Albuminuria within the Normal Range Can Predict All-Cause Mortality and Cardiovascular Mortality

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Key Points

- Despite interest in low-grade albuminuria and poor clinical outcomes, evidence from a large-scale population is lacking.
- In this large cohort study, low-grade albuminuria was associated with all-cause and cardiovascular mortality.
- In the general population, low-grade albuminuria should be carefully monitored.

Abstract

Background Despite interest in low-grade albuminuria and poor clinical outcomes, evidence from a large-scale population is lacking. Therefore, we identified the association of low-grade albuminuria within the normal range with all-cause and cardiovascular (CV) mortality.

Methods After excluding individuals with urine albumin-creatinine ratio (ACR) $\geq$30 mg/g ($n=6094$), this cohort study analyzed 43,396 adults who participated in the National Health and Nutrition Examination Survey (1999–2016). Participants were divided into four quartiles of ACR. The primary outcome was all-cause mortality, and the secondary outcome was CV mortality. Multivariable Cox proportional hazards models were used.

Results During a median 7.9 years of follow-up, 3516 (9%) participants died. Compared with the reference group (Q1, ACR <4.171 mg/g), low-grade albuminuria groups were associated with all-cause mortality (Q3, ACR $\geq$6.211 to <10.010 mg/g, hazard ratio [HR], 1.25 [95% CI, 1.11 to 1.41]; Q4, ACR $\geq$10.010 mg/g, HR, 1.57 [95% CI, 1.41 to 1.76]) in a multivariable hazards model. A similar pattern was also seen in the association of low-grade albuminuria with CV mortality. Subgroup analyses showed that low-grade albuminuria was also associated with all-cause mortality in the nondiabetic group, nonhypertensive group, and non-CKD group (eGFR $\geq$60 ml/min per 1.73 m^2).

Conclusions Our findings suggest that low-grade albuminuria is associated with all-cause and CV mortality. Low-grade albuminuria should be monitored, even for patients with low CV risk.

Introduction

Albuminuria is a known predictor of all-cause and cardiovascular (CV) mortality (1,2). Thus, the importance of albuminuria has been emphasized and monitoring of albuminuria is recommended in patients who are high risk, such as those with diabetes mellitus (DM) or CKD (3,4). In patients with diabetes, albuminuria is a characteristic finding of diabetic kidney disease (DKD) (5,6). Previously, albuminuria was thought to be a sequential process of DKD that followed glomerular hyperfiltration (7); recently, however, albuminuria was also considered to be an activated state of DKD, that is, an already deteriorated state (8). Albuminuria is a marker of kidney damage (9). Therefore, if albuminuria (urine albumin excretion rate $\geq$30 mg/24 h; random urine albumin-creatinine ratio [ACR] $\geq$30 mg/g [3 mg/mmol]) persists for >3 months, it is defined as CKD. In addition, albuminuria was reported to

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be associated with obesity (10) and dementia in elderly individuals (11).

Albuminuria could be caused by a variety of factors. Endothelial dysfunction could cause albuminuria by increasing glomerular pressure and permeability of the glomerular basement membrane (12). Moreover, albuminuria could be caused by dietary habits. Eating more protein and fewer lipids of vegetable origin could cause albuminuria (13). Genetic variants related to albuminuria were also discovered through a genome-wide association study (14). For example, rs116907128 and rs1801239 are genetic variants associated with ACR in the general adult population, and rs13427836 and rs649529 are genetic variants associated with ACR in the DM population.

