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Long-term cardiovascular risk and mortality associated with uric acid to HDL-C ratio: a 20-year cohort study in adults over 40

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Cardiovascular diseases (CVD) and mortality remain significant public health challenges, especially among middle-aged and older adults. However, their relationship with Uric Acid to High-Density Lipoprotein Cholesterol Ratio (UHR) has not been extensively studied in the US population. This study aimed to examine these associations in adults aged ≥ 40 based on the National Health and Nutrition Examination Survey (NHANES) 1999–2018. 29,742 participants' data in NHANES between 1999 and 2018 were retrospectively analyzed. Multivariable logistic regression, Cox proportional hazards models, restricted cubic spline (RCS) analyses, and subgroup analyses were used to assess the associations between UHR and various CVD outcomes. Among the participants, 4,505 (15.15%) reported a history of CVD. A positive association was observed between UHR and the risk of total CVD, including coronary heart disease, heart attack, heart failure, angina pectoris, and stroke ($P_{\text{all}} < 0.05$). UHR was associated with increased risks of all-cause mortality (HR = 1.02, 95% CI: 1.02–1.03) and CVD-specific mortality (HR = 1.03, 95% CI: 1.02–1.05). UHR had a linear dose-response relationship with CVD and a nonlinear relationship with all-cause mortality by RCS analyses. Subgroup analyses confirmed that these associations remained stable across different groups. The findings highlight UHR as a significant predictor of CVD risk and mortality in middle- and older-age adults. Given its strong association with adverse health outcomes, UHR can be a valuable indicator in facilitating the early identification of individuals at elevated cardiovascular risk.

Keywords UHR, Cardiovascular diseases, Cardiovascular disease mortality, All-cause mortality, Middle-aged and older adults

Abbreviations

AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
HDL-C	High-density lipoprotein cholesterol
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
RCS	Restricted cubic spline
VIFs	Variance inflation factors

Cardiovascular disease (CVD) is a significant contributor to mortality and morbidity in the US, particularly among adults aged 40 and older^{1–3}. Among US adults over 40, CVD affects between 3.6% and 24.2%⁴. With the aging population and increased chronic diseases such as hypertension and diabetes, the prevalence of CVD has risen substantially⁵. In addition to its health impact⁶, CVD imposes a significant economic burden; from 2019 to 2020, heart disease alone was responsible for an estimated \$252.2 billion in healthcare costs in the US⁷. Given its high mortality risk, early identification and intervention among high-risk populations are essential for reducing the burden of CVD.

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The development of CVD involves the interactions of multilevel factors encompassing genetic, metabolic, and environmental variables. Among these, sociodemographic variables (such as sex and age), lifestyle choices (such as smoking), and comorbidities (such as hypertension, diabetes, and cancer) are significant contributors. However, metabolic factors, particularly lipid metabolism disorders, are of special interest due to their ability to accelerate cardiovascular events through oxidative stress⁸, endothelial dysfunction^{9,10}, and atherosclerosis¹¹. Recent evidence has shown that lipid-related markers, such as high-density lipoprotein cholesterol (HDL-C)^{12–14}, may decrease CVD risk, potentially facilitating CVD management. Nonetheless, further research is needed to identify new biomarkers or clinical indicators for predicting or diagnosing cardiovascular risk in individuals aged 40 and older.

Recently, a novel composite lipid marker, Uric Acid to High-Density Lipoprotein Cholesterol Ratio (UHR), has gained recognition for its superior accuracy in predicting a range of conditions, including obesity¹⁵, hypertension^{16,17}, metabolic syndrome¹⁸, arrhythmias¹⁹, diabetes²⁰, non-alcoholic fatty liver disease²¹, insulin resistance²², and circulating α -klotho²³. The advantage of UHR lies in its combination of a risk factor for CVD (uric acid)²⁴ and a protective factor (HDL-C)^{13,25}, providing a more comprehensive risk assessment. Among these, uric acid has been linked to oxidative stress, endothelial dysfunction, and chronic inflammation, all of which contribute to atherosclerosis and cardiovascular events^{24,26}. Conversely, HDL-C plays a protective role by promoting cholesterol efflux and exhibiting anti-inflammatory properties^{25,27}. The balance between these two factors, quantified by UHR, may represent a promising composite biomarker for cardiovascular health, as it captures both risk and protective metabolic influences. Moreover, technological advancements in biosensing and point-of-care diagnostics have enabled more rapid, accessible, and user-friendly measurement of metabolic markers, supporting their potential role in preventive healthcare^{28,29}. For example, recent studies have demonstrated the development of highly sensitive and selective biosensors for uric acid detection using nanocomposite-based electrochemical platforms²⁸, as well as innovative dual-mode sensors for accurate cholesterol measurement²⁹. These technologies may facilitate the broader implementation of composite indicators such as UHR in clinical and home-based settings, allowing for real-time cardiovascular risk assessment. However, despite its potential, large-scale epidemiological studies investigating the association between UHR and CVD risk and mortality remain limited. Understanding this relationship is essential for determining whether UHR can be used as a practical and reliable biomarker for cardiovascular disease prevention, allowing for real-time cardiovascular risk assessment.

To explore this understudied area, we investigated the associations between UHR and various CVD outcomes among adults aged ≥ 40 based on the National Health and Nutrition Examination Survey. Our first hypothesis of a positive association between UHR and CVD risk was tested using weighted logistic regression and restricted cubic spline (RCS) curves. Our second hypothesis of positive associations between UHR and all-cause and CVD-specific mortality was tested using various analytical methods, including weighted Cox regression, RCS, and subgroup analyses. Our findings will help us understand the etiology of CVD. Moreover, understanding UHR's role in CVD is crucial for developing targeted prevention and treatment strategies, ultimately aiding in improving the care and management of this widespread and burdensome disease.

Methods

Study design and participants

This study was based on data from the National Health and Nutrition Examination Survey (NHANES), a nationwide program conducted by the U.S. Centers for Disease Control and Prevention to evaluate the health and nutritional status of the non-institutionalized civilian population. We used data from ten consecutive 2-year cycles spanning 1999 to 2018. Ethical approval was granted by the Research Ethics Review Board of the National Center for Health Statistics (NCHS). Informed consent was obtained from all individuals before any data collection took place.

