism. J Transl Med. 2023;21:199.
9. Yang S, Yu B, Yu W, Dai S, Feng C, Shao Y, Zhao X, Li X, He T, Jia P. Development and validation of an age-sex-ethnicity-specific metabolic syndrome score in the Chinese adults. Nat Commun. 2023;14:6988.
10. Xie D, Zhao H, Lu J, He F, Liu W, Yu W, Wang Q, Hisatome I, Yamamoto T, Koyama H, Cheng J. High uric acid induces liver fat accumulation via ROS/JNK/AP-1 signaling. Am J Physiol Endocrinol Metab. 2021;320:E1032-e1043.
11. Linton MF, Yancey PG, Tao H, Davies SS. HDL Function and Atherosclerosis: Reactive Dicarbonyls as Promising Targets of Therapy. Circ Res. 2023;132:1521–45.
12. Tall AR, Thomas DG, Gonzalez-Cabodevilla AG, Goldberg IJ. Addressing dyslipidemic risk beyond LDL-cholesterol. J Clin Invest. 2022;132(1):e148559.
13. Yu X, Sun F, Ming J, Liang S, Zhang W, Wang L, Li Q, Xu Q, Wang L, Shi L, et al. Serum uric acid to high-density lipoprotein cholesterol ratio is a promising marker for identifying metabolic syndrome in nondiabetic Chinese men. Postgrad Med. 2023;135:741–9.
14. Xu J, Du X, Zhang S, Zang X, Xiao Z, Su R, Huang X, Liu L. Diagnostic value of uric acid to high-density lipoprotein cholesterol ratio in abdominal aortic aneurysms. Ann Med. 2024;56:2357224.
15. Zhou X, Xu J. Association between serum uric acid-to-high-density lipoprotein cholesterol ratio and insulin resistance in patients with type 2 diabetes mellitus. J Diabetes Investig. 2024;15:113–20.
16. Wang Y, Xu Y, Hu T, Xiao Y, Wang Y, Ma X, Yu H, Bao Y. Associations of Serum Uric Acid to High-Density Lipoprotein Cholesterol Ratio with Trunk Fat Mass and Visceral Fat Accumulation. Diabetes Metab Syndr Obes. 2024;17:121–9.
17. Sun H, Su H, Zheng R, Liu C, Wang Y, Fang C. Serum Uric Acid to High-density Lipoprotein Cholesterol Ratio is Associated with Visceral Fat in Patients with Type 2 Diabetes. Diabetes Metab Syndr Obes. 2023;16:959–67.
18. Jiang F, Peng Y, Hong Y, Cai M, Li S, Xie Y, Chen L, Lin Y. Correlation Between Uric Acid/High Density Lipoprotein Cholesterol Ratio and Postoperative AKI in Patients with CABG. Int J Gen Med. 2024;17:6065–74.
19. Ding L, Guo H, Zhang C, Jiang B, Zhang S, Zhang J, Sui X. Serum uric acid to high-density lipoprotein cholesterol ratio is a predictor for all-cause and cardiovascular disease mortality in patients with diabetes: Evidence from NHANES 2005–2018. Nutr Metab Cardiovasc Dis. 2024;34:2480–8.
20. Kurtkulagi O, Tel BMA, Kahveci G, Bilgin S, Duman TT, Ertürk A, Balci B, Aktas G. Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. Rom J Intern Med. 2021;59:403–8.
21. Liu G, Zhang Q, Zhou M, Li B, Zhao J, Bai R, Song X, Qin W, Zhang Y. Correlation between serum uric acid to high-density lipoprotein cholesterol ratio and atrial fibrillation in patients with NAFLD. PLoS ONE. 2024;19:e0305952.
22. Liu R, Peng Y, Wu H, Diao X, Ye H, Huang X, Yi C, Mao H, Huang F, Yu X, Yang X. Uric acid to high-density lipoprotein cholesterol ratio predicts cardiovascular mortality in patients on peritoneal dialysis. Nutr Metab Cardiovasc Dis. 2021;31:561–9.
23. Skopp NA, Smolenski DJ, Schwesinger DA, Johnson CJ, Metzger-Abamukong MJ, Reger MA: Evaluation of a methodology to validate National Death Index retrieval results among a cohort of US. service members. Ann Epidemiol. 2017;27:397–400.
24. Mazidi M, Katsiki N, Mikhailidis DP, Banach M. Associations of serum uric acid with total and cause-specific mortality: Findings from individuals and pooling prospective studies. Atherosclerosis. 2020;296:49–58.
25. Yan Z, Xu Y, Li K, Liu L. Association between high-density lipoprotein cholesterol and type 2 diabetes mellitus: dual evidence from NHANES database and Mendelian randomization analysis. Front Endocrinol (Lausanne). 2024;15:1272314.
26. Westgard JO. Precision and accuracy: concepts and assessment by method evaluation testing. Crit Rev Clin Lab Sci. 1981;13:283–330.

27. Yang Y, Zhang J, Jia L, Su J, Ma M, Lin X. Uric acid to high-density lipoprotein cholesterol ratio predicts adverse cardiovascular events in patients with coronary chronic total occlusion. Nutr Metab Cardiovasc Dis. 2023;33:2471–8.
28. Xu L, Li D, Song Z, Liu J, Zhou Y, Yang J, Wen P. The association between monocyte to high-density lipoprotein cholesterol ratio and chronic kidney disease in a Chinese adult population: a cross-sectional study. Ren Fail. 2024;46:2331614.
29. Dogan M, Uz O, Aparci M, Atalay M. Confounders of uric acid level for assessing cardiovascular outcomes. J Geriatr Cardiol. 2016;13:197–8.
30. Zoccali C, Maio R, Mallamaci F, Sesti G, Perticone F. Uric acid and endothelial dysfunction in essential hypertension. J Am Soc Nephrol. 2006;17:1466–71.
31. Doehner W, Landmesser U. Xanthine oxidase and uric acid in cardiovascular disease: clinical impact and therapeutic options. Semin Nephrol. 2011;31:433–40.
32. Rabadi MM, Kuo MC, Ghaly T, Rabadi SM, Weber M, Goligorsky MS, Ratliff BB. Interaction between uric acid and HMGB1 translocation and release from endothelial cells. Am J Physiol Renal Physiol. 2012;302:F730-741.
33. Yan S, Zhang P, Xu W, Liu Y, Wang B, Jiang T, Hua C, Wang X, Xu D, Sun B. Serum Uric Acid Increases Risk of Cancer Incidence and Mortality: A Systematic Review and Meta-Analysis. Mediators Inflamm. 2015;2015:764250.
34. Tian X, Chen S, Zhang Y, Zhang X, Xu Q, Wang P, Wu S, Luo Y, Wang A. Serum uric acid variation and the risk of cardiovascular disease: A prospective cohort study. Eur J Intern Med. 2023;112:37–44.
35. Xie Y, Wang M, Zhang Y, Zhang S, Tan A, Gao Y, Liang Z, Shi D, Huang Z, Zhang H, et al. Serum uric acid and non-alcoholic fatty liver disease in non-diabetic Chinese men. PLoS ONE. 2013;8:e67152.
36. Zhang Y, Cai M, Dilimulati D, Lin Z, Sun H, Cui R, Fei H, Gao X, Zeng Q, Shao X, et al. Correlation Between Serum Uric Acid and Body Fat Distribution in Patients With Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 2021;12:782808.
37. Choi YJ, Shin HS, Choi HS, Park JW, Jo I, Oh ES, Lee KY, Lee BH, Johnson RJ, Kang DH. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. Lab Invest. 2014;94:1114–25.
38. Chen S, Chen D, Yang H, Wang X, Wang J, Xu C. Uric acid induced hepatocytes lipid accumulation through regulation of miR-149-5p/FGF21 axis. BMC Gastroenterol. 2020;20:39.
39. Endo Y, Fujita M, Ikewaki K. HDL Functions-Current Status and Future Perspectives. Biomolecules. 2023;13(1):105.
40. Chen JX, Li Y, Zhang YB, Wang Y, Zhou YF, Geng T, Liu G, Pan A, Liao YF. Nonlinear relationship between high-density lipoprotein cholesterol and cardiovascular disease: an observational and Mendelian randomization analysis. Metabolism. 2024;154:155817.
41. Andersson C, Johnson AD, Benjamin EJ, Levy D, Vasan RS. 70-year legacy of the Framingham Heart Study. Nat Rev Cardiol. 2019;16:687–98.
42. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117:743–53.
43. Chen Z, Cheang I, Qu Q, Zhu X, Fu Y, Gao R, Zhou Y, Li X. Associations of serum uric acid-to-high density lipoprotein cholesterol ratio with age-related diseases and mortality among older population in the United States. Arch Gerontol Geriatr. 2024;130:105707.
44. Yang Y, Zhang J, Jia L, Su J, Ma M, Lin X. The interaction between uric acid and high-density lipoprotein cholesterol on the prognosis of patients with acute myocardial infarction. Front Cardiovasc Med. 2023;10:1226108.
45. Zheng J, Cen K, Zhang J, Zhang H, Zhao M, Hou X. Uric acid levels and heart failure: A mendelian randomization study. Nutr Metab Cardiovasc Dis. 2024;34:1008–13.
46. Wittenbecher C, Eichelmann F, Toledo E, Guasch-Ferré M, Ruiz-Canela M, Li J, Arós F, Lee CH, Liang L, Salas-Salvadó J, et al. Lipid Profiles and Heart Failure Risk: Results From Two Prospective Studies. Circ Res. 2021;128:309–20.
47. Lokkanahalli SS, Handargal NH, Papali MM, Subash N. Serum Uric Acid and Lipid Levels in Patients With Acute Ischemic Stroke: A Cross-Sectional Study. Cureus. 2022;14:e28114.
48. Kurajoh M, Fukumoto S, Emoto M, Murase T, Nakamura T, Ishihara T, Go H, Yamamoto K, Nakatani S, Tsuda A, et al. Independent association of plasma xanthine oxidoreductase activity with serum uric acid level based on stable isotope-labeled xanthine and liquid chromatography/triple quadrupole mass spectrometry: MedCity21 health examination registry. Clin Chem Lab Med. 2020;58:780–6.
49. Yin JL, Yang J, Song XJ, Qin X, Chang YJ, Chen X, Liu FH, Li YZ, Xu HL, Wei YF, et al. Triglyceride-glucose index and health outcomes: an umbrella review of systematic reviews with meta-analyses of observational studies. Cardiovasc Diabetol. 2024;23:177.
50. Hashemi SM, Kheirandish M, Rafati S, Ghazalgoo A, Amini-Salehi E, Keivanlou MH, Abbaszadeh S, Saberian P, Rahimi A. The association between neutrophil and lymphocyte to high-density lipoprotein cholesterol ratio and metabolic syndrome among Iranian population, finding from Bandare Kong cohort study. Lipids Health Dis. 2024;23:393.
51. Tamaki S, Nagai Y, Shutta R, Masuda D, Yamashita S, Seo M, Yamada T, Nakagawa A, Yasumura Y, Nakagawa Y, et al. Combination of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios as a Novel Predictor of Cardiac Death in Patients With Acute Decompensated Heart Failure With Preserved Left Ventricular Ejection Fraction: A Multicenter Study. J Am Heart Assoc. 2023;12:e026326.

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