In the current guidelines, the lowest level of albuminuria considered to be of clinical importance is microalbuminuria with an ACR of $\geq$30 mg/g (3 mg/mmol) (9). Most guidelines recommend screening for ACR in patients who are at risk, such as those with DM, hypertension, obesity, or CKD; those who are smokers; and elderly individuals (9,15–17). However, some previous studies have garnered interest for albuminuria and poor clinical outcomes in individuals with normoalbuminuria (ACR <30 mg/g). Several previous studies showed that low-grade albuminuria was associated with all-cause mortality (18), left ventricular hypertrophy (19), incident heart failure events (20), and DKD (21). An observational study from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that high-normal albuminuria was associated with heart failure in patients with low CV risk (20). However, these studies were limited to patients who were high risk, such as those with DKD (21) and hypertension (19), and those who were elderly (18,20). Additionally, the previous studies did not analyze >40,000 subjects as we have done in this study.

We analyzed the general United States adult population without albuminuria (ACR <30 mg/g), not restricted to specific age groups. We sought to show that albuminuria within the normal range (*i.e.*, low-grade albuminuria) is associated with all-cause and CV mortality using a dataset from the National Health and Nutrition Examination Survey (NHANES).

Materials and Methods
Study Participants
We analyzed adults ($\geq$18 years) who participated in NHANES from 1999 to 2016. Among the 53,348 adult NHANES participants from 1999 to 2016, we excluded those without a random urine ACR (n=3858) and those with an ACR of $\geq$30 mg/g (n=6094), which constituted 12% of the whole adult cohort (Supplemental Figure 1). As a result, 43,396 adults were included in the analysis. This observational cohort study was approved by the institutional review board of Seoul National University Boramae Medical Center (approval number 07-2021-3).

Data Collection and Definitions
Information related to demographics, laboratory values, and mortality was obtained from the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm;

demographic, examination, questionnaire, and laboratory dataset) in March 2019.

DM was defined as a history of DM, fasting glucose level >126 mg/dl, or random glucose level >200 mg/dl. Hypertension was defined as at least two measurements with a systolic BP >140 mm Hg or diastolic BP >90 mm Hg, a history of hypertension, or current use of antihypertensive medications. CV event was defined as the composite of congestive heart failure, coronary heart disease, angina, history of heart attack, and stroke. Serum and urine creatinine levels were measured by the Jaffe rate method with standardization to the isotope dilution mass spectrometry reference method (22). Urine albumin levels were measured by solid-phase fluorescent immunoassay. In the surveys of 1999–2000 and 2005–2006, corrected serum creatinine levels were used (23,24). The eGFR was calculated using the CKD Epidemiology Collaboration equation (25). Participants were categorized according to quartile of ACR.

The primary outcome was all-cause mortality on the basis of the data retrieved from the NHANES linked to National Death Index data. The secondary outcome was CV mortality, which was defined as death due to heart disease or cerebrovascular disease. The code of causes of death follows the International Statistical Classification of Diseases, Injuries, and Causes of Death, Tenth Revision guidelines. The codes for heart disease were I00–I09, I11, I13, and I20–I51; the codes for cerebrovascular disease were I60–I69. The participants who were lost to follow-up were censored at the time of last visit. Survival time was calculated from the date of interview to the date of death or the end of the mortality period.

Statistical Analyses
All statistical analyses were performed using SPSS software (version 25; IBM Corp., Armonk, NY) and R software (version 3.6.3; www.r-projectorg; R Foundation for Statistical Computing, Vienna, Austria). Categoric variables are presented as numbers and percentages. Continuous variables are presented as the mean$\pm$SD or as medians with interquartile ranges (IQRs). The Kolmogorov–Smirnov test was used to test for normality. To compare the baseline characteristics according to quartile of ACR, the chi-squared test was used for categoric variables (or Fisher exact test if the chi-squared test was not applicable), whereas one-way ANOVA was used for continuous variables (or the Kruskal–Wallis test if ANOVA was not applicable). For P values for trend, the linear-by-linear association was used for categoric variables, and the Jonckheere–Terpstra test was used for continuous variables. Kaplan–Meier curves were drawn according to quartile of ACR, and they were compared using the log-rank test. The hazard ratios (HRs) of all-cause and CV mortality were analyzed using Cox proportional hazards models. Model 1 was a univariable model. Model 2 was adjusted for sociodemographic information (age, sex, race, and education). Model 3 was further adjusted for body mass index (BMI), baseline eGFR, smoking, and comorbidities such as DM, hypertension, and CV event. The percentages of missing values of education, BMI, baseline eGFR, smoking, and CV event were 8%, 1%, 5%, 6%, and 8%, respectively. The multivariable models were analyzed except for covariates