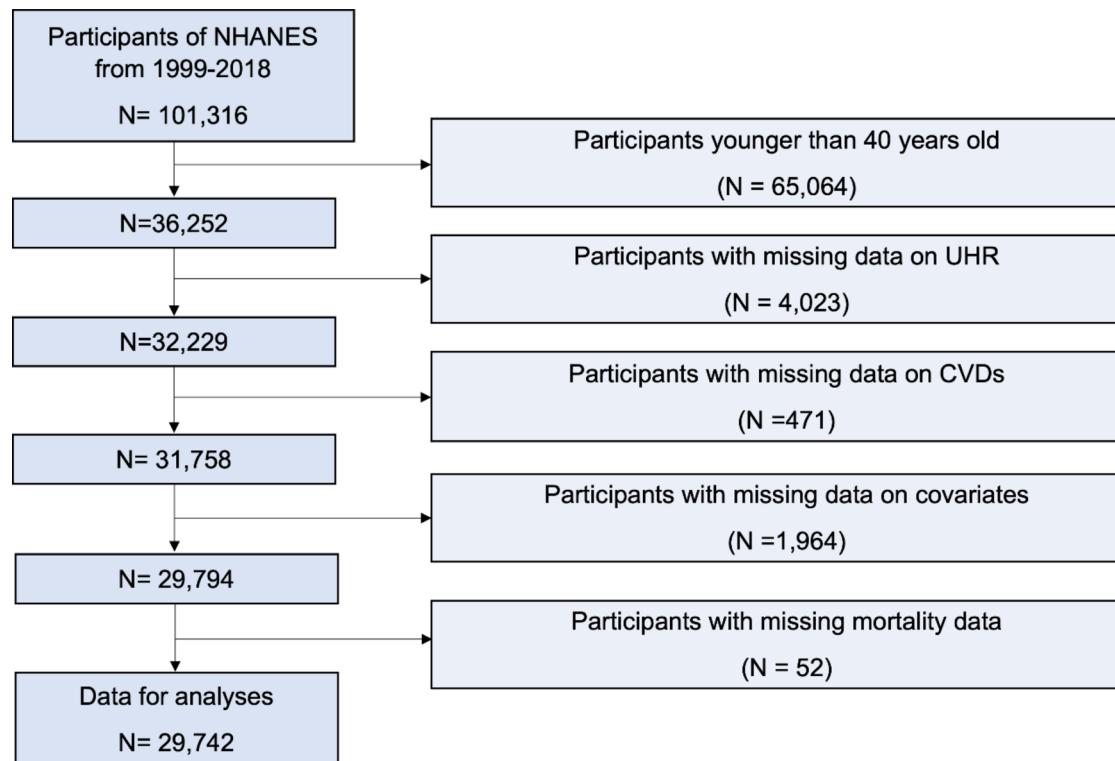
As illustrated in Fig. 1, participants were selected based on specific inclusion and exclusion criteria from an initial pool of 101,316 individuals. First, we excluded 65,064 participants under the age of 40. Next, participants with incomplete data on UHR (4,023 individuals), CVDs (471 individuals), or covariates (1,964 individuals) were also removed. Additionally, 52 participants without mortality data were excluded. Finally, 29,742 participants were included in the analysis.

Assessment of UHR

UHR is a percentage calculated as uric acid (mg/dL)/ HDL-C (mg/dL) * 100²³. Both uric acid and HDL-C measurements were obtained from blood samples collected in the morning after participants had fasted. Uric acid concentrations were determined using the uricase enzymatic method, which measures the production of allantoin and hydrogen peroxide after uric acid oxidation. HDL-C levels were quantified using a direct enzymatic method that selectively removes non-HDL cholesterol fractions, followed by enzymatic reactions converting HDL-C to a colored product measured photometrically. The measurement of uric acid and HDL-C in NHANES followed standardized laboratory procedures. The main reagents and instruments used for these assays are summarized in Table 1.

Assessment of CVDs

This research evaluated several CVD indicators, including coronary heart disease, heart attack, heart failure, angina pectoris, stroke, and total CVD. CVDs were determined based on self-reported physician diagnoses collected from the Medical Conditions section of the NHANES Questionnaire Data. Participants were asked if they had been informed by a physician or other medical staff that they had any of the CVDs mentioned above, with a positive response indicating the individual had total CVD. Each specific condition was similarly defined according to corresponding survey questions.

**Fig. 1.** Flow chart of the study participants.

Item	Vendor (Manufacturer)	Instrument model	Catalog number in NHANES
uricase enzymatic assay reagent	Beckman Coulter	Synchron LX20, UniCel DxC800	LBDHDD
HDL-C direct enzymatic assay reagent	Roche Diagnostics	Roche Modular P	LBXSUA

Table 1. Reagents and instruments used for uric acid and HDL-C measurements in NHANES 1999–2018.

Assessment of all-cause and CVD-specific mortality

We assessed both all-cause and CVD-specific mortality using publicly available mortality records from the NCHS. These records are linked with NHANES through the National Death Index (NDI) via probabilistic matching. Participants were followed up till death or the end of the survey to calculate the follow-up period. Deaths were coded according to the International Classification of Diseases, 10th Revision (ICD-10). CVD-specific mortality was identified using specific ICD-10 codes (I00-I09, I11, I13, I20-I51, and I60-I69).

Assessment of covariates

A wide range of covariates was included to control for potential confounders, including sociodemographics (race, sex, age, marital status, education), health-related variables (BMI, total cholesterol, smoking status), and medical history (hypertension, diabetes, cancer). A complete list of all variables used in the analysis, along with their corresponding NHANES variable names, data cycles, and coding details, is provided in Supplementary Table S1.

Analytical framework

The overall design and analytical approach of this study are illustrated in Fig. 2. This schematic provides a visual summary of the study population, exposure and outcome variables, covariates, and the statistical methods applied. Detailed variable names and coding information used in this framework can be found in Supplementary Table S1.

Statistical analysis

In line with general principles of model-based optimization under uncertainty as discussed in previous theoretical work³⁰, the selection of regression models and statistical procedures in this study was guided by the aim to balance interpretability, flexibility, and robustness in population-level health data analysis.

To ensure sample representativeness, we applied the NHANES standard sample weighting guidelines. Participants were grouped into quartiles based on UHR, and baseline characteristics across these quartiles were compared using chi-squared and Wilcoxon rank-sum tests. Weighted multivariable logistic regression models

