Title

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Urinary albumin-to-creatinine ratio within normal range and all-cause or cardiovascular mortality among U.S. adults enrolled in the NHANES during 1999–2015

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Abstract

Purpose: Urinary albumin-to-creatinine ratio (UACR) is one of the important diagnostic markers of chronic kidney disease. We aimed to investigate the association between UACR within normal range and cardiovascular or all-cause mortality.

Methods: This study included a nationally representative sample of 31,413 U.S. adults aged greater than or equal to 20 years enrolled in the National Health and Nutrition Examination Survey 1999–2014. Mortality was ascertained through 2015. We used multivariable Cox proportional models to investigate the association of UACR with all-cause and cardiovascular mortality. Stratum-specific analyses were conducted by age, sex, race, education status, and comorbidities (e.g., hypertension, diabetes, cardiovascular disease, and chronic kidney disease).

Results: Over a median follow-up of 7.6 years, 2854 all-cause deaths and 454 cardiovascular deaths were identified. Higher UACR (per 10 mg/g) was associated with increased risk of all-cause mortality (adjusted hazard ratio = 1.29, 95% confidence interval = 1.22–1.37) and cardiovascular mortality (adjusted hazard ratio = 1.34, 95% confidence interval = 1.17–1.55). The

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Authors' contributions:

K.I. and H.K. contributed to the design of the study. K.I. was involved in data collection, data management, and data analysis. K.I. and H.K. interpreted the results and wrote the manuscript. K.I., E.S., T.T., and H.K. reviewed and revised the manuscript.

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association was larger among women for both all-cause and cardiovascular mortality, and among younger and highly educated participants only for all-cause mortality. The association did not differ by the presence of comorbidities.

Conclusions: Elevated UACR within normal range was associated with higher all-cause and cardiovascular mortality risk across almost all subgroups including participants without comorbidities. Our findings suggest the importance of the early detection of albuminuria and careful evaluation of UACR even within normal range to reduce mortality risk.

Keywords

Urinary albumin-creatinine ratio; Normal range; Mortality; NHANES; Stratification

Introduction

Chronic kidney disease (CKD) affects approximately 37 million people (15%) of the U.S. adults (aged ≥18 years), resulting in an increased risk of hospitalization, mortality, and health care spending [1,2]. CKD is referred to as a “disease multiplier” by increasing the risks of cardiovascular disease (CVD) and death because it often occurs along with multiple comorbidities (e.g., hypertension, diabetes, obesity, etc) [1]. Although mortality rates have decreased for dialysis and transplant patients since 1996, there is still a substantial number of patients suffering from long-term adverse health outcomes of CKD [1,2]. A urinary albumin-to-creatinine ratio (UACR) is a well-known marker of glomerular damage and therefore, one of the important diagnostic markers of CKD [1]. Ample evidence has shown that microalbuminuria (UACR, 30–300 mg per g), as well as macroalbuminuria (UACR, >300 mg per g), is associated with the progression to end-stage renal disease [3,4]. Furthermore, previous studies have shown the association of microalbuminuria with CVD and all-cause mortality in the general populations [5–7], underscoring the importance of screening and early intervention of albuminuria.

Although a linear relationship between UACR levels within normal range and all-cause mortality has also been indicated [8–10], it is still unclear whether and in which subpopulations we need to consider clinical interventions when individuals show mildly elevated UACR levels within the normal range (i.e., <30 mg per g). Identifying the high-risk population susceptible to even mildly elevated UACR could help clinicians effectively measure UACR focusing on these populations to prevent long-term adverse health outcomes. As the distribution of UACR levels and mortality risks due to elevated UACR might vary by individuals’ socioeconomic status [11–13] as well as comorbidities [9,10], it is important to investigate the association between UACR within normal range and long-term adverse health outcomes in accordance with each status. In addition, given the recent advancement of treatment and change in CKD epidemiology, new evidence using the updated data would help us to understand the current situation and provide additional insight for future clinical management of albuminuria.

Therefore, using the most recent national survey of the U.S. general population linked to the mortality data, we examined the association between UACR and cardiovascular or all-cause mortality among the U.S. general population. We also examined whether the association

differs by participants' characteristics including age, sex, race, education status, and comorbidities.