Table 1.   Baseline participant characteristics

Variable	Total (n=43,396)	Urine Albumin-Creatinine Ratio, mg/g				P for Trend
		<4.171 (n=10,849)	4.171 to <6.211 (n=10,848)	6.211 to <10.010 (n=10,931)	≥10.010 (n=10,768)	
Age, yr, median (IQR)	44 (29–61)	38 (26–52)	43 (29–58)	46 (30–62)	52 (34–68)	<0.001
Male, n (%)	20,988 (48)	7195 (66)	5328 (49)	4344 (40)	4121 (38)	<0.001
Race and ethnicity, n (%)						<0.001
Mexican American	8203 (19)	1757 (16)	2097 (19)	2244 (21)	2105 (20)	
Other Hispanic	3498 (8)	785 (7)	881 (8)	920 (8)	912 (9)	
Non-Hispanic White	19,088 (44)	4671 (43)	4830 (45)	4796 (44)	4791 (45)	
Non-Hispanic Black	9022 (21)	2806 (26)	2126 (20)	2010 (18)	2080 (19)	
Other race	3585 (8)	830 (8)	914 (8)	961 (9)	880 (8)	
Body mass index, kg/m^2, n (%)						<0.001
<30	28,427 (66)	7317 (68)	7259 (68)	7098 (66)	6753 (64)	
≥30	14,431 (34)	3428 (32)	3475 (32)	3693 (34)	3835 (36)	
Diabetes mellitus, n (%)	4351 (10)	562 (5)	842 (8)	1144 (11)	1803 (17)	<0.001
Hypertension, n (%)	15,227 (35)	2626 (24)	3315 (31)	4121 (38)	5165 (48)	<0.001
Cardiovascular event, n (%)	3474 (9)	549 (6)	685 (7)	913 (9)	1327 (13)	<0.001
Education, n (%)						<0.001
High school or lower	19,801 (46)	4425 (41)	4781 (44)	5157 (47)	5438 (51)	
College or graduate	20,228 (47)	5377 (50)	5231 (48)	4983 (46)	4637 (43)	
Smoking, n (%)						<0.001
Current smoker	8574 (21)	2293 (22)	2156 (21)	2115 (20)	2010 (19)	
Exsmoker	9591 (23)	2179 (21)	2359 (23)	2433 (23)	2620 (25)	
Never smoker	22,419 (54)	5468 (53)	5645 (54)	5720 (54)	5586 (53)	
Laboratory findings, median (IQR)						
uACR, mg/g	6.21 (4.17–10.00)	3.26 (2.67–3.73)	5.11 (4.63–5.63)	7.69 (6.88–8.71)	14.83 (11.91–19.83)	<0.001
Fasting glucose, mg/dl	97.7 (90.7–106.1)	96.0 (90.0–103.0)	97.0 (90.1–105.0)	98.0 (90.7–107.0)	99.3 (92.0–112.0)	<0.001
eGFR <60 ml/min per 1.73 m^2, n (%)	2,830 (7)	506 (5)	530 (5)	696 (7)	1098 (11)	<0.001