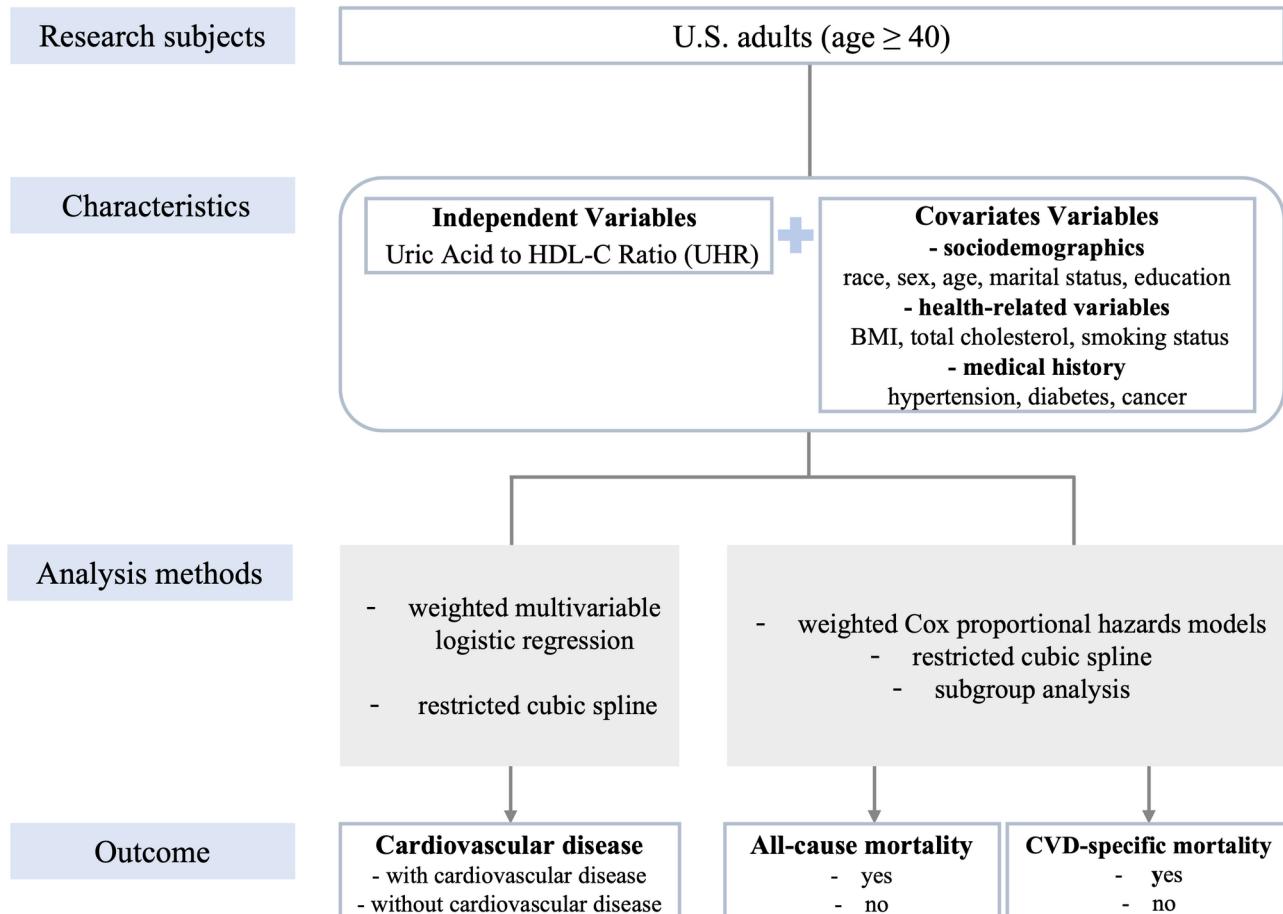


Fig. 2. Schematic overview of the study design and analytical approach.

were used to measure the association between UHR and various CVD outcomes, represented as odds ratios (ORs) and 95% confidence intervals (CIs). To explore the link between UHR and all-cause and CVD-specific mortality, we utilized weighted Cox proportional hazards models, represented as hazard ratios (HRs) with 95% CIs. P-values in these regression models were derived from Wald tests to assess the statistical significance of associations.

Three models were used, with Model 1 as the unadjusted model. Model 2 (partial adjustment) controlled for sociodemographics such as race, sex, age, marital status, and education. Model 3 (full adjustment) incorporated additional variables, including BMI, smoking status, hypertension, diabetes, total cholesterol, and a history of cancer. Variance inflation factors (VIFs) were calculated, all of which were below 5, indicating no significant multicollinearity between the variables. To test the linear dose-response relationships between UHR and CVD outcomes, restricted cubic spline (RCS) models were applied, fully adjusting for the covariates in Model 3. P-values for non-linearity in RCS models were derived from likelihood ratio tests. Subgroup analyses were employed to test the stability of results across different subgroups stratified by sociodemographics and medical history.

R software version 4.4.1 was used for data analyses. A P-value of <0.05 on two sides indicates statistical significance. Bonferroni correction ($\alpha=0.05/8=0.00625$ for subgroup interaction tests) was applied to account for multiple comparisons and establish significance.

Results

Sample characteristics

Among the 29,742 participants included in the analysis, 4,505 (15.15%) reported a history of CVD. Their mean age was 57.21 ± 11.89 years, and 47.38% were male. The average UHR was 11.27 ± 5.18 mg/dL. The weighted sample characteristics across UHR quartiles are shown in Table 2. The higher UHR quartile group tends to be older, have more males, and have a higher body mass index (BMI). Furthermore, the higher UHR quartile group has more CVD cases, including coronary heart disease, heart attack, heart failure, angina pectoris, and stroke, and higher all-cause and CVD-specific mortality. These findings suggest positive associations between UHR and CVD risk and mortality.

Characteristic	N ¹	Overall, N=119,403,471 ²	Q1 (< 7,708) N=29,883,374 ²	Q2 (7,708–10,612) N=29,874,746 ²	Q3 (10,612–14,285) N=29,849,977 ²	Q4 (> 14,285) N=29,795,373 ²	p-value ³
Sex	29,742						< 0.001
Male		14,584 (47.38%)	1,267 (14.87%)	2,974 (37.66%)	4,482 (59.41%)	5,861 (77.69%)	
Female		15,158 (52.62%)	5,528 (85.13%)	4,654 (62.34%)	3,118 (40.59%)	1,858 (22.31%)	
Age	29,742	57.21± (11.89)	56.85± (11.92)	57.51± (11.97)	57.42± (11.78)	57.06± (11.88)	0.013
Race	29,742						< 0.001
Mexican American		4,802 (5.89%)	989 (4.84%)	1,281 (6.33%)	1,328 (6.44%)	1,204 (5.94%)	
Non-Hispanic Black		2,439 (4.56%)	505 (3.71%)	697 (4.94%)	609 (4.69%)	628 (4.88%)	
Non-Hispanic White		14,037 (73.79%)	3,312 (75.81%)	3,397 (72.21%)	3,539 (73.33%)	3,789 (73.81%)	
Other Hispanic		5,986 (9.65%)	1,416 (9.79%)	1,594 (10.44%)	1,516 (9.57%)	1,460 (8.82%)	
Other Race		2,478 (6.11%)	573 (5.85%)	659 (6.09%)	608 (5.97%)	638 (6.54%)	
Education Level	29,742						< 0.001
Less than 9th grade		4,349 (6.77%)	803 (4.98%)	1,155 (7.02%)	1,164 (7.35%)	1,227 (7.75%)	
9–11th grade		4,301 (10.82%)	878 (8.95%)	1,130 (11.40%)	1,105 (10.62%)	1,188 (12.29%)	
High school graduate		6,837 (24.21%)	1,453 (21.30%)	1,735 (24.01%)	1,786 (25.23%)	1,863 (26.32%)	
Some college or AA degree		7,858 (29.42%)	1,852 (29.19%)	1,982 (28.86%)	2,006 (29.89%)	2,018 (29.74%)	
College, graduate or above		6,397 (28.78%)	1,809 (35.59%)	1,626 (28.71%)	1,539 (26.91%)	1,423 (23.90%)	
Marital Status	29,742						< 0.001
Married		17,573 (64.48%)	3,730 (62.38%)	4,334 (62.92%)	4,652 (65.79%)	4,857 (66.85%)	
Widowed		3,652 (8.93%)	963 (10.08%)	1,037 (10.41%)	897 (8.43%)	755 (6.79%)	
Divorced		3,961 (13.17%)	1,044 (15.03%)	1,053 (13.60%)	916 (11.91%)	948 (12.13%)	
Separated		1,081 (2.57%)	259 (2.61%)	310 (2.78%)	279 (2.84%)	233 (2.06%)	
Never married		2,241 (6.67%)	544 (6.32%)	586 (6.37%)	537 (6.68%)	574 (7.31%)	
Living with partner		1,234 (4.17%)	255 (3.58%)	308 (3.92%)	319 (4.33%)	352 (4.86%)	
BMI (kg/m ²)	29,742	29.16± (6.50)	25.80± (5.36)	28.75± (6.22)	30.31± (6.43)	31.79± (6.39)	< 0.001
Total Cholesterol (mg/dL)	29,742	202.49± (42.38)	207.92± (37.21)	203.77± (40.20)	200.26± (43.35)	197.98± (47.43)	< 0.001
HDL-C (mg/dL)	29,742	54.24± (17.01)	73.15± (16.64)	57.23± (10.50)	48.02± (8.06)	38.52± (7.21)	< 0.001
UHR	29,742	11.27± (5.18)	5.75± (1.17)	8.94± (0.85)	12.11± (1.04)	18.31± (4.25)	< 0.001
Smoking	29,742						< 0.001
Yes		14,624 (49.06%)	2,807 (42.89%)	3,526 (46.59%)	3,913 (51.52%)	4,378 (55.25%)	
No		15,118 (50.94%)	3,988 (57.11%)	4,102 (53.41%)	3,687 (48.48%)	3,341 (44.75%)	
Hypertension	29,742						< 0.001
Yes		13,606 (40.96%)	2,414 (29.76%)	3,290 (38.11%)	3,676 (44.69%)	4,226 (51.31%)	
No		16,136 (59.04%)	4,381 (70.24%)	4,338 (61.89%)	3,924 (55.31%)	3,493 (48.69%)	
Diabetes	29,742						< 0.001
Yes		5,160 (13.05%)	706 (6.64%)	1,203 (11.03%)	1,454 (15.22%)	1,797 (19.32%)	
No		24,582 (86.95%)	6,089 (93.36%)	6,425 (88.97%)	6,146 (84.78%)	5,922 (80.68%)	
Cancer	29,742						0.428
Yes		3,765 (13.42%)	828 (13.70%)	957 (12.89%)	979 (14.02%)	1,001 (13.08%)	
No		25,977 (86.58%)	5,967 (86.30%)	6,671 (87.11%)	6,621 (85.98%)	6,718 (86.92%)	
Total CVD	29,742						< 0.001
Yes		4,505 (12.42%)	618 (7.35%)	987 (10.77%)	1,221 (13.68%)	1,679 (17.89%)	
No		25,237 (87.58%)	6,177 (92.65%)	6,641 (89.23%)	6,379 (86.32%)	6,040 (82.11%)	
Heart Failure	29,742						< 0.001
Yes		1,315 (3.36%)	126 (1.50%)	225 (2.22%)	360 (3.52%)	604 (6.19%)	
No		28,427 (96.64%)	6,669 (98.50%)	7,403 (97.78%)	7,240 (96.48%)	7,115 (93.81%)	
Coronary heart disease	29,742						< 0.001
Yes		1,784 (5.24%)	199 (2.55%)	350 (3.86%)	490 (6.02%)	745 (8.56%)	
No		27,958 (94.76%)	6,596 (97.45%)	7,278 (96.14%)	7,110 (93.98%)	6,974 (91.44%)	
Angina pectoris	29,742						< 0.001
Yes		1,195 (3.57%)	164 (2.07%)	247 (2.86%)	325 (3.87%)	459 (5.49%)	
No		28,547 (96.43%)	6,631 (97.93%)	7,381 (97.14%)	7,275 (96.13%)	7,260 (94.51%)	
Heart attack	29,742						< 0.001
Yes		1,789 (4.95%)	205 (2.54%)	363 (3.85%)	480 (5.51%)	741 (7.93%)	
No		27,953 (95.05%)	6,590 (97.46%)	7,265 (96.15%)	7,120 (94.49%)	6,978 (92.07%)	
Stroke	29,742						< 0.001
Continued							

Characteristic	N ¹	Overall, N=119,403,471 ²	Q1 (< 7.708) N=29,883,374 ²	Q2 (7.708–10.612) N=29,874,746 ²	Q3 (10.612–14.285) N=29,849,977 ²	Q4 (> 14.285) N=29,795,373 ²	p-value ³
Yes		1,502 (3.88%)	245 (2.85%)	363 (3.77%)	394 (3.93%)	500 (4.98%)	
No		28,240 (96.12%)	6,550 (97.15%)	7,265 (96.23%)	7,206 (96.07%)	7,219 (95.02%)	
Death of cardiovascular diseases	29,742						< 0.001
Yes		1,618 (3.90%)	276 (2.80%)	342 (3.29%)	436 (3.95%)	564 (5.54%)	
No		28,124 (96.10%)	6,519 (97.20%)	7,286 (96.71%)	7,164 (96.05%)	7,155 (94.46%)	
Death of all-cause	29,742						< 0.001
Yes		6,298 (15.58%)	1,218 (12.89%)	1,491 (14.47%)	1,572 (14.99%)	2,017 (19.99%)	
No		23,444 (84.42%)	5,577 (87.11%)	6,137 (85.53%)	6,028 (85.01%)	5,702 (80.01%)	

Table 2. Baseline characteristics according to UHR quartiles: NHANES, 1999–2018 (weighted). UHR: Uric acid to High-density lipoprotein cholesterol ratio, CVD: Cardiovascular disease, BMI: Body mass index, TC: Total cholesterol, HDL-C: High-density lipoprotein-cholesterol. ¹N not Missing (unweighted). ²N (unweighted); (%) (weighted); Mean ± SD (weighted). ³Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

Relationship between UHR and CVDs

Table 3 presents the relationships between UHR and various CVDs using multiple logistic regression models, both with and without adjustments for covariates. The results indicate that UHR is significantly and positively correlated with total CVD, including coronary heart disease, heart attack, heart failure, angina pectoris, and stroke ($P_{\text{all}} < 0.05$).

A positive association between UHR and the total CVD risk was consistently observed in Model 1 (OR = 1.07, 95% CI: 1.06–1.08, $P < 0.001$), Model 2 (OR = 1.07, 95% CI: 1.06–1.08, $P < 0.001$), and Model 3 (OR = 1.04, 95% CI: 1.03–1.05, $P < 0.001$). Model 3 revealed that each unit increase in UHR was associated with a 4% increase in the total CVD risk. Quartile analysis further showed that the highest UHR quartile group had significantly higher total CVD risk than the lowest quartile group (OR = 1.60, 95% CI: 1.38–1.81, $P < 0.001$) after full adjustment.