Methods

Data sources and study population

We used a total of eight cycles of the continuous U.S. National Health and Nutrition Examination Survey (NHANES) 1999–2014, which has been conducted every two years. The NHANES is a multistage, stratified probability sample of noninstitutionalized U.S. adults conducted by the National Center for Health Statistics (NCHS). In the NHANES, individual data were corrected from interviews, physical examinations, and laboratory assays on collected blood and urine samples. Among adults enrolled in the NHANES during 1999–2014, the unweighted response rates for the household interview and physical examinations were 71%–84% and 70%–80%, respectively [14]. We included 35,891 participants aged greater than or equal to 20 years who had the information on urine albumin and creatine concentrations, below-mentioned covariates, and mortality. As our study focused on the mortality risks of UACR within the normal range, participants with UACR greater than or equal to 30 mg per g were also excluded (n = 4,478), resulting in the final analytical cohort of 31,413 participants. All NHANES protocols were approved by the NCHS Research Ethics Review, and all participants signed written informed consent forms [15].

Urinary albumin-to-creatinine ratio

In NHANES, spot urine specimens were collected from participants, and frozen urine samples (≤−20° C) were sent to the laboratory. Specimen stability was demonstrated at 5°C and less than or equal to −20°C [16]. Urine albumin was measured using a solid-phase fluorescent immunoassay, and urine creatinine was measured using the kinetic Jaffe rate reaction before 2007 and the enzymatic method from the 2007–2008 cycle [17–19]. Therefore, we used the following equations to adjust urine creatinine before 2007 to compare with urine creatinine from 2007 forward based on the NHANES recommendation [17]: i) urine creatinine less than 75 mg per dL, $Y(adjustment\ creatinine) = [1.02 \times \sqrt{unadjusted\ creatinine} - 0.36]^2$; ii) urine creatinine 75 to less than 250 mg per dL, $Y(adjustment\ creatinine) = [1.05 \times \sqrt{unadjusted\ creatinine} - 0.74]^2$; iii) urine creatinine greater than or equal to 250 mg per dL, $Y(adjustment\ creatinine) = [1.01 \times \sqrt{\ unadjusted\ creatinine} - 0.10]^2$. Among participants with UACR, participants were substratified into three categories by UACR as follows: very low, less than 5 mg per g; low, 5–9 mg per g; medium to high, 10–29 mg per g.

Outcome ascertainment

Our primary outcome was all-cause mortality, and the secondary outcome was cardiovascular mortality. Using respondent sequence number assigned for each participant, we linked the NHANES database from 1999 to 2014 with the mortality data which contain the National Death Index ascertained from the NCHS using probabilistic matching based on social security number, name, date of birth, race, sex, state of birth, and state of residence [20]. Mortality follow-up was available through December 31, 2015. The cardiovascular

mortality was determined based on the International Classification of Diseases, 10th version: I00–09,111, 113, and I20–51. We used the time-to-event information (month) from the examination date (i.e., measurement of UACR) to the death record as the previous study did [21,22]. We excluded 34 participants who were missing for mortality data due to insufficient identifying information.

Other covariates

We included the following demographic characteristics of the study participants: age, sex (male, female), race (non-Hispanic white, non-Hispanic black, Mexican-American, or others), education status (less than ninth grade, 9–11th grade, high school or General Education Degree, or more than high school), marital status, and income (poverty income ratio). Participants reported their smoking status (never, current, or former) and the history of comorbidities including cancer, diabetes, hypertension, dyslipidemia, CVD, and stroke at baseline. Statin, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) were ascertained from the examination of the containers provided by the participants. Body mass index was calculated using measured weight and height. Blood pressure measurements were obtained in the mobile examination center by trained physicians following a standard protocol. Serum creatinine (Scr), fasting glucose, and HbA1c measurements were performed in accordance with the laboratory procedure manual for the continuous NHANES. An estimated glomerular filtration rate (eGFR) was calculated from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration equation: $eGFR = 141 \times \min[Scr/k, 1]^{a} \times \max[Scr/k, 1]^{-1.209} \times 0.993^{age} \times 1.018$ [if female] × 1.159 [if black]; k = 0.9 for male and 0.7 for female, a = −0.411 for male and −0.329 for female, min[Scr/k, 1] = the minimum of Scr/k or 1, and max[Scr/k, 1] = the maximum of Scr/k or 1 [21].

Statistical analyses

Descriptive statistics for patient characteristics across each UACR group were compared using X^2 tests for categorical variables and analysis of variance for continuous variables. We calculated the distribution of baseline characteristics in accordance with UACR substratified groups. Then, we used multivariable Cox proportional hazards regression models adjusting for potential confounders to estimate hazard ratios (HRs) of all-cause and cardiovascular mortality in accordance with low or medium to high UACR compared with very low UACR. The proportional hazard assumption was tested using Schoenfeld residuals *(estat phtest* in Stata). We first adjusted for age and sex, and then, additionally adjusted for race, education status, income, marital status, and smoking (model 1). In our final model, we further adjusted for body mass index, eGFR, previous history of cancer, hypertension, diabetes, CVD, stroke, statin prescriptions, and ACE inhibitors or ARB prescriptions in addition to covariates in model 1 (model 2). We also investigated the continuous associations between UACR (per 10 mg per g increase) and all-cause mortality by using restricted cubic spline models fitted for Cox proportional hazard models with three knots at 10th, 50th, and 90th percentile of UACR [23].

We conducted the stratum-specific analyses to estimate the effects of UACR on all-cause or cardiovascular mortality in accordance with age (<65, ≥65 years), sex (male, female), race

(non-Hispanic white, non-Hispanic black, Hispanic, and others), education status (<12 grade, ≥12 grade), previous history of comorbidities such as hypertension, diabetes, and CVD, and eGFR categories (<60, 60 to <90, and ≥90 mL per min/1.73 m^2). We formally tested whether the interaction was statistically significant by the insertion of a multiplicative term into each model. In additional analyses, we investigated the association of UACR with all-cause or cardiovascular mortality additionally adjusting for blood pressure (systolic and diastolic), fasting glucose levels, and HbA1c (n = 27,204). Finally, to assess the sensitivity of our findings to cutoff points, we reanalyzed the data using tertiles of UACR (low-normal, 0.01–4.76 mg per g; medium-normal, 4.77–8.30 mg per g; and high-normal, 8.31–29.99 mg per g).

Statistical analyses were conducted using Stata, version 15. We applied the NHANES sampling weights which were provided by the NCHS to account for the complex survey design (including oversampling), survey nonresponse, and poststratification so that we can calculate estimates among the civilian, noninstitutionalized U.S. population [24].

Results

The mean age ± standard deviation of participants was 47.5 ± 17.7 years, and 48.1% were men. Participants with medium to high UACR were generally older, women, less educated, and had lower poverty income ratio compared with those with very low UACR (Table 1). The mean of eGFR was slightly lower among participants with medium to high UACR. Patients in the higher UACR group also tended to have a higher prevalence of comorbidities including cancer, hypertension, diabetes, CVD, and stroke as well as statin and ACEI/ARB prescriptions than those in the lower UACR group.

Urinary albumin-to-creatinine ratio and mortality

The median duration of follow-up was 7.6 years (interquartile range, 4.3–11.6) years, and 2854 all-cause deaths and 454 cardiovascular deaths were identified. We found no evidence for violation of the proportional hazard assumption for UACR. After adjusting for all potential confounders, the estimated HRs per 10 mg per g increase in UACRwas 1.29(1.22–1.37) for all-cause mortality and 1.34(1.17–1.55) for cardiovascular mortality, respectively (Table 2, Supplementary Table 1). The restricted cubic spline curve showed a curvilinear association of UACR with all-cause mortality (Fig. 1) and cardiovascular mortality (Supplementary Fig. 1). We also found higher HRs (95% confidence interval [95% CI]) of all-cause mortality and cardiovascular mortality among participants with medium to high UACR (all-cause, 1.48 [1.31–1.67]; cardiovascular, 1.71 [1.17–2.50]) compared with participants with very low UACR (Table 2). The results did not substantially change when we additionally adjusted for blood pressure, glucose levels, and HbA1c (Supplementary Table 2) and when we used different cutoff points based on UACR tertiles for exposure categories instead (Supplementary Table 3).

Subgroup analyses

In stratified analyses, we found higher HRs of all-cause mortality per 10 mg/g increase in UACR among younger participants than older participants (P for interaction = .01), women

than men (*P* for interaction = .06), and participants with greater than or equal to 12 grades than those with less than 12 grades (*P* for interaction = .01) (Fig. 2). The association was found among non-Hispanic whites and blacks, but not among Hispanics and other races with wide 95% CIs because of a small number of outcome events. We also found higher HRs of cardiovascular mortality per 10 mg/g increase in UACR in women than in men (*P* for interaction = .02) (Fig. 3). Other races showed high HR of cardiovascular mortality, but the 95% CI was wide. The magnitude of the association between UACR and all-cause or cardiovascular mortality did not differ by the presence of comorbidities.

Discussion

Using the national survey of the U.S. general population, we found that within normal range UACR (<30 mg per g), there was a linear relationship between higher UACR levels and risk of all-cause and cardiovascular mortality. We found the increased risk of all-cause mortality even among participants with mildly elevated UACR (i.e., 5 to <10 mg per g). The association between UACR and all-cause or cardiovascular mortality tended to be larger among women than that among men, and the association was even found among the low-risk population (i.e., individuals without hypertension, diabetes, CVD, and CKD).

Urinary albumin excretion is a robust predictor of long-term adverse health outcomes including cardiovascular and all-cause mortality in general population [5–7]. Although it is unclear whether slightly elevated UACR is associated with such long-term outcomes, albuminuria has been reported to have an association with several risk factors of mortality including hyperglycemia, hypertension, dyslipidemia, and smoking [25–27]. Moreover, albuminuria reflects the increased renal endothelial permeability that may represent diffuse endothelial dysfunction [28,29], leading to the occurrence of CVD [30]. A recent cross-sectional study showed the association between elevated UACR and subclinical atherosclerosis (carotid intima-media thickness and plaque) among Japanese men without diabetes [31]. As such, UACR is a potentially useful tool to improve risk stratification for all-cause and cardiovascular mortality, and early detection of pathologic urinary albuminuria would be critical to identify the high-risk population of CVD and all-cause mortality. Our findings of the association between UACR and all-cause or cardiovascular mortality even among participants without comorbidities corroborate the idea.

The present study advances our current state of knowledge about the association between UACR within normal range and mortality [5–7], by using the recent data through 2015, adjusting for many important potential confounders including socioeconomic status (which was not often included in the previous studies), and conducting a variety of stratified analyses. It has been a challenging and important topic to define what the “normal” UACR is because such definition directly affects clinical decision-making (i.e., eligibility of treatment and therapeutic targets). Consistent with prior literature including the large collaborative meta-analysis [8] and more recent single-center study from Korea [32], we found that the lower UACR the better long-term adverse health outcomes among individuals with UACR less than 30 mg per g, a well-established cutoff value in clinical practice [8]. Of note, we found that even UACR levels of 5 to less than 10 mg per g were associated with the increased risk of all-cause mortality compared with very low UACR levels (i.e., < 5 mg per

g). Given that more than half of individuals with UACR less than 10 mg per g had UACR levels of 5 to less than 10 mg per g, we may need careful monitoring for those with mildly elevated UACR to reduce long-term adverse health outcomes that requires further investigation.

We found the larger association between UACR and all-cause or cardiovascular mortality among women than men. Our findings are consistent with previous literature including meta-analysis showing a higher risk of all-cause mortality and CVD in accordance with UACR among women than men [33–35] and demonstrate that this is also the case for the general population with the normal range of UACR (i.e., <30 mg per g). Although the underlying mechanisms are unclear about the sex-specific association between UACR and long-term adverse health outcomes, microvascular dysfunction related to albuminuria might be more involved in the occurrence of CVD or death among women than men [36,37]. We found the larger HR for all-cause mortality among the younger population than the older population as shown in some [38] but not all [39] previous studies. The younger population is generally healthier and therefore might have fewer opportunities to examine and control UACR than the older population. The association was also larger among highly educated participants than that among those with education less than 12 grades. Given that we focus on UACR within the normal range, the observed association might be attenuated (or competed) by other comorbidities causing death in such high-risk populations (i.e., older and less-educated participants). More evidence about pathophysiological interaction by sex, age, and education status would be warranted. Despite the wide CI due to insufficient statistical power, our null findings for both all-cause and cardiovascular mortality among Hispanic might reflect the “Hispanic paradox” (i.e., lower mortality despite a higher incidence of traditional cardiovascular risk factors [40,41]) that also requires future research focusing on this largest minority group in the United States. We found the association between UACR and all-cause or cardiovascular mortality regardless of the previous history of hypertension, diabetes, CVD, or low eGFR. These findings corroborate the previous research among nonhypertensive and nondiabetic individuals [42], indicating the potential clinical effectiveness of active screening for albuminuria to prevent long-term adverse health outcomes even among people without risk factors of CVD or death.

A major strength of our study is that we used the most recent well-established national survey of the noninstitutionalized U.S. population. Leveraging the extensive set of covariates and large sample size in the NHANES, we could have performed multiple subgroup analyses in accordance with participants’ characteristics. Another strength is that our data had long follow-up periods of hard endpoints by linking mortality data based on the National Death Index. However, our study also has several limitations. First, although we included many potential confounders between UACR and mortality, we cannot rule out the unmeasured or residual confounding because of the nature of the observational study. Second, urinary albumin excretion was evaluated only from a single spot urine measurement in NHANES. Although repeat sampling or 24-hour urinary albumin excretion is recommended in clinical practice, a recent study showed the high agreement between early morning UACR and 24-hour UAE categories, and reclassification for the outcome assessment is limited [43]. Given the clinical usefulness and cost saving of UACR in a spot urine sample to assess the prognosis of CKD, our findings could be informative in clinical

practice. Third, as the comorbidities (i.e., history of cancer, hypertension, diabetes, CVD, and stroke) were self-reported in NHANES, we might have a risk of mismeasurement of such confounders. Fourth, as the baseline characteristics were obtained simultaneously, we could not clarify the temporality between UACR and other covariates at baseline. To overcome these limitations and understand the causal relationship between UACR within normal range and mortality in the general population, further investigations with larger sample size of medical records and longitudinal follow-up would be needed. Finally, given that NHANES participants are the U.S. noninstitutionalized citizens, our findings may not be generalizable to the non-U.S. or institutionalized population.

Conclusions

Using the recent large survey data on noninstitutionalized U.S. citizens, we found the association between UACR within normal range and all-cause and cardiovascular mortality. The association was found even among participants without risk factors of CVD. These findings indicate that early detection of pathologic urinary albuminuria and careful evaluation of UACR even within normal range might be important to effectively reduce the risk of long-term adverse health outcomes. Future studies with longer follow-up period would be needed to examine whether active screening of albuminuria is recommended even for previously unidentified subpopulations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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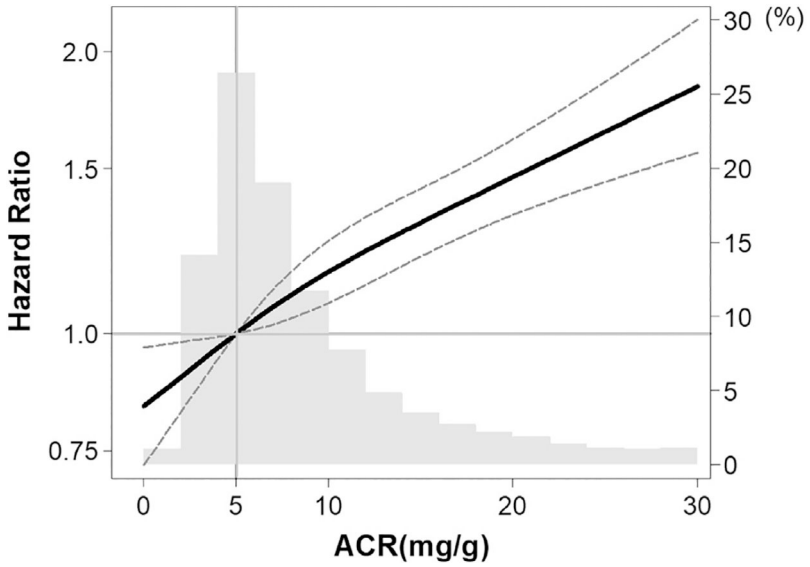

Fig. 1.

Associations between UACR and all-cause mortality using a restricted cubic spline regression model in NHANES 1999–2014 followed through 2015. The Y-axis (left) shows HRs (log scale) adjusted for age, sex, race, education status, income, marital status, smoking, previous history of cancer, hypertension, diabetes, cardiovascular disease, and stroke, statin prescription, ACE-I/ARB prescription, BMI, and eGFR. The Y-axis (right) shows prevalence of each ACR level among study population. The dashed lines represent the confidence intervals for the restricted cubic spline model (reference is 5 mg per g). BMI = body mass index.

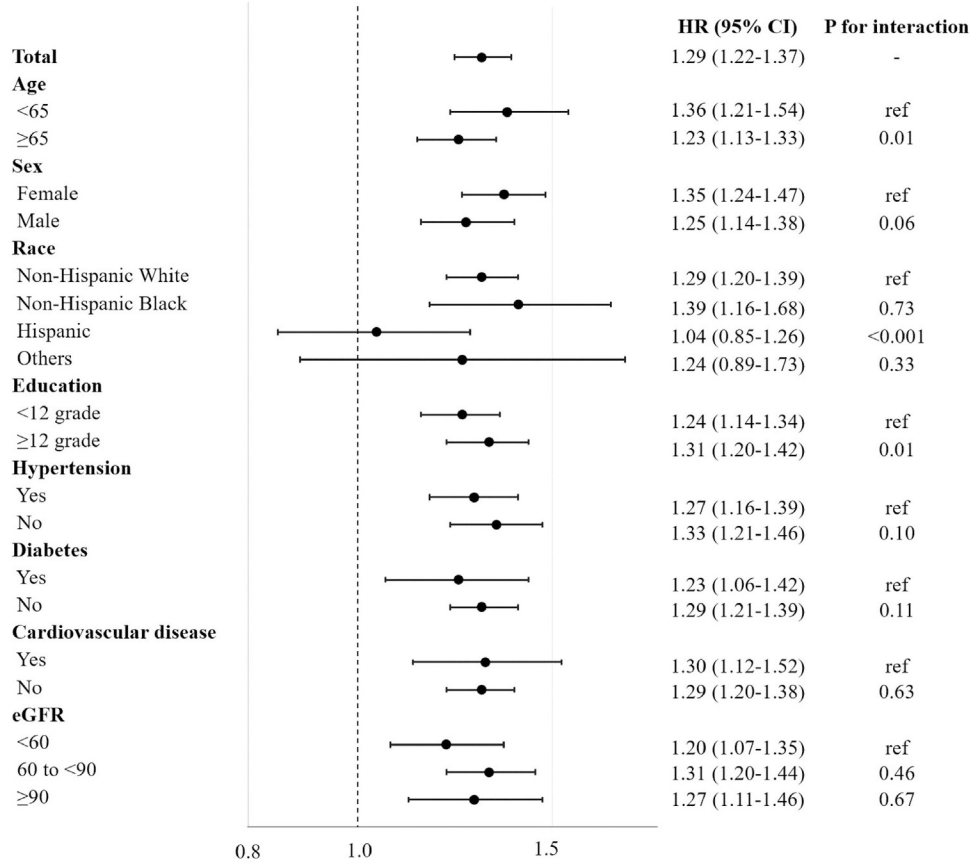

Fig. 2.

Associations between UACR and all-cause mortality stratified by NHANES 1999–2014 followed through 2015. HR per 10 mg per g increase in UACR adjusted for age, sex, race, education status, income, marital status, smoking, previous history of cancer, hypertension, diabetes, cardiovascular disease, and stroke, statin prescription, ACE-I/ARB prescription, BMI, and eGFR. BMI = body mass index.

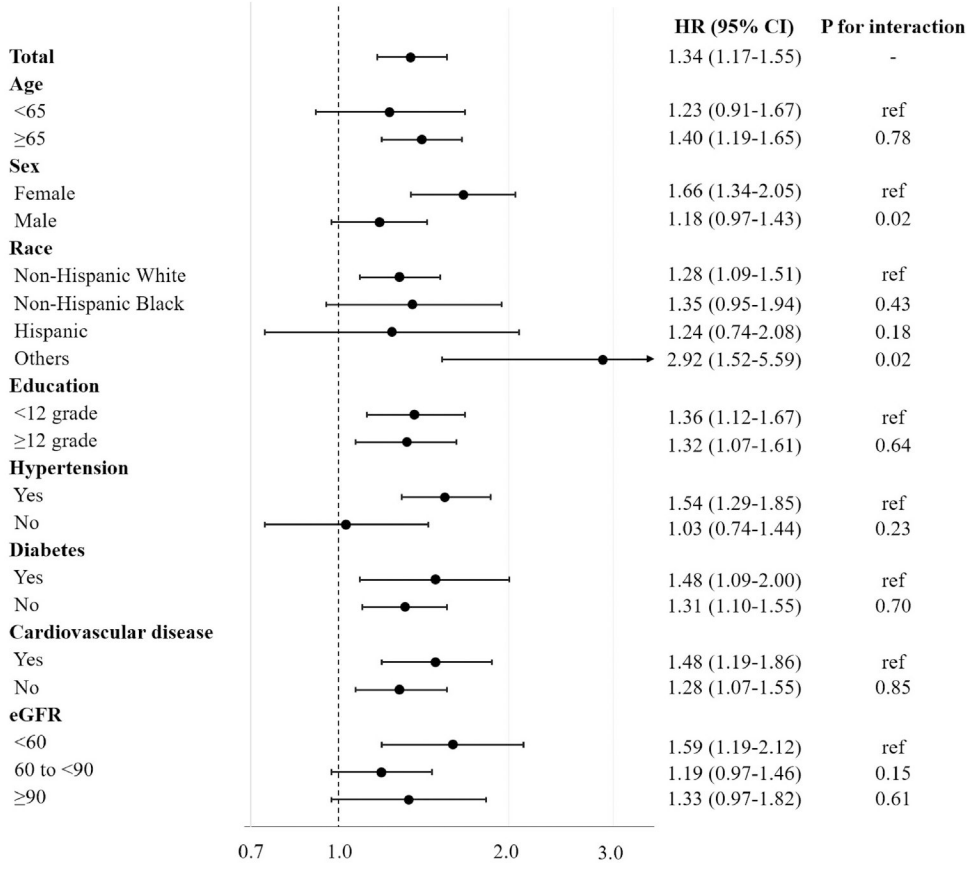

Fig. 3.

Associations between UACR and cardiovascular mortality stratified by NHANES 1999–2014 followed through 2015. HR per 10 mg per g increase in UACR adjusted for age, sex, race, education status, income, marital status, smoking, previous history of cancer, hypertension, diabetes, cardiovascular disease, and stroke, statin prescription, ACE-I/ARB prescription, BMI, and eGFR. BMI = body mass index.

Table 1

Baseline characteristics in accordance with urinary albumin-to-creatinine ratio in NHANES 1999–2014 followed through 2015

	Urinary albumin-to-creatinine ratio (ACR)			*P*-value*
	<5 mg/g	5 to <10 mg/g	10 to <30 mg/g	
Total, n (%)	11,036	12,289	8088	
UACR (mg/g)	3.56 ± 0.95	6.98 ± 1.38	16.24 ± 5.34	
Age (years)	43.3 ± 15.8	47.7 ± 17.4	52.9 ± 18.9	<.001
Sex (male), n (%)	6898 (62.5)	5130 (41.7)	3111 (38.5)	<.001
Race, n (%)				<.001
Non-Hispanic white	5290 (47.9)	5996 (48.8)	3912 (48.4)	
Non-Hispanic black	2598 (23.5)	2179 (17.7)	1499 (18.5)	
Mexican-American	1674 (15.2)	2268 (18.5)	1471 (18.2)	
Others	1474 (13.4)	1846 (15.0)	1206 (14.9)	
Education status, n (%)				<.001
Less than 9th grade	948 (8.6)	1321 (10.8)	1086 (13.4)	
9th–11th grade	1497 (13.6)	1846 (15.0)	1346 (16.6)	
High school or GED	2508 (22.7)	2867 (23.3)	1910 (23.6)	
Higher than high school	6083 (55.1)	6255 (50.9)	3746 (46.3)	
Poverty income ratio (%)	2.74 ± 1.66	2.59 ± 1.64	2.44 ± 1.60	<.001
Married, n (%)	6103 (55.3)	6798 (55.3)	4262 (52.7)	<.001
Smoking, n (%)				<.001
Never	5969 (54.1)	6674 (54.3)	4358 (53.9)	
Current	2557 (23.2)	2602 (21.2)	1624 (20.1)	
Former	2510 (22.7)	3013 (24.5)	2106 (26.0)	
Cancer, n (%)	667 (6.0)	1043 (8.5)	947 (11.7)	<.001
Hypertension, n (%)	2492 (22.6)	3806 (31.0)	3266 (40.4)	<.001
Diabetes, n (%)	529 (4.8)	1036 (8.4)	1107 (13.7)	<.001
Cardiovascular disease, n (%)	418 (3.8)	708 (5.8)	722 (8.9)	<.001
Stroke, n (%)	175 (1.6)	335 (2.7)	335 (4.1)	<.001
Statin prescription, n (%)	1073 (9.7)	1762 (14.3)	1507 (18.6)	<.001
ACEI or ARB prescription, n (%)	885 (8.0)	1445 (11.8)	1385 (17.1)	<.001

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	Urinary albumin-to-creatinine ratio (ACR)			*P*-value*
	<5 mg/g	5 to <10 mg/g	10 to <30 mg/g	
BMI (kg/m2)	28.5 ± 6.0	28.6 ± 6.6	28.9 ± 7.0	<.001
eGFR (mL/min/1.73 m2)	97.3 ± 22.8	99.1 ± 25.0	94.9 ± 26.9	<.001
Systolic blood pressure (mm Hg)†	119.6 ± 14.7	122.6 ± 17.9	128.6 ± 21.3	<.001
Diastolic blood pressure (mm Hg)†	70.2 ± 11.6	70.4 ± 12.6	70.5 ± 14.3	.23
Fasting glucose levels (mg/dL)†	93.2 ± 20.6	96.7 ± 28.0	104.7 ± 42.6	<.001
HbA1c %†	5.4 ± 0.6	5.5 ± 0.8	5.8 ± 1.2	<.001

BMI = body mass index; GED = general educational development.

*X^2 tests and analysis of variance were used to compare categorical or continuous variables across each UACR group.

†Blood pressure, fasting glucose levels, and HbA1c were available for 87% (n = 27,204) of study participants (these variables were included in the sensitivity analysis).

Table 2

Associations between UACR and all-cause or cardiovascular mortality in NHANES 1999–2014 followed through 2015

Outcomes	Event N/total N	Adjusted HR (95% CI)		
		Age and sex	Model 1*	Model 2†
All-cause mortality				
Continuous (per 10 mg per g increase)	2854/31,413	1.43 (1.35–1.52)	1.33 (1.25–1.41)	1.29 (1.22–1.37)
UACR categories				
<5 mg/g	618/11,036	Ref	Ref	Ref
5 to <10 mg/g	1004/12,289	1.24 (1.11–1.39)	1.15 (1.02–1.29)	1.13 (1.00–1.28)
10 to <30 mg/g	1232/8088	1.80 (1.64–1.98)	1.57 (1.41–1.76)	1.48 (1.31–1.67)
Cardiovascular mortality				
Continuous (per 10 mg per g increase)	454/31,413	1.59 (1.37–1.83)	1.46 (1.26–1.68)	1.34 (1.17–1.55)
UACR Categories				
<5 mg/g	84/11,036	Ref	Ref	Ref
5 to <10 mg/g	151/12,289	1.42 (0.98–2.06)	1.31 (0.88–1.96)	1.28 (0.85–1.93)
10 to <30 mg/g	219/8088	2.43 (1.71–3.44)	1.97 (1.35–2.86)	1.71 (1.17–2.50)

*HR adjusted for age, sex, race, education status, income, marital status, and smoking.

†HR adjusted for age, sex, race, education status, income, marital status, smoking, previous history of cancer, hypertension, diabetes, cardiovascular disease, and stroke, statin prescription, ACE-I/ARB prescription, BMI, and eGFR.