IQR, interquartile range; uACR, random urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

with missing values. A cubic spline curve was used to demonstrate the association between continuous ACR and mortality. The reference was set to ACR 3.00 mg/g, which was within the first quartile of ACR (<4.171 mg/g). Subgroup analyses were performed. We performed subgroup analyses regarding age group, sex, DM, hypertension, obesity (BMI ≥30 kg/m^2), baseline eGFR, education status, and smoking status. Subgroup analyses were also performed in the group without DM, CKD (eGFR <60 ml/min per 1.73 m^2), and hypertension, and in the groups with at least one of these conditions. A P value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics according to quartile of ACR are shown in Table 1. Overall, the median (IQR) age was 44 (29–61) years, and the number of male participants was 20,988 (48%). As the ACR increased, the patients were older and more likely to be female (P for trend <0.001). Our data consisted of 44% non-Hispanic White, 21% non-Hispanic Black, 19% Mexican American, and 8% other Hispanic individuals. Participants who were obese were more likely to have a high ACR than participants who were not obese (P

for trend <0.001). Groups with higher ACR tended to have more individuals with DM, hypertension, and CV events (P for trend <0.001). A higher ACR was associated with more people with high school education or lower and fewer current smokers (P for trend <0.001). More participants with CKD (eGFR <60 ml/min per 1.73 m^2) tended to have a higher ACR (P for trend <0.001).

Albuminuria and Mortality

During a median (IQR) follow-up of 7.9 (4.4−12.0) years, 3516 (9%) participants died. The Kaplan–Meier curve showed that the higher the ACR was the lower the survival probability for all-cause mortality (log-rank P<0.001) (Figure 1A). The survival probability for CV mortality showed a similar pattern (Figure 1B). The incidence rates of all-cause mortality from the lowest to the highest quartile of ACR were 539 (6.18 per 1000 person-years), 645 (8.05 per 1000 person-years), 865 (11.11 per 1000 person-years), and 1467 (19.87 per 1000 person-years), respectively. The crude HRs of all-cause mortality (compared with that of the lowest quartile) were 1.31 (95% CI, 1.17 to 1.47), 1.82 (95% CI, 1.64 to 2.03), and 3.30 (95% CI, 2.99 to 3.64) for the second, third, and fourth quartiles of ACR, respectively (model 1 of all-cause mortality in Table 2). After adjustments for sociodemographic information, BMI,
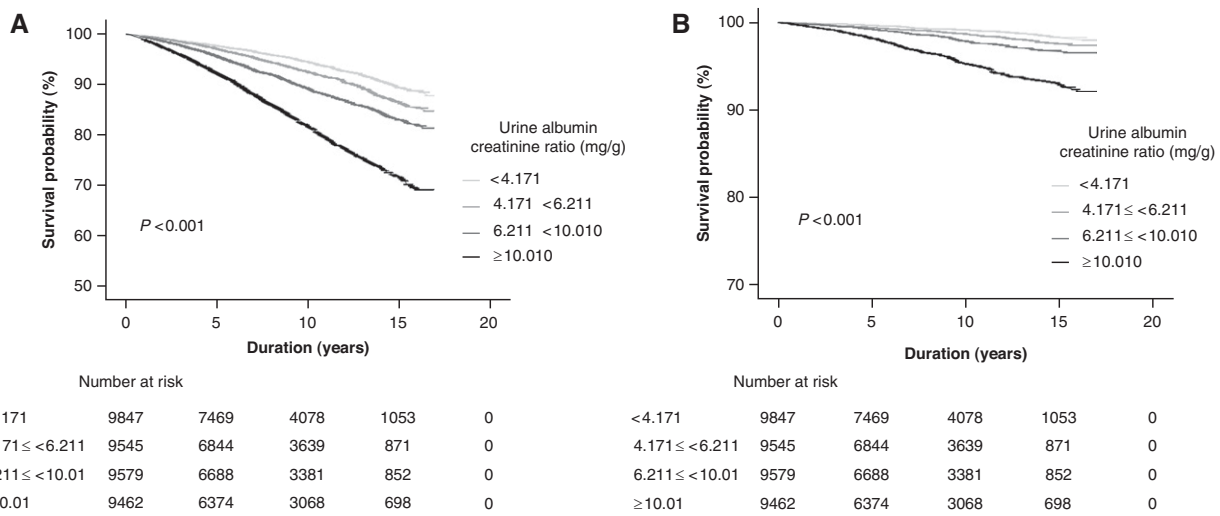
Figure 1. | **High urine albumin-creatinine ratio was associated with low survival probability.** (A) The survival probability for all-cause mortality. (B) The survival probability for cardiovascular mortality.