The association between UHR and heart failure was similarly robust, with every unit increase in UHR corresponding to a 7% increased risk in Model 3 (OR = 1.07, 95% CI: 1.05–1.08, $P < 0.001$). Quartile comparisons showed that the highest UHR quartile group had over twice the risk of heart failure than the lowest quartile group (OR = 2.23, 95% CI: 1.69–2.95, $P < 0.001$).

For coronary heart disease, angina pectoris, and heart attack, UHR remained significantly associated with increased risk in all models, with risk increments of approximately 4% per unit increase in UHR. Participants in the highest quartile consistently exhibited significantly higher risks for these conditions compared to the lowest quartile. Finally, stroke risk was also positively associated with UHR, with a 3% increase in risk per unit of UHR in Model 3 (OR = 1.03, 95% CI: 1.01–1.04, $P < 0.001$). The highest UHR quartile group had a higher risk of stroke than the lowest quartile group (OR = 1.32, 95% CI: 1.04–1.67, $P = 0.024$).

RCS analysis investigating the relationship between UHR and CVDs

Figure 3 illustrates the flexible modeling of the relationship between UHR and various CVD types, including coronary heart disease, heart attack, heart failure, angina pectoris, stroke, and total CVD, using restricted cubic splines (RCS). In Model 3, UHR showed linear associations with heart attack, heart failure, angina pectoris, stroke, and total CVD ($P_{\text{overall}} < 0.001$, $P_{\text{nonlinear}} > 0.05$) and a nonlinear association with coronary heart disease ($P_{\text{overall}} < 0.001$, $P_{\text{nonlinear}} = 0.018$).

Associations between UHR and All-Cause and CVD-specific mortality

Over 9.14 years of follow-up, 6,298 participants (15.58%) died, of which 1,618 deaths (3.90%) were attributed to cardiovascular disease. Table 4 shows the associations between UHR and all-cause and CVD-specific mortality based on weighted Cox regression models, both unadjusted and adjusted for covariates. The analyses revealed a significant positive relationship between UHR and the two outcomes ($P < 0.05$).

For all-cause mortality, higher UHR consistently correlated with increased risk in all models, including Model 1 (HR = 1.03, 95% CI: 1.02–1.04), Model 2 (HR = 1.03, 95% CI: 1.02–1.04), and Model 3 (HR = 1.02, 95% CI: 1.02–1.03, $P < 0.001$). In Model 3, every one-unit increase in UHR corresponded to a 2% rise in mortality risk. Quartile analysis further revealed that the highest UHR quartile group had significantly higher all-cause mortality risk than the lowest quartile group (HR = 1.36, 95% CI: 1.15–1.61, $P < 0.001$).

Regarding cardiovascular disease mortality, a similar positive association was observed in all models. In Model 3, if UHR increased by one unit, CVD-specific mortality would increase by 3% (HR = 1.03, 95% CI: 1.02–1.05, $P < 0.001$). Quartile comparisons also highlighted that the highest UHR quartile group had a higher CVD-specific mortality risk than the lowest quartile group (HR = 1.37, 95% CI: 1.00–1.89, $P = 0.049$).

RCS analyses

RCS was applied within the Cox proportional hazards model further to test the linear association between UHR and mortality (Fig. 4). In Model 3, UHR presented a significant nonlinear relationship with all-cause mortality ($P_{\text{overall}} < 0.001$, $P_{\text{nonlinear}} < 0.001$) and a linear association with CVD-specific mortality ($P_{\text{overall}} < 0.001$, $P_{\text{nonlinear}} = 0.408$).

Exposure	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Total CVD						
UHR	1.07 (1.06,1.08)	<0.001	1.07 (1.06,1.08)	<0.001	1.04 (1.03,1.05)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.52 (1.33,1.73)	<0.001	1.40 (1.21,1.62)	<0.001	1.19 (1.03,1.39)	0.020
Quartile 3	2.00 (1.74,2.30)	<0.001	1.83 (1.58,2.13)	<0.001	1.33 (1.14,1.55)	0.001
Quartile 4	2.75 (2.40,3.15)	<0.001	2.53 (2.20,2.91)	<0.001	1.60 (1.38,1.85)	<0.001
<i>P</i> for trend		<0.001		<0.001		<0.001
Heart Failure						
UHR	1.10 (1.08,1.12)	<0.001	1.10 (1.08,1.12)	<0.001	1.07 (1.05,1.08)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.49 (1.15,1.93)	0.003	1.36 (1.03,1.79)	0.031	1.07 (0.82,1.41)	0.614
Quartile 3	2.39 (1.82,3.14)	<0.001	2.26 (1.70,3.01)	<0.001	1.44 (1.08,1.92)	0.012
Quartile 4	4.27 (3.39,5.39)	<0.001	4.15 (3.12,5.53)	<0.001	2.23 (1.69,2.95)	<0.001
<i>P</i> for trend		<0.001		<0.001		<0.001
Coronary Heart Disease						
UHR	1.08 (1.07,1.09)	<0.001	1.06 (1.05,1.08)	<0.001	1.04 (1.02,1.05)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.54 (1.23,1.91)	<0.001	1.27 (1.01,1.59)	0.043	1.10 (0.87,1.39)	0.413
Quartile 3	2.45 (1.95,3.07)	<0.001	1.83 (1.45,2.32)	<0.001	1.37 (1.08,1.74)	0.009
Quartile 4	3.58 (2.88,4.46)	<0.001	2.50 (2.00,3.14)	<0.001	1.65 (1.28,2.12)	<0.001
<i>P</i> for trend		<0.001		<0.001		<0.001
Angina Pectoris						
UHR	1.07 (1.05,1.08)	<0.001	1.06 (1.05,1.08)	<0.001	1.04 (1.02,1.05)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.39 (1.07,1.80)	0.013	1.29 (0.99,1.67)	0.059	1.09 (0.83,1.43)	0.515
Quartile 3	1.90 (1.49,2.43)	<0.001	1.74 (1.35,2.23)	<0.001	1.25 (0.96,1.62)	0.100
Quartile 4	2.75 (2.13,3.54)	<0.001	2.46 (1.89,3.21)	<0.001	1.52 (1.15,2.02)	0.004
<i>P</i> for trend		<0.001		<0.001		0.003
Heart Attack						
UHR	1.07 (1.06,1.08)	<0.001	1.06 (1.05,1.07)	<0.001	1.04 (1.03,1.05)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.54 (1.20,1.98)	0.001	1.26 (0.97,1.63)	0.078	1.12 (0.86,1.45)	0.392
Quartile 3	2.24 (1.76,2.85)	<0.001	1.66 (1.29,2.13)	<0.001	1.28 (0.99,1.66)	0.059
Quartile 4	3.31 (2.69,4.07)	<0.001	2.24 (1.80,2.80)	<0.001	1.54 (1.23,1.94)	<0.001
<i>P</i> for trend		<0.001		<0.001		0.001
Stroke						
UHR	1.04 (1.03,1.05)	<0.001	1.05 (1.04,1.06)	<0.001	1.03 (1.01,1.04)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.33 (1.04,1.70)	0.021	1.30 (1.00,1.68)	0.049	1.15 (0.89,1.48)	0.293
Quartile 3	1.39 (1.10,1.76)	0.007	1.44 (1.12,1.86)	0.004	1.11 (0.85,1.44)	0.442
Quartile 4	1.78 (1.45,2.19)	<0.001	1.94 (1.54,2.43)	<0.001	1.32 (1.04,1.67)	0.024
<i>P</i> for trend		<0.001		<0.001		0.045

Table 3. Association between the UHR and CVDs: NHANES,1999–2018 (weighted). Model 1: Unadjusted model. Model 2: Adjusted for age, sex, race, education level and marital status. Model 3: Additionally adjusted for BMI, smoking, hypertension, diabetes, total cholesterol, and cancer. UHR: Uric acid to High-density lipoprotein cholesterol ratio, OR: odds ratio, CI: confidence interval.

Subgroup analyses

Subgroup analyses were conducted to test whether the relationship between UHR and all-cause and CVD-specific mortality varied across various subgroups stratified by sociodemographics (e.g., race, sex, age, education, marital status) and medical history (e.g., diabetes, hypertension, and cancer). As shown in Table 5, the associations between UHR and both mortality outcomes remained stable across all subgroups ($P_{\text{interaction}} > 0.00625$), indicating no significant interactions with these stratification variables.

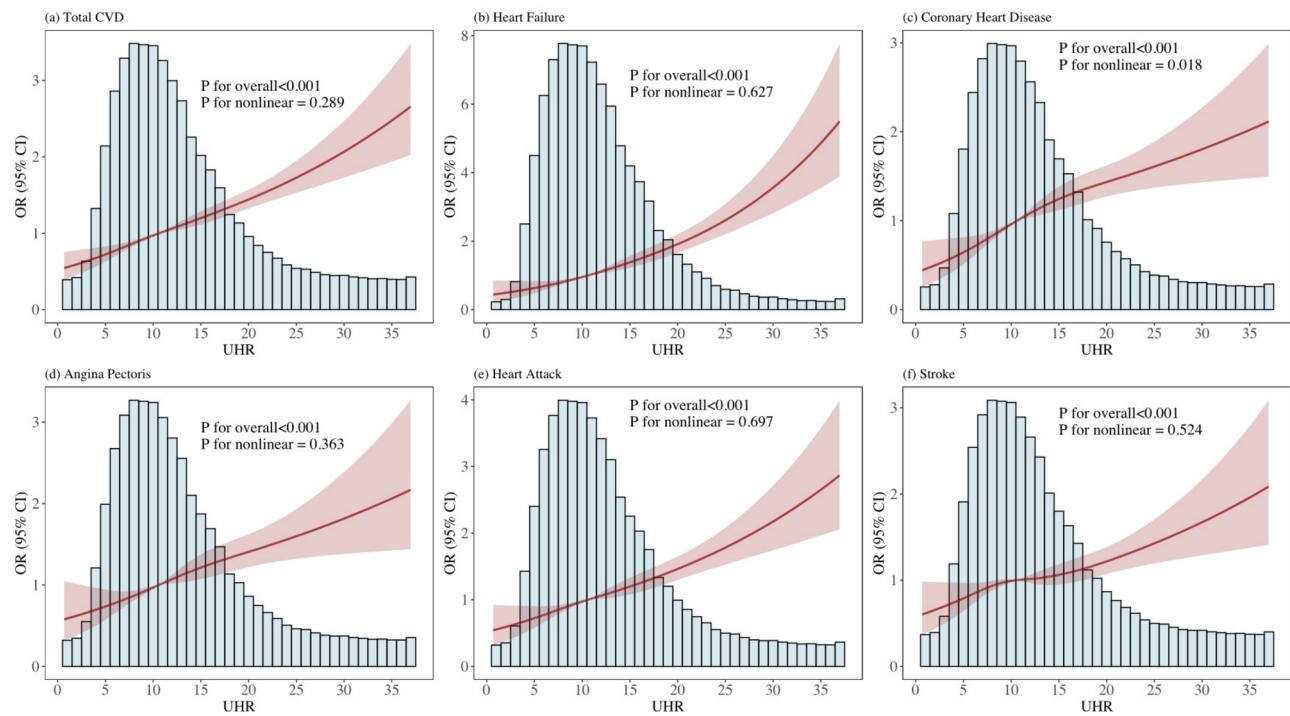


Fig. 3. Restricted cubic spline curve for the association between UHR and CVDs risk in model 3 (adjusted for age, sex, race, education levels, marital status, BMI, smoking, hypertension, diabetes, total cholesterol, and cancer). **(a)** Restricted cubic spline curve for the association between UHR and Total CVD. **(b)** Restricted cubic spline curve for the association between UHR and Heart Failure. **(c)** Restricted cubic spline curve for the association between UHR and Coronary Heart Disease. **(d)** Restricted cubic spline curve for the association between UHR and Angina Pectoris. **(e)** Restricted cubic spline curve for the association between UHR and Heart Attack. **(f)** Restricted cubic spline curve for the association between UHR and Stroke. Lines represent odds ratios (OR), and colored areas represent 95% confidence intervals (CI). UHR, Uric acid to High-density lipoprotein cholesterol ratio.

Exposure	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause mortality						
UHR	1.03 (1.02,1.04)	<0.001	1.03 (1.02,1.04)	<0.001	1.02 (1.02,1.03)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.12 (1.03,1.22)	0.011	0.93 (0.84,1.03)	0.165	0.96 (0.85,1.09)	0.512
Quartile 3	1.16 (1.07,1.27)	<0.001	0.94 (0.85,1.04)	0.248	0.98 (0.85,1.13)	0.745
Quartile 4	1.57 (1.43,1.74)	<0.001	1.28 (1.15,1.44)	<0.001	1.36 (1.15,1.61)	<0.001
P for trend		<0.001		<0.001		<0.001
Cardiovascular disease mortality						
UHR	1.04 (1.03,1.06)	<0.001	1.05 (1.04,1.06)	<0.001	1.03 (1.02,1.05)	<0.001
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.17 (0.99,1.38)	0.067	0.96 (0.81,1.15)	0.677	0.90 (0.72,1.12)	0.348
Quartile 3	1.41 (1.20,1.66)	<0.001	1.13 (0.95,1.34)	0.163	0.99 (0.77,1.28)	0.957
Quartile 4	2.01 (1.68,2.39)	<0.001	1.64 (1.36,1.97)	<0.001	1.37 (1.00,1.89)	0.049
P for trend		<0.001		<0.001		0.043

Table 4. Association between the UHR and mortality: NHANES,1999–2018 (weighted). Model 1: Unadjusted model. Model 2: Adjusted for age, sex, race, education level and marital status, Model 3: Additionally adjusted for BMI, smoking, hypertension, diabetes, total cholesterol, and cancer. UHR: Uric acid to High-density lipoprotein cholesterol ratio, HR: Hazard ratio, CI: confidence interval.

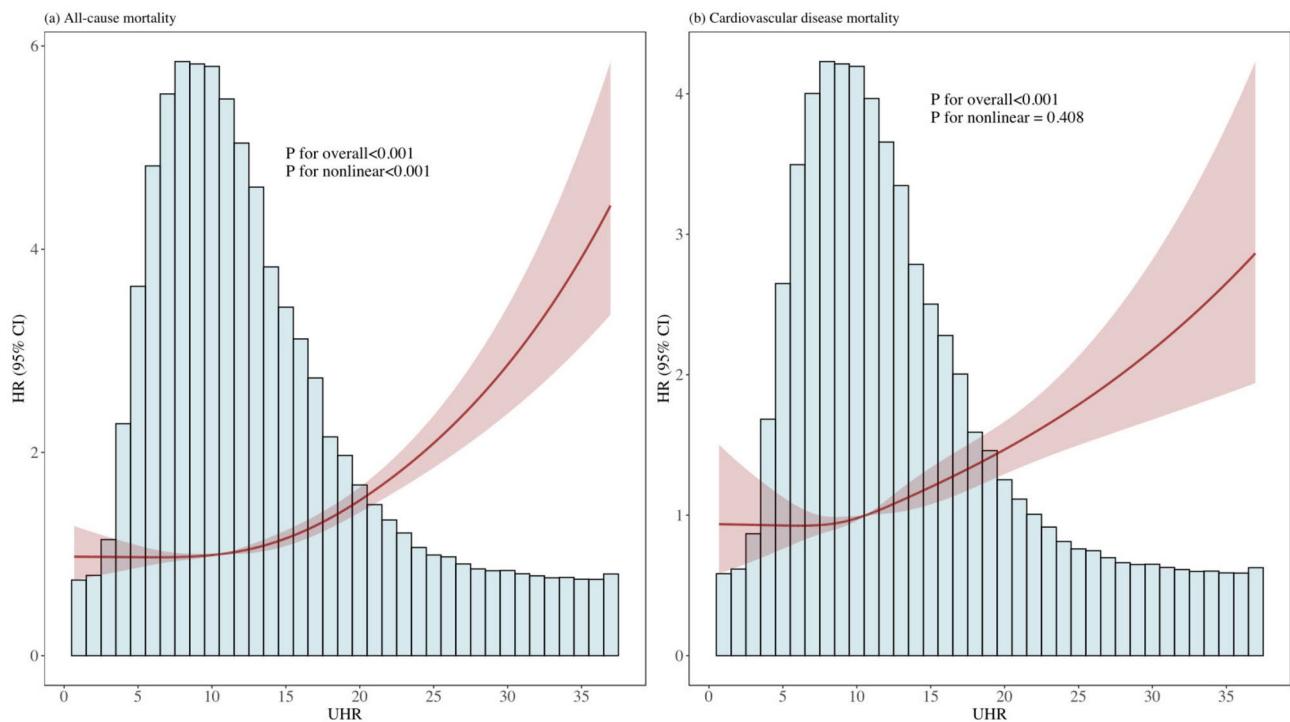


Fig. 4. Restricted cubic spline curve for the association between UHR and mortality in model 3 (adjusted for age, sex, race, education levels, marital status, BMI, smoking, hypertension, diabetes, total cholesterol, and cancer). **(a)** Restricted cubic spline curve for the association between UHR and All-cause mortality. **(b)** Restricted cubic spline curve for the association between UHR and Cardiovascular disease mortality. Lines represent hazard ratios (HR), and colored areas represent 95% confidence intervals (CI). UHR, Uric acid to High-density lipoprotein cholesterol ratio.

Discussion

As far as we know, our study is the first to examine the association between UHR and CVD outcomes in adults aged ≥ 40 based on a nationwide survey of NHANES. Our findings confirm a significant positive correlation between UHR and CVDs (coronary heart disease, heart attack, heart failure, angina pectoris, stroke, and total CVD), consistent across various models and analytical approaches. Furthermore, UHR was significantly associated with all-cause and CVD-specific mortality across different models and analytical methods. Additionally, no substantial differences were observed in this relationship across various subgroups. Our study suggests that UHR can be used as a critical clinical prognostic indicator for CVD risk and mortality.

CVDs are among the most prevalent health issues affecting adults aged 40 and above. However, few studies have investigated the relationship between UHR and CVD risk. Several studies have supported the role of UHR as a predictive marker for cardiovascular events. For instance, a study conducted in a Korean non-diabetic population demonstrated that UHR was positively associated with the incidence of ischemic heart disease, including angina pectoris³¹. Additionally, research on acute coronary syndrome patients showed that UHR is significantly associated with plaque rupture, a critical event in coronary artery disease progression and that it outperforms traditional lipid markers in predicting this risk³². Furthermore, elevated UHR has been linked to higher CVD-specific mortality, particularly in patients with certain metabolic disorders¹⁹. By confirming the positive correlations between UHR and CVD risk and mortality, our study builds on these findings. The results emphasize that UHR plays an essential role in the development of CVD, suggesting that UHR could emerge as a novel biomarker for cardiovascular risk assessment. This biomarker not only provides insights into oxidative stress and lipid metabolism imbalance but also offers potential clinical utility for identifying high-risk individuals at an early stage.

The UHR reflects the interplay between two biomarkers with distinct physiological roles—uric acid and HDL-C, both of which are important in the pathogenesis of CVDs. Uric acid, a byproduct of purine metabolism, has antioxidant properties under normal conditions^{33,34}. However, when its levels are elevated, the risk of inflammation, oxidative stress, and endothelial dysfunction also increase, all of which are critical drivers in the progression of CVDs^{35,36}. Alternatively, HDL-C plays an essential role in cardiovascular protection, primarily through its anti-inflammatory, endothelial-protective, and antioxidant properties^{37–40}. This study showed that UHR was significantly associated with various CVDs, including coronary heart disease, heart attack, heart failure, angina pectoris, stroke, and total CVD. This indicates that as UHR increases, the balance between these two biomarkers is disrupted, with elevated uric acid levels exacerbating pro-inflammatory and oxidative processes, thereby promoting vascular damage and atherosclerosis. Concurrently, reduced HDL-C levels reflect a diminished capacity to mitigate these adverse processes. This imbalance appears to be a key

Characteristic	All-cause mortality		Cardiovascular disease mortality	
	HR (95%CI)	P for interaction	HR (95%CI)	P for interaction
Sex		0.007		0.383
Male	1.04(1.03,1.05)		1.04(1.02,1.05)	
Female	1.07(1.05,1.08)		1.05(1.02,1.07)	
Race		0.118		0.177
Mexican American	1.02(1.01,1.04)		1.03(1.00,1.06)	
Non-Hispanic Black	1.05(1.02,1.08)		1.05(1.02,1.09)	
Non-Hispanic White	1.06(1.04,1.07)		1.04(1.03,1.06)	
Other Hispanic	1.05(1.04,1.07)		1.04(1.01,1.06)	
Other Race	1.04(1.01,1.08)		0.97(0.91,1.05)	
Education Level		0.656		0.804
Less than 9th grade	1.04(1.02,1.05)		1.02(1.00,1.04)	
9–11th grade	1.05(1.03,1.07)		1.03(1.01,1.06)	
High school graduate	1.05(1.03,1.06)		1.04(1.02,1.06)	
Some college or AA degree	1.05(1.04,1.07)		1.06(1.03,1.08)	
College, graduate or above	1.06(1.04,1.08)		1.05(1.02,1.08)	
Marital Status		0.197		0.533
Married	1.05(1.04,1.06)		1.04(1.03,1.06)	
Widowed	1.05(1.03,1.07)		1.02(0.99,1.04)	
Divorced	1.07(1.05,1.09)		1.06(1.03,1.09)	
Separated	1.04(1.01,1.08)		1.01(0.96,1.07)	
Never married	1.03(1.00,1.05)		1.05(1.02,1.09)	
Living with partner	1.04(1.00,1.07)		1.03(0.96,1.10)	
Smoking		0.476		0.121
Yes	1.04(1.03,1.06)		1.04(1.03,1.06)	
No	1.06(1.04,1.07)		1.04(1.02,1.06)	
Diabetes		0.89		0.062
Yes	1.05(1.03,1.06)		1.03(1.01,1.05)	
No	1.05(1.04,1.06)		1.04(1.03,1.06)	
Hypertension		0.708		0.612
Yes	1.05(1.04,1.06)		1.04(1.02,1.06)	
No	1.05(1.03,1.06)		1.04(1.02,1.06)	
Cancer		0.229		0.944
Yes	1.04(1.02,1.06)		1.04(1.02,1.07)	
No	1.05(1.04,1.06)		1.04(1.02,1.05)	

Table 5. Subgroup analysis of the associations between UHR and all-cause and cardiovascular mortality. CI, confidence interval; HR, hazard ratio.

factor in the positive association between UHR and CVD risk. These findings support the conceptual rationale for UHR, which integrates two metabolically antagonistic components into a single risk index—reflecting the dynamic interplay between oxidative stress and lipid protection in CVD pathophysiology. In addition, UHR was consistently associated with both all-cause and CVD-specific mortality across different models and analytical approaches, which further emphasizes the predictive value of UHR. Elevated UHR not only suggests an increased cardiovascular burden, but may also serve as an indicator of broader metabolic disturbances that contribute to overall mortality. Additionally, the lack of significant subgroup differences in these relationships suggests that UHR is a broadly applicable marker across diverse populations, making it a potentially valuable tool for widespread clinical use.

The clinical implications of this study lie in the identification of UHR as a promising biomarker for predicting CVD risk and mortality. By emphasizing the association between UHR and CVD, this research introduces a new avenue for clinicians to enhance risk assessment, particularly among individuals aged 40 and above. Routine evaluations of UHR in clinical practice could help identify individuals at high risk for CVD events, facilitating the development of tailored prevention strategies and treatment plans. For instance, patients with elevated UHR could benefit from proactive measures such as lifestyle modifications (dietary and exercise interventions) and pharmacological treatments (statins or uric acid-lowering agents). Moreover, recognizing UHR's role in all-cause and CVD-specific mortality can further refine predictive models, allowing for more precise risk stratification and targeted interventions aimed at improving long-term outcomes. The integration of UHR into clinical practice has the potential to enhance early detection, personalize therapeutic approaches, and optimize the prevention and management of cardiovascular conditions. Moreover, with the advancement of biosensor technologies that

allow for point-of-care testing of uric acid and HDL-C, UHR may become a feasible, low-cost marker in routine screening settings. Its integration into clinical practice could complement existing risk models and enable more proactive, personalized CVD prevention strategies. Looking ahead, further investigation into the molecular mechanisms by which UHR influences cardiovascular pathophysiology will provide deeper insights into its clinical utility and potential therapeutic targets.

Strengths, limitations, and challenges

This study utilized representative data from a 20-year nationwide survey conducted in the US. We employed a variety of analytical methods, including weighted logistic regression, weighted Cox regression, RCS, and subgroup analyses, to explore the association between UHR and CVD risk and mortality. Our results indicate a potential dose-response relationship between UHR and these outcomes. Notably, we were the first to identify that UHR was associated with an increased risk of CVD and mortality, positioning it as a promising marker for future risk prediction.

However, our study has several limitations. First, the cross-sectional design cannot establish causality between UHR and CVDs. Future longitudinal studies are needed to explore their causal associations. Second, CVDs were determined based on self-reported questionnaires that are subject to recall bias. Future studies should incorporate objective measurements for more accurate assessments. Third, this study only evaluated the prognostic value of baseline UHR and did not examine how changes in UHR over time may be linked to mortality. Further studies should use multiple UHR measurements to assess how its fluctuations may influence all-cause and CVD-specific mortality over time. Fourth, our subgroup analyses were limited to certain sample characteristics, which may not have accounted for other potential confounding factors. Future research should include broader subgroup analyses to address these limitations.

In addition to these limitations, there are several potential challenges in applying UHR in clinical practice and public health. First, while both uric acid and HDL-C are routinely measured in some settings, UHR is not yet an established marker in cardiovascular risk guidelines, and its clinical cut-off points remain undefined. Second, the interpretation of UHR may be influenced by demographic or comorbidity-related factors (e.g., chronic kidney disease, gout, or liver dysfunction), which may complicate its clinical application. These issues highlight the need for further standardization, validation, and prospective evaluation of UHR before it can be widely adopted.

Conclusions

This study confirms that UHR is associated with an increased risk of CVD and mortality and can be used as an effective indicator for CVD risk prediction. Our results provide new insights into the link between lipid metabolism disorders and cardiovascular diseases. The predictive ability of UHR in CVD and mortality risk is suggested to be validated by further prospective studies in the future, which will be crucial in guiding the prevention and treatment of angina and other related conditions.

Data availability

The data underlying this study are freely accessible to all interested researchers through the National Health and Nutrition Examination Survey (NHANES) database. The data can be obtained by visiting the following website: <https://wwwn.cdc.gov/nchs/nhanes/>.

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Author contributions

YC conceived and designed the study. YC performed the data analysis, interpreted the results, and drafted the manuscript. WZ provided critical revisions and contributed to the refinement of the manuscript. All authors have read and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The NHANES protocols were approved by the Institutional Review Board of the National Center for Health Statistics (https://www.cdc.gov/nchs/nhanes/about/erb.html?CDC_AAref_Val=https://www.cdc.gov/nchs/nhanes/irba98.htm). Written informed consent was obtained from all participants.

Additional information

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