Diabetology & Metabolic Syndrome

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Impact of metabolic abnormalities on the association between normal-range urinary albumin-to-creatinine ratio and cardiovascular mortality: evidence from the NHANES 1999–2018

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Abstract

Background The urinary albumin to creatinine ratio (UACR) is associated with adverse cardiovascular outcomes, even when within the normal range. However, the potential modification of this effect by metabolic abnormalities remains unclear. This study explored whether metabolic abnormalities modify the association between normal-range UACR and cardiovascular mortality.

Methods This cohort study included 27,298 U.S. adults from the National Health and Nutrition Examination Survey 1999–2018, with mortality follow-up through December 31, 2019. Normal UACR (< 30 mg/g) was considered. Metabolic abnormalities were categorized into three groups based on the number of metabolic abnormality components: metabolic health (0 components), pre-metabolic syndrome (Pre-MetS, 1–2 components), and metabolic syndrome (MetS, 3–5 components). Multivariable Cox proportional hazards regression was used to estimate the association between normal UACR and cardiovascular mortality, stratified by metabolic abnormality groups.

Results Over a median follow-up of 9.67 years, 764 cardiovascular deaths occurred. In the fully adjusted model, higher normal UACR was associated with an increased risk of cardiovascular death in metabolically abnormal individuals, but not in metabolically healthy individuals. When UACR was divided into tertiles, the highest tertile was associated with a 60% and 79% higher risk of cardiovascular mortality in the Pre-MetS and MetS groups, respectively, compared with the lowest tertile (Pre-MetS: HR, 1.60 [95% CI: 1.19–2.15]; MetS: HR, 1.79 [95% CI: 1.34–2.41]).

Conclusion A higher normal UACR was associated with an increased risk of cardiovascular death in metabolically abnormal individuals, underscoring the need for early renal risk management in this population.

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Keywords Urinary albumin-to-creatinine ratio, Metabolic abnormalities, Cardiovascular mortality, American adults

Introduction

Chronic kidney disease (CKD) represents a significant global health issue [1, 2]. It frequently coexists with hypertension, diabetes, and obesity, substantially increasing the incidence and mortality rates of cardiovascular disease (CVD) [2]. In the United States, CKD affects over 35.5 million adults, representing 14% of the population [3]. Unfortunately, the early stages of CKD are often asymptomatic, leading to delayed diagnosis [4]. The urinary albumin to creatinine ratio (UACR) serves as a critical indicator of glomerular injury, significantly contributing to the early diagnosis of CKD [2]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, UACR is recommended due to its excellent specificity and sensitivity. A UACR threshold of 30 mg/g or higher is indicative of renal damage [5]. Substantial evidence indicates that both microalbuminuria (UACR 30–300 mg/g) and macroalbuminuria (UACR > 300 mg/g) are associated with the progression to end-stage renal disease [6, 7]. Furthermore, research also shows that even normal UACR levels (< 30 mg/g) are linked to increased risks of CVD, and cardiovascular mortality [8–11]. Given these findings, it is crucial to identify individuals at high risk for elevated UACR within the traditionally considered normal range. Early detection and targeted management can prevent CKD progression and reduce associated cardiovascular risks and mortality.

Metabolic abnormalities associated with high-fat and high-carbohydrate diets, such as obesity, diabetes, atherogenic dyslipidemia, and hypertension, have surged over the past few decades, paralleling the rise in CKD prevalence [12]. Metabolic-related CVD is a major contributor to mortality and morbidity worldwide [13]. Furthermore, growing evidence suggests that these metabolic abnormalities are significant risk factors for the development and progression of CKD [14, 15]. Given the bidirectional and additive effects of renal insufficiency and metabolic abnormalities on CVD [16], it is critical to explore their combined impact on cardiovascular mortality. Specifically, the traditionally considered normal renal function (UACR < 30 mg/g) may have different effects when metabolic abnormalities are present. While associations between normal UACR levels and cardiovascular outcomes are well-documented, there is still limited understanding of how metabolic abnormalities influence the relationship between normal-range UACR and cardiovascular mortality.

To address this gap, we utilized data from a national survey of the U.S. general population linked to mortality data, to examine how metabolic abnormalities influence the association between normal UACR and cardiovascular mortality.

Methods

Study design and participants

The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS), utilizes a complex, stratified probability sampling method to survey the noninstitutionalized US population. Data from NHANES were collected via interviews, physical assessments, and laboratory evaluations of blood and urine specimens collected from participants. This study used 10 cycles of the continuous NHANES from 1999 to 2018. Of the 55,081 participants aged 20 years or older, we excluded those with missing measurements for waist circumference, blood pressure, high-density lipoprotein (HDL), triglycerides (TG), and fasting plasma glucose (FPG) (n = 7,118); those lacking data on urine albumin, urine creatinine, estimated glomerular filtration rate (eGFR), and UACR ≥ 30 mg/g (n = 8,396); those missing information on relevant covariates (n = 12,236); and those with unclear mortality status (n = 33). The final analytical cohort comprised 27,298 participants (see Supplement Figure S1).

UACR definition and grouping

Urine samples were collected by trained investigators and frozen at -20 °C before being transported to the laboratory. A solid-phase fluorescence immunoassay measured urine albumin levels. Before 2007, urinary creatinine was measured using the kinetic Jaffe rate method. After 2007, an enzymatic method was employed for creatinine measurement. Comprehensive details of laboratory testing procedures are available on the NHANES website [17]. To minimize discrepancies in urine creatinine measurement techniques, we applied the NHANES-endorsed algorithm to adjust creatinine levels for data collected before 2007 [18]. UACR is calculated by dividing urine albumin by urine creatinine. Participants were classified into tertiles according to their UACR levels within the normal range: low (< 4.62 mg/g), medium (4.62–7.94 mg/g), and high (> 7.94 to < 30 mg/g).

Metabolic abnormalities definition and grouping

All relevant metabolic factors were measured at the time of the initial NHANES investigation. Metabolic abnormalities were defined based on the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria [13], which included the following: central obesity (waist circumference ≥ 102 cm for men or ≥ 88 cm for women), hypertriglyceridemia

(serum TG≥150 mg/dL), dyslipidemia (HDL cholesterol<40 mg/dL for men or <50 mg/dL for women), hypertension (systolic/diastolic blood pressure≥130/85 mmHg or treatment for hypertension), and hyperglycemia (FPG≥100 mg/dL or treatment for diabetes). According to the NCEP-ATP III definitions of metabolic syndrome (MetS), metabolic abnormalities were divided into three groups based on the number of components: metabolically healthy (0 components), Pre-MetS (1–2 components), and MetS (3–5 components).

Outcomes and covariates

The primary outcome was cardiovascular mortality, classified according to the International Classification of Diseases, 10th Edition (I00-I09, I11, I13, and I20-I51). We linked the 1999–2018 NHANES data with National Death Index (NDI) mortality data using probabilistic matching. The cause-specific mortality data in the NDI have been demonstrated to accurately classify deaths with a minimal likelihood of misclassification [19]. Mortality follow-up data were available until December 31, 2019. The follow-up duration was calculated by measuring the interval between each participant's baseline examination and the last known survival date or censoring date from the mortality file.

The demographic and clinical characteristics of the study participants included age, sex (male or female), ethnic (Non-Hispanic White, Non-Hispanic Black, Mexican American, or Other race/multiracial), education status (less than high school, high school, or more than high school). Smoking status was categorized as never, former, or current based on participants' reports of having smoked at least 100 cigarettes in their lifetime and their current smoking status. The poverty income ratio reflects the ratio of annual household income to the federal poverty line. Physical activity was classified into three categories: low (<600 MET-minutes per week), moderate (600–3000 MET-minutes per week), and high (≥3000 MET-minutes per week). CVD was defined by self-reported diagnosis of five major cardiovascular events: congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke. Cancer status was also self-reported. The eGFR was calculated using the abbreviated Chronic Kidney Disease Epidemiology Collaboration equation [20].

Statistical analyses

All analyses accounted for the complex sampling strategy of NHANES, including stratification, clustering, and weights [21]. Baseline and metabolic factor distributions were estimated by dividing participants into tertiles (low, medium, high) based on UACR levels. Continuous variables are expressed as mean±SE, while categorical variables are presented as percentages. Differences between UACR tertiles were evaluated using linear regression for continuous variables and chi-square tests for categorical variables.

The hazard ratio (HR) and 95% confidence interval (CI) for cardiovascular mortality associated with normal UACR were estimated using a multivariate Cox proportional hazards regression model. UACR was analyzed both as a continuous variable (per 10 mg/g increment) and as a categorical variables (UACR tertiles) across the cohort and within subgroups defined by metabolic abnormalities. We adjusted for potential confounders using two multivariate models with progressive degrees of adjustment. Model 1 adjusted for age, sex, ethnicity, education level, poverty income ratio, smoking status, physical activity level, and eGFR. Model 2 was further adjusted for self-reported cancer and CVD. The associations between tertiles of normal UACR and cardiovascular mortality were analyzed within each metabolic abnormality group, with the lowest tertile serving as the reference. Combined effects were assessed using tertile groupings of UACR (low, medium, high) and metabolic abnormality groupings (metabolically healthy, Pre-MetS, and MetS). Trend tests for the 9-categorical groups used the metabolically healthy and low UACR groups as references. Kaplan-Meier survival curves visualized survival rates for the 9-categorical groups, and log-rank tests assessed the significance of associations between groups. Restricted cubic spline regressions with three knots were used to evaluate the dose-response relationship between continuous UACR levels and cardiovascular mortality. The likelihood ratio test evaluated non-linearity.

Subgroup analyses were conducted by age (<60 years, ≥60 years) and sex (male, female) to estimate the effect of continuous normal UACR on cardiovascular mortality within each metabolic abnormality stratum. Effect modification was assessed by including multiplicative interaction term in the models and using the likelihood ratio test. Sensitivity analyses were performed to test the robustness of the findings by: incorporating continuous variables for metabolic factors (waist circumference, systolic blood pressure, diastolic blood pressure, FPG, TG, and HDL) as covariates in the final model; excluding individuals with impaired kidney function (eGFR<60 mL/min/1.73 m^2); and omitting subjects who passed away within the first two years of follow-up to minimize reverse causality bias.

R version 4.2.0 and Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) were used for the analysis. All statistical analyses were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Study participants and baseline characteristics

The study included 27,298 participants aged 20 and older from NHANES from 1999 to 2018. The age (mean ± SE) was 44.94 ± 0.21 years, and 52.09% of the participants were male. A total of 23,165 individuals (84.86%) were identified as having metabolic abnormalities. Among them, 19,781 subjects (72.46%) had central obesity, 7,207 (26.40%) had hyperglycemia, 9,033 (33.09%) had hypertriglyceridemia, 7,904 (28.95%) had dyslipidemia, and 8,543 (31.30%) had hypertension. Figure 1 displays the distribution of components of metabolic abnormalities. Baseline demographics by tertiles of UACR are presented in Table 1. Participants with higher UACR had a marginally lower mean eGFR. Compared to the lower UACR group, those in the higher UACR group exhibited a greater prevalence of all individual metabolic abnormality components, Pre-MetS, and MetS. The baseline characteristics were slightly different between the participants with complete data and those with missing variables for the metabolic component (see Supplementary Table S1).

Association of metabolic abnormalities and normal UACR with cardiovascular mortality

The median follow-up period was 9.67 years (interquartile range: 5.42–14.25 years), during which 764 cardiovascular deaths occurred. In the fully adjusted models, the estimated HR for a 10 mg/g increase in normal UACR was 1.39 (95% CI: 1.25–1.54) for cardiovascular mortality (Fig. 2). The restricted cubic spline curve showed a nearly linear relationship between normal UACR and cardiovascular mortality (Fig. 2). As the number of metabolic abnormal components increased from 1 to 5, the HRs for cardiovascular mortality were 1.13 (95% CI: 0.79–1.62), 1.33 (95% CI: 0.95–1.87), 1.48 (95% CI: 1.05–2.08), 1.50 (95% CI: 1.05–2.16), and 1.67 (95% CI: 1.10–2.53), respectively, compared with the metabolically healthy group. When metabolic abnormality was considered as a continuous variable, the hazard of cardiovascular death increased by 10% (HR: 1.10, 95% CI: 1.04–1.17) for each additional component. Furthermore, within the metabolic abnormality group, the hazard of cardiovascular mortality increased by 25% in the Pre-MetS group (HR: 1.25, 95% CI: 0.90–1.74) and by 50% in the MetS group (HR: 1.50, 95% CI: 1.08–2.09), compared to the metabolically healthy group (see Fig. 2).

Combined association of normal UACR and metabolic abnormalities with cardiovascular mortality

Table 2 displays the relationship between normal UACR and cardiovascular mortality within the metabolic abnormality strata. Continuous normal UACR was significantly associated with an elevated risk of cardiovascular mortality in the Pre-MetS and MetS groups, but not among metabolically healthy individuals. When continuous UACR was divided into tertiles, the highest UACR tertiles in both the Pre-MetS and MetS groups were linked to a significantly higher risk of cardiovascular mortality compared to the lowest tertiles. The adjusted HRs increased by 60% and 79% in the Pre-MetS (HR: 1.60, 95% CI: 1.19–2.15) and MetS (HR: 1.79, 95% CI: 1.34–2.41) groups, respectively. However, this association was not observed in metabolically healthy participants (HR: 1.02, 95% CI: 0.46–2.27).

We further explored the combined impact of normal UACR and metabolic abnormalities on cardiovascular death by integrating UACR tertiles and metabolic abnormality categories into nine joint exposure variables. Among these combinations, participants with higher normal UACRs in the Pre-MetS and MetS groups

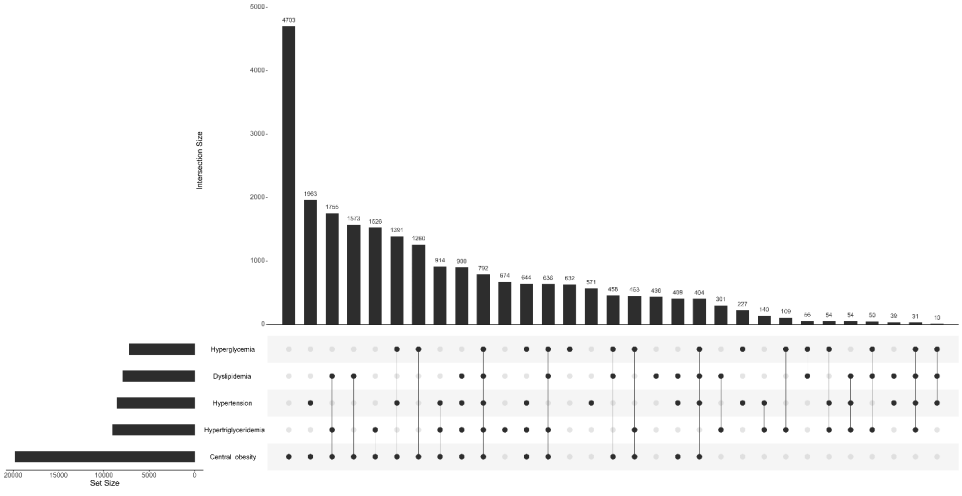

Fig. 1 UpSet plot of distribution of metabolic abnormality components

Table 1 Baseline characteristics of participants by tertiles of urinary albumin-to-creatinine ratio (UACR) in the National Health and Nutrition Examination Survey, 1999–2018 [a]

Characteristic [b]	Total (*n* = 27,298)	UACR tertiles, mg/g [c]			*P*-value*
		Low (*n* = 9,075)	Medium (*n* = 9,123)	High (*n* = 9,100)	
Age, year	44.94 ± 0.21	41.71 ± 0.24	45.31 ± 0.28	48.35 ± 0.29	< 0.001
Sex, n (%)					< 0.001
Female	12,860 (47.91)	2956 (32.92)	4651 (52.38)	5253 (60.61)	
Male	14,438 (52.09)	6119 (67.08)	4472 (47.62)	3847 (39.39)	
Ethnic, n (%)					< 0.001
Non-Hispanic White	13,338 (72.69)	4403 (72.29)	4530 (73.64)	4405 (72.09)	
Non-Hispanic Black	5083 (9.08)	2020 (10.63)	1489 (7.72)	1574 (8.79)	
Mexican American	4237 (7.03)	1211 (6.21)	1489 (7.35)	1537 (7.65)	
Other race/multiracial	4640 (11.19)	1441 (10.87)	1615 (11.29)	1584 (11.47)	
Education, n (%)					< 0.001
< high school	2203 (3.76)	598 (3.30)	727 (3.65)	878 (4.44)	
high school	9577 (32.00)	3058 (30.73)	3163 (31.81)	3356 (33.71)	
≥ high school	15,518 (64.24)	5419 (65.97)	5233 (64.54)	4866 (61.84)	
Poverty income ratio[d], %	3.18 ± 0.03	3.32 ± 0.03	3.19 ± 0.03	3.02 ± 0.03	< 0.001
Smoking status, n (%)					0.04
Never	14,906 (54.43)	5015 (55.50)	4941 (53.82)	4950 (53.85)	
Former	6611 (24.49)	2044 (23.22)	2295 (25.64)	2272 (24.70)	
Current	5781 (21.08)	2016 (21.28)	1887 (20.53)	1878 (21.45)	
Physical activity level[e], n (%)					< 0.001
low	8875 (32.77)	2962 (33.50)	2847 (31.25)	3066 (33.64)	
moderate	10,114 (37.73)	3175 (35.64)	3507 (39.74)	3432 (37.95)	
high	8309 (29.49)	2938 (30.87)	2769 (29.01)	2602 (28.41)	
eGFR, mL/min/1.73 m^2	95.67 ± 0.28	95.21 ± 0.30	96.74 ± 0.36	95.00 ± 0.37	< 0.001
Cancer, n (%)	2194 (8.33)	505 (5.92)	740 (8.61)	949 (10.87)	< 0.001
CVD[f], n (%)	2010 (5.89)	459 (4.07)	631 (5.77)	920 (8.19)	< 0.001
Metabolic factors[g], n (%)					
Central obesity	19,781 (72.25)	6060 (68.49)	6696 (72.92)	7025 (75.93)	< 0.001
Hyperglycemia	7207 (23.52)	1937 (19.96)	2341 (23.51)	2929 (27.76)	< 0.001
Hypertriglyceridemia	9033 (32.95)	2801 (31.56)	3020 (33.01)	3212 (34.51)	< 0.001
Dyslipidemia	7904 (28.23)	2353 (26.07)	2668 (28.50)	2883 (30.50)	< 0.001
Hypertension	8543 (28.11)	1985 (20.33)	2805 (28.50)	3753 (36.87)	< 0.001
Metabolic abnormality group[h], n (%)					< 0.001
Metabolically healthy	4133 (16.32)	1761 (18.96)	1319 (16.05)	1053 (13.51)	
Pre-MetS	14,210 (53.00)	4985 (55.81)	4832 (52.87)	4393 (49.81)	
MetS	8955 (30.68)	2329 (25.23)	2972 (31.08)	3654 (36.68)	

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; CVD, cardiovascular disease; MetS, Metabolic Syndrome

[a] Data are weighted to account for complex survey designs

[b] Mean ± SE or N (%) shown in the table

[c] Grouped by tertiles into low (< 4.62 mg/g), medium (4.62–7.94 mg/g), high (> 7.94 to < 30 mg/g)

[d] Poverty income ratio is the ratio of annual household income to the federal poverty line

[e] The physical activity categories were based on the distribution of MET-minute levels for the present NHANES sample

[f] CVD was defined by self-reported diagnosis of five major cardiovascular events: congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke

[g] Metabolic abnormalities were defined based on the criteria from the National Cholesterol Education Program-Adult Treatment Panel III

[h] Metabolic abnormalities were grouped according to the number of cumulative metabolic abnormality components: metabolic normal group (0 component), Pre-MetS group (1–2 components), and Mets group (3–5 components)

* Differences were considered to be significantly different if $P < 0.05$

showed a rising risk trend for cardiovascular mortality (P for trend < 0.001), although the HRs within the Pre-MetS group were not significant, likely due to broad classification (see Fig. 3). Compared to metabolically healthy individuals with low UACR tertiles, those in the MetS group with high UACR tertiles had the highest risk of cardiovascular death (HR: 1.88, 95% CI: 1.11–3.19) (see Fig. 3). Kaplan-Meier survival analysis indicated a higher

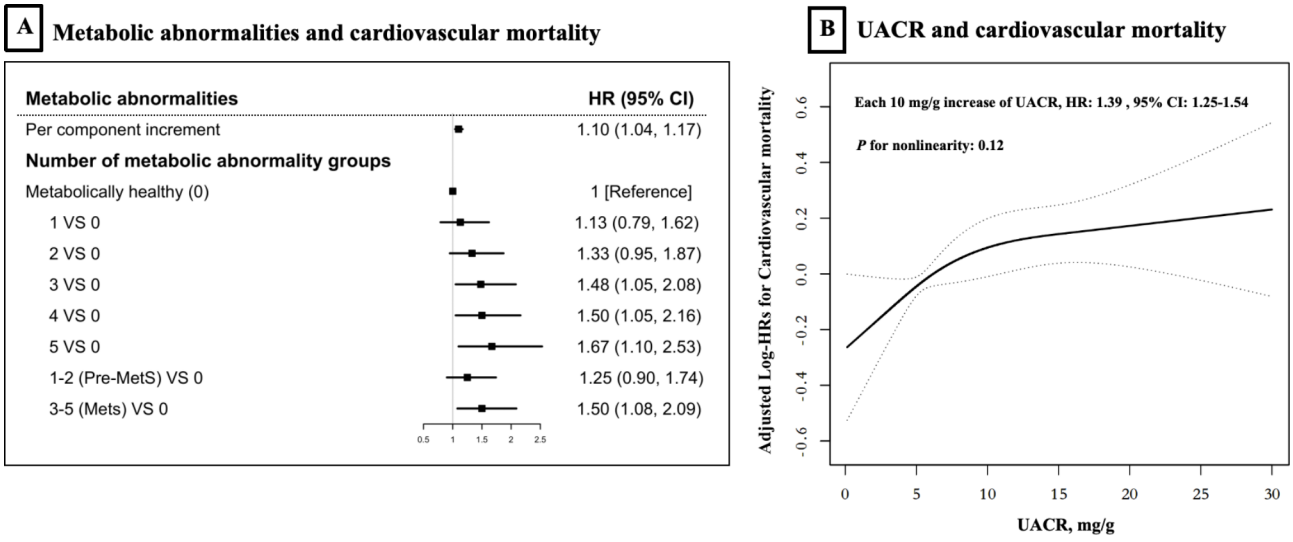

Fig. 2 Association of metabolic abnormalities and normal UACR with cardiovascular mortality. Hazard ratios and 95% CIs were estimated after adjusting for age, sex, ethnicity, education level, poverty income ratio, smoking status, physical activity level, estimated glomerular filtration rate, cancer, and cardiovascular disease. Metabolic abnormalities were grouped according to the number of cumulative metabolic abnormality components: metabolic normal group (0 components), Pre-MetS group (1–2 components), and Mets group (3–5 components). A restricted cubic spline regression model was performed using 3 nodes at the 10th, 50th, and 90th percentiles of UACR

Table 2 Associations of urinary albumin-to-creatinine ratio (UACR) with cardiovascular mortality stratified by number of metabolic abnormalities

Subgroup [a]	No. of participants (deaths)	HR (95% CI)		
		Crude model [b]	Model 1 [c]	Model 2 [d]
Metabolically healthy				
Each 10 mg/g increase of UACR	4,133 (40)	1.58 (0.97, 2.60)	1.00 (0.55, 1.83)	1.00 (0.54, 1.84)
UACR low	1,761 (15)	1 [Reference]	1 [Reference]	1 [Reference]
UACR medium	1,319 (10)	1.02 (0.46, 2.28)	0.93 (0.41, 2.11)	0.96 (0.42, 2.20)
UACR high	1,053 (15)	1.82 (0.89, 3.72)	1.01 (0.46, 2.20)	1.02 (0.46, 2.27)
Pre-MetS				
Each 10 mg/g increase of UACR	14,210 (331)	2.27 (1.96, 2.62)	1.52 (1.29, 1.79)	1.47 (1.25, 1.73)
UACR low	4,985 (67)	1 [Reference]	1 [Reference]	1 [Reference]
UACR medium	4,832 (98)	1.70 (1.25, 2.32)	1.24 (0.91, 1.71)	1.19 (0.87, 1.64)
UACR high	4,393 (166)	3.31 (2.49, 4.40)	1.67 (1.24, 2.25)	1.60 (1.19, 2.15)
MetS				
Each 10 mg/g increase of UACR	8,955(393)	1.85 (1.62, 2.11)	1.36 (1.18, 1.56)	1.34 (1.17, 1.54)
UACR low	2,329 (60)	1 [Reference]	1 [Reference]	1 [Reference]
UACR medium	2,972 (112)	1.70 (1.24, 2.32)	1.37 (1.00, 1.89)	1.36 (0.99, 1.87)
UACR high	3,654 (221)	2.94 (2.21, 3.92)	1.84 (1.37, 2.47)	1.79 (1.34, 2.41)

Abbreviation: HR, hazard ratio; UACR, urinary albumin-to-creatinine ratio; MetS, metabolic syndrome

[a] Grouped by tertiles into low (< 4.62 mg/g), medium (4.62–7.94 mg/g), high (> 7.94 to < 30 mg/g)

[b] No covariates were adjusted

[C] Adjusted for age, sex, ethnicity, education level, poverty income ratio, smoking status, physical activity level, and estimated glomerular filtration rate

[d] Adjusted for age, sex, ethnicity, education level, poverty income ratio, smoking status, physical activity level, estimated glomerular filtration rate, cancer, and cardiovascular disease

cumulative probability of cardiovascular mortality with increasing normal UACR tertiles and the number of metabolically abnormal components (see Supplement Figure S2).

Subgroup and sensitivity analyses

In subgroup analyses, subjects were stratified by age (< 60 years vs. ≥60 years) and sex (male vs. female). No significant interactions were found between the subgroups (*P* for interaction > 0.05), indicating a consistent association between continuous normal UACR and cardiovascular

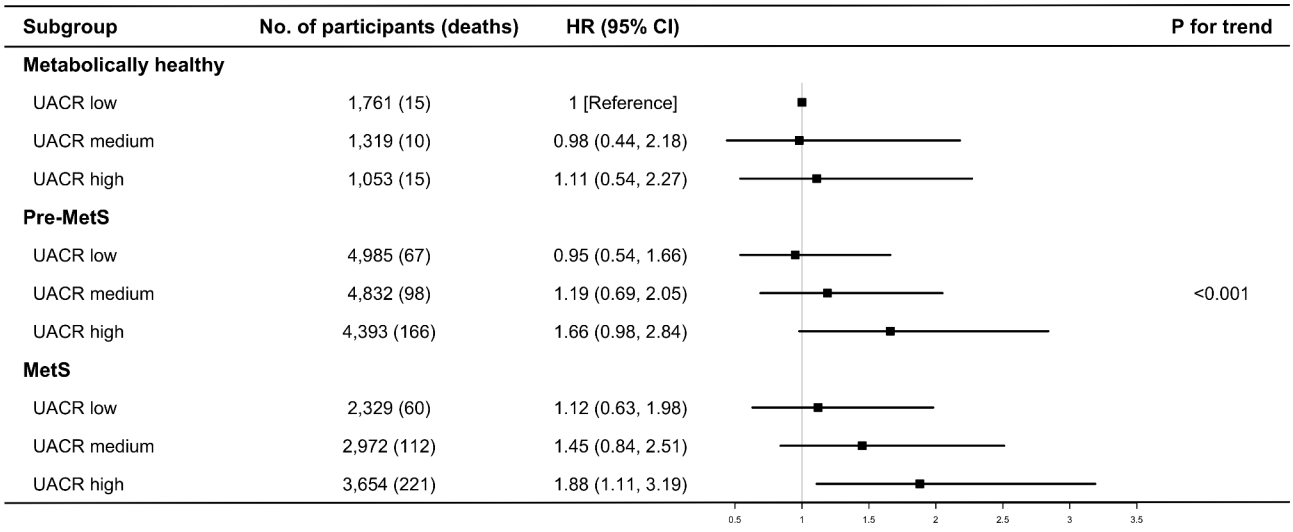

Fig. 3 joint effect analysis of normal UACR and metabolic abnormalities groups with risks of cardiovascular mortality. The multivariable Cox regression model was adjusted for age, sex, ethnicity, education level, poverty income ratio, smoking status, physical activity level, estimated glomerular filtration rate, cancer, and cardiovascular disease

mortality in each metabolic abnormality group (see Supplementary Table S2 and Table S3).

In sensitivity analyses, consistent results were observed when adding components of all metabolic parameters as covariates to the final model (see Supplementary Table S4), excluding participants with chronic kidney disease (eGFR < 60 mL/min/1.73m^2) (see Supplementary Table S5), or excluding participants who experienced cardiovascular death within 2 years of follow-up (see Supplementary Table S6).

Discussion

This longitudinal observational study is the first to examine the impact of metabolic abnormalities on the association between UACR within the normal range and cardiovascular mortality in a U.S. general population. We found that higher levels of normal UACR were independently associated with cardiovascular mortality in metabolically abnormal participants, but not in metabolically healthy participants. These findings provide valuable insights into the long-term management of individuals traditionally considered to be in the normal range of UACR. Early identification and targeted intervention for high-risk individuals with normal UACR in the context of metabolic abnormalities could hold significant public health value by offering an opportunity to prevent cardiovascular deaths through earlier risk stratification and management.

Most previous studies have demonstrated an independent link between elevated normal UACR and a heightened risk of both all-cause and cardiovascular mortality [8–11]. For instance, a study using NHANES 1999–2015 data revealed that, compared to those with low UACR (< 5 mg/g), those with high UACR (10 to < 30 mg/g) had a 1.48-fold and 1.71-fold increased risk of all-cause death and cardiovascular mortality in the general population [8]. Similarly, in a South Korean health screening program, HRs for all-cause mortality and cardiovascular mortality increased significantly as UACR quartiles ascended among participants with UACR < 30 mg/g [10]. Additionally, a large meta-analysis involving over 100,000 participants with UACR data and more than 1.1 million with urine protein dipstick measurements from 21 cohorts of the general population demonstrated a linear, positive association between UACR and all-cause and cardiovascular mortality, with no apparent threshold effect [22]. These studies consistently show that UACR, even within normal ranges, can predict cardiovascular risk.

Our study builds upon these findings by investigating how metabolic health status modifies the relationship between UACR and cardiovascular mortality. While previous studies have primarily examined the general population, we focused on how this relationship is influenced by the presence of metabolic abnormalities. Our results indicate a significant positive association between high-normal UACR and cardiovascular mortality, but this association was observed only in individuals with metabolic abnormalities. No such association was found in metabolically healthy individuals.

Our findings are in line with those of Mahemuti et al., who also observed a near-linear relationship between continuous normal UACR and all-cause mortality, which was influenced by cardiovascular health status as assessed by the Life's Essential 8 score [11]. However, our study adds to the existing literature by demonstrating

that this association is heavily influenced by metabolic status, suggesting that UACR may have different implications for cardiovascular risk depending on an individual's metabolic health. This insight is particularly relevant for clinical practice, as it highlights the need for more targeted cardiovascular risk assessments that account for both UACR levels and metabolic health.

There is a well-defined bidirectional relationship between metabolic and renal health [16, 23, 24]. The Framingham Heart Study has shown that metabolic risk factors, such as obesity, hypertension, diabetes, and dyslipidemia, are linked to the development of new kidney disease [23]. Conversely, a progressive decline in renal function can cause inflammation, oxidative stress, and insulin resistance, resulting in increased arterial blood pressure, dyslipidemia, and plasma glucose abnormalities [24]. Metabolic disorders such as obesity, hypertension, diabetes, hyperlipidemia, and CKD often occur simultaneously [2]. Notably, the presence of concurrent renal and metabolic diseases significantly elevates the risk of both morbidity and mortality associated with CVD [25]. Considering the complex interaction between cardiovascular-renal-metabolic diseases and the concept of early prevention and management of cardiovascular diseases [26], the American Heart Association (AHA) recently introduced a definition for cardiovascular-kidney-metabolic syndrome [16]. The consensus advises that clinicians should measure UACR and eGFR to evaluate the risk of cardiovascular morbidity and mortality in patients with CKD and metabolic abnormalities. However, among individuals typically classified as having normal UACR levels (<30 mg/g), there is still insufficient evidence regarding the impact of metabolic abnormalities on the relationship between UACR and adverse cardiovascular events. In our study, the high UACR group showed a 60% and 79% heightened risk of cardiovascular mortality in the Pre-MetS and MetS groups, respectively, compared to the low UACR tertile. In the metabolically healthy group, higher normal UACR was not linked to greater cardiovascular mortality risk (HR: 1.02, 95% CI: 0.46–2.27). Future studies are necessary to further determine the threshold level of UACR within the normal range in individuals with metabolic abnormalities and whether early UACR management can reduce the risk of cardiovascular death.

Although the mechanisms linking high-normal UACR and CVD mortality are largely unknown, several possible explanations exist. UACR is considered a biomarker reflecting systemic endothelial leakage and vascular endothelial injury [27, 28]. Increased UACR levels can lead to a greater atherosclerotic burden, increased severity of CVD, and a higher risk of cardiovascular death [29, 30]. Additionally, microalbuminuria induces changes in coagulation factors (e.g., von Willebrand factor, fibrinogen, and thrombomodulin) [31, 32], stimulates inflammation [33], and activates platelet activity, leading to vascular smooth muscle proliferation [34]. These changes also increase the incidence and progression of CVD, leading to a worse prognosis.

Our research has several strengths, including the use of a large, representative sample of adults from the U.S., which enhances the generalizability of our findings. Additionally, the NHANES database adheres to rigorous quality standards in data collection, ensuring the accuracy of the data. Furthermore, sensitivity analyses confirmed the robustness of our results. However, our study also has several limitations. First, due to the observational nature of the study, causality cannot be established, and the influence of unmeasured or residual confounders, such as genetic factors, lifestyle changes, psychological health, and medication use, could not be fully accounted for. Second, the use of single-point urine protein and urine creatinine tests to calculate UACR is a limitation, although studies have demonstrated that UACR from a single urination is highly correlated with a 24-hour sample [35, 36]. Third, NHANES did not track changes in metabolic variables over time, so the effect of such changes on cardiovascular mortality could not be estimated. Future longitudinal studies are needed. Fourth, Demographic and comorbidity information were self-reported, potentially leading to misclassification. Finally, our study included participants from the U.S. non-institutionalized population, which may limit the generalizability of our findings to non-U.S. or institutionalized groups.

Conclusion

In conclusion, elevated normal UACR significantly increases the risk of cardiovascular mortality in individuals with metabolic abnormalities. Early detection and management of UACR in these populations are essential to reducing long-term cardiovascular events. Future research should focus on longitudinal and mechanistic studies to further elucidate the underlying pathways and validate these findings across diverse populations.

Acknowledgements

We thank all the survey teams of the NHANES Group for their contribution and the study participants who contributed their information.

Abbreviations

UACR	Urinary albumin-to-creatinine ratio
NHANES	National Health and Nutrition Examination Survey
Pre-MetS	Pre-metabolic syndrome
MetS	Metabolic syndrome
CKD	Chronic kidney disease
CVD	cardiovascular disease
NCHS	National Center for Health Statistics
HDL	High-density lipoprotein
TG	Triglycerides
FPG	Fasting plasma glucose

eGFR	Estimated glomerular filtration rate
NCEP-ATP III	National Cholesterol Education Program-Adult Treatment Panel III
NDI	National Death Index
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01488-5.

Supplementary Material 1

Acknowledgements
We thank all the survey teams of the NHANES Group for their contribution and the study participants who contributed their information.

Author contributions
MHL and RJ wrote the manuscript. MHL, RJ, ZL, SZ, XL and YJW conducted the data extraction and data analysis. MHL, RJ, ZL, RL, and SZ did the statistical analyses. MHL, XL and YJW reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by the Natural Science Foundation Project of the Inner Mongolia Autonomous Region of China (2022LHQN08003), the Central High Level Hospital Clinical Research Operating Expenses, China (Zero Balance 2022-GSP-GG-15).

Data availability
Publicly available data sets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent participate
The study protocol was approved by the National Center for Health Statistics Ethics Review Committee. All individuals provided written informed consent before participating in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 31 July 2024 / Accepted: 16 October 2024
Published online: 22 October 2024

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