smoking, baseline eGFR, and comorbidities, the HRs for all-cause mortality were significant for the third and fourth quartiles of ACR (models 2 and 3 of all-cause mortality in Table 2). The spline curve clearly showed a relatively linear relationship between ACR and the risk of all-cause mortality (Figure 2A).

During the follow-up period, 676 (2%) participants died of heart disease or cerebrovascular disease. The incidence rates of CV mortality from the lowest to the highest quartile of ACR were 80 (0.91 per 1000 person-years), 111 (1.38 per 1000 person-years), 155 (1.99 per 1000 person-years), and 330 (4.46 per 1000 person-years), respectively. The results for CV mortality were similar to those of all-cause mortality. The crude HRs for CV mortality (compared with that of

the lowest quartile) were 1.52 (95% CI, 1.14 to 2.03), 2.20 (95% CI, 1.68 to 2.88), and 4.98 (95% CI, 3.90 to 6.36) for the second, third, and fourth quartiles of ACR, respectively (model 1 of CV mortality in Table 2). After adjustments for sociodemographic information, BMI, smoking, baseline eGFR, and comorbidities, the HRs for CV mortality were significant for the third and fourth quartiles of ACR (models 2 and 3 of CV mortality in Table 2). The spline curve clearly showed a relatively linear relationship between ACR and the risk of CV mortality (Figure 2B).

Subgroup Analyses

To assess modification effects of subgroups on the association between ACR and all-cause mortality, analyses were

Table 2.   Risk of mortality according to quartile of random albumin-creatinine ratio

	Urine Albumin-Creatinine Ratio (mg/g)							
	Quartile 1 (<4.171)		Quartile 2 (4.171 to <6.211)		Quartile 3 (6.211 to <10.010)		Quartile 4 (≥10.010)	
Outcome	Hazard Ratio (95% Confidence Interval)	P	Hazard Ratio (95% Confidence Interval)	P	Hazard Ratio (95% Confidence Interval)	P	Hazard Ratio (95% Confidence Interval)	P
All-cause mortality								
Model 1[a]	1.0 (ref)		1.31 (1.17 to 1.47)	<0.001	1.82 (1.64 to 2.03)	<0.001	3.30 (2.99 to 3.64)	<0.001
Model 2[b]	1.0 (ref)		1.08 (0.96 to 1.21)	0.18	1.27 (1.14 to 1.43)	<0.001	1.68 (1.51 to 1.87)	<0.001
Model 3[c]	1.0 (ref)		1.08 (0.95 to 1.22)	0.20	1.25 (1.11 to 1.41)	<0.001	1.57 (1.41 to 1.76)	<0.001
Number of events, %	539 (6)		645 (7)		865 (9)		1467 (16)	
Cardiovascular mortality								
Model 1[a]	1.0 (ref)		1.52 (1.14 to 2.03)	0.004	2.20 (1.68 to 2.88)	<0.001	4.98 (3.90 to 6.36)	<0.001
Model 2[b]	1.0 (ref)		1.18 (0.88 to 1.57)	0.26	1.43 (1.09 to 1.88)	0.01	2.20 (1.71 to 2.83)	<0.001
Model 3[c]	1.0 (ref)		1.28 (0.94 to 1.75)	0.11	1.51 (1.12 to 2.03)	0.006	2.14 (1.62 to 2.82)	<0.001
Number of events, %	80 (0.8)		111 (1)		155 (2)		330 (4)	

ref, reference.
[a]Unadjusted.
[b]Adjusted for age, sex, race, and education.
[c]Model 2 plus adjustment for body mass index, smoking, diabetes mellitus, hypertension, cardiovascular event, and baseline eGFR.
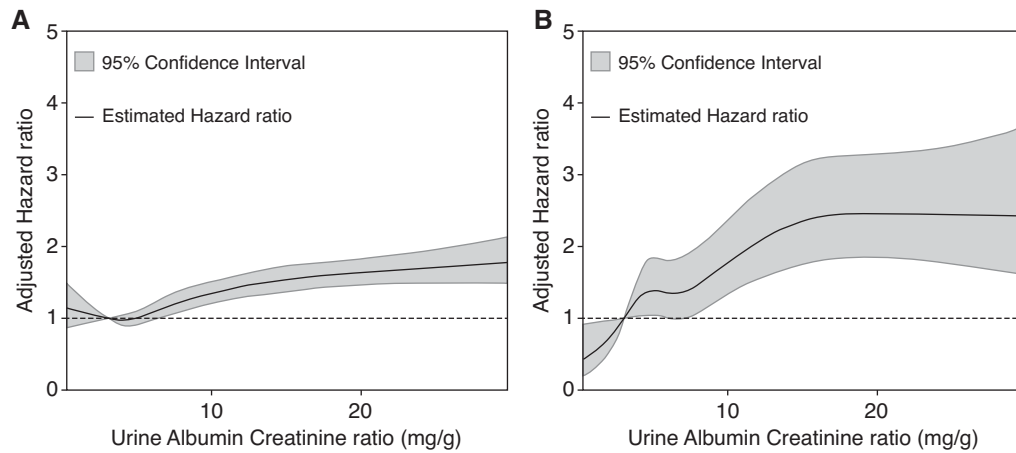
Figure 2. | **There was a linear association of the urine albumin-creatinine ratio with mortality.** (A) All-cause mortality. (B) Cardiovascular mortality.

performed in subgroups stratified by age (<60 or ≥60 years old), sex (male or female), DM (with or without), hypertension (with or without), obesity (BMI ≥30 kg/m² or <30 kg/m²), eGFR (<60 or ≥60 ml/min per 1.73 m²), education, and smoking. The risk of the fourth quartile of ACR (≥10.010 mg/g) was compared with the risk of the first quartile of ACR. *P* values for interactions were nonsignificant for the subgroups by age, sex, DM, hypertension, obesity, eGFR, education, and smoking, suggesting the

increased risk of all-cause mortality associated with low-grade albuminuria (ACR ≥10.010 mg/g) was evident regardless of these factors (Figure 3). For sensitivity analysis, we performed a subgroup analysis on the risk of the third quartile (ACR of 6.211 to <10.010 mg/g), not the risk of the fourth quartile. Similar results of subgroup analyses were observed when the risks of the third quartile (ACR 6.211 to <10.010 mg/g) were compared with the risk of the first quartile of ACR (Supplemental Figure 2). Subgroup
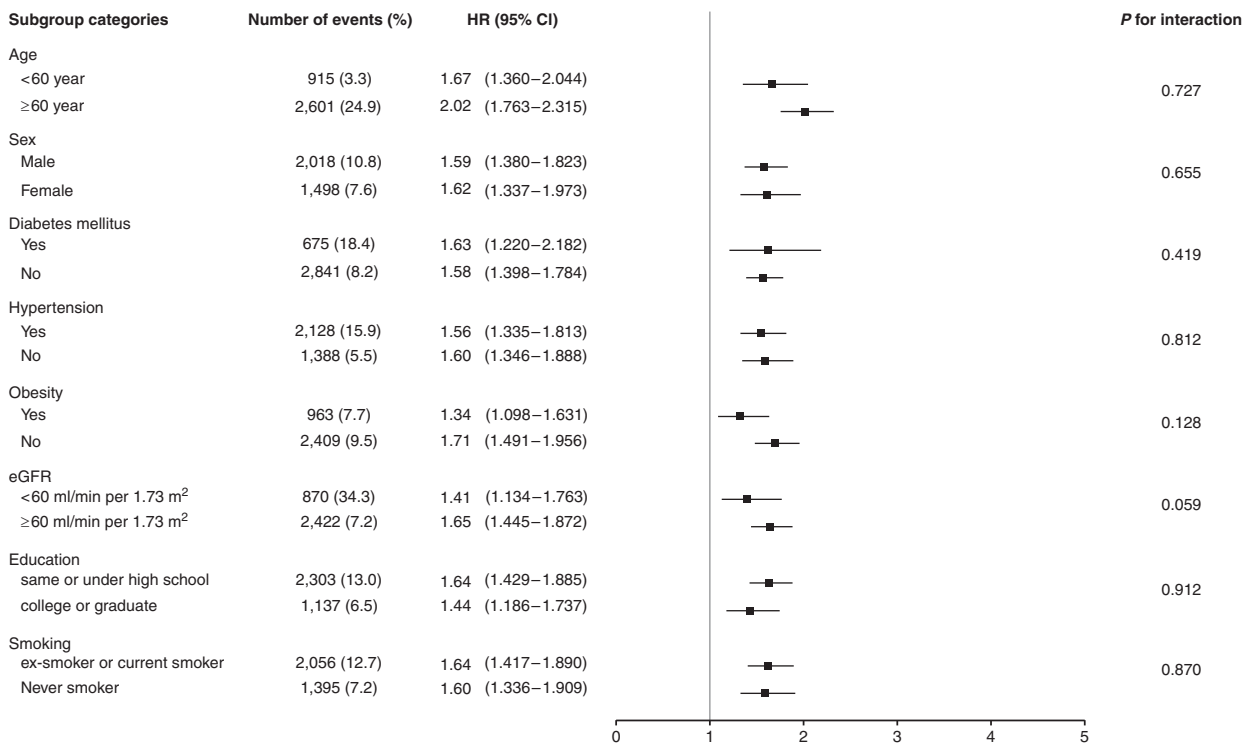
Subgroup categories	Number of events (%)	HR (95% CI)		*P* for interaction
Age				
<60 year	915 (3.3)	1.67 (1.360−2.044)		0.727
≥60 year	2,601 (24.9)	2.02 (1.763−2.315)		
Sex				
Male	2,018 (10.8)	1.59 (1.380−1.823)		0.655
Female	1,498 (7.6)	1.62 (1.337−1.973)		
Diabetes mellitus				
Yes	675 (18.4)	1.63 (1.220−2.182)		0.419
No	2,841 (8.2)	1.58 (1.398−1.784)		
Hypertension				
Yes	2,128 (15.9)	1.56 (1.335−1.813)		0.812
No	1,388 (5.5)	1.60 (1.346−1.888)		
Obesity				
Yes	963 (7.7)	1.34 (1.098−1.631)		0.128
No	2,409 (9.5)	1.71 (1.491−1.956)		
eGFR				
<60 ml/min per 1.73 m²	870 (34.3)	1.41 (1.134−1.763)		0.059
≥60 ml/min per 1.73 m²	2,422 (7.2)	1.65 (1.445−1.872)		
Education				
same or under high school	2,303 (13.0)	1.64 (1.429−1.885)		0.912
college or graduate	1,137 (6.5)	1.44 (1.186−1.737)		
Smoking				
ex-smoker or current smoker	2,056 (12.7)	1.64 (1.417−1.890)		0.870
Never smoker	1,395 (7.2)	1.60 (1.336−1.909)		

Figure 3. | **The increased risk of all-cause mortality associated with low-grade albuminuria (ACR ≥10.010 mg/g) was evident regardless of age, sex, diabetes mellitus, hypertension, obesity, eGFR, education, and smoking.**
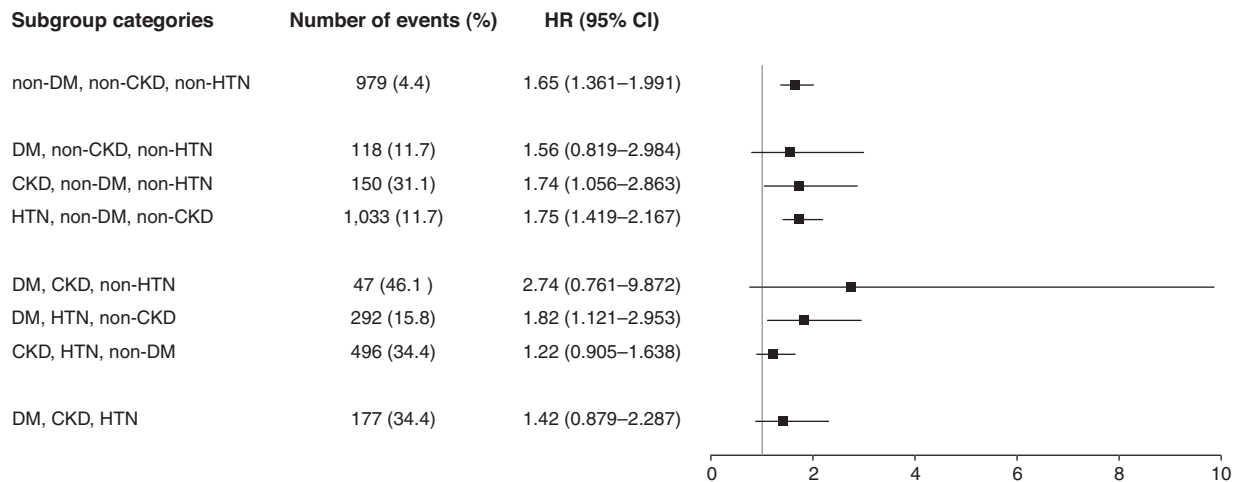
Subgroup categories	Number of events (%)	HR (95% CI)
non-DM, non-CKD, non-HTN	979 (4.4)	1.65 (1.361–1.991)
DM, non-CKD, non-HTN	118 (11.7)	1.56 (0.819–2.984)
CKD, non-DM, non-HTN	150 (31.1)	1.74 (1.056–2.863)
HTN, non-DM, non-CKD	1,033 (11.7)	1.75 (1.419–2.167)
DM, CKD, non-HTN	47 (46.1)	2.74 (0.761–9.872)
DM, HTN, non-CKD	292 (15.8)	1.82 (1.121–2.953)
CKD, HTN, non-DM	496 (34.4)	1.22 (0.905–1.638)
DM, CKD, HTN	177 (34.4)	1.42 (0.879–2.287)

Figure 4. | **The association of low-grade albuminuria with all-cause mortality was significant in individuals with low cardiovascular risks.**

analyses were also performed in the group without DM, CKD (eGFR <60 ml/min per 1.73 m^2), and hypertension, and in the groups with at least one of these conditions (Figure 4). In subgroup analyses, compared with the reference group (ACR <4.171 mg/g), we analyzed the association of low-grade albuminuria (ACR ≥10.010 mg/g) with all-cause mortality and found the association was significant in individuals with low CV risks.

Sensitivity Analyses

For sensitivity analyses, we drew cubic spline curves with different reference points of ACR. The cubic spline curves demonstrated a relatively linear relationship between ACR and the risk of all-cause mortality for the reference points of 4.00 mg/g, 5.00 mg/g, and 6.00 mg/g (Supplemental Figure 3).

Discussion

Although there was interest in the association between low-grade albuminuria and poor clinical outcomes, the current guidelines consider ACR ≥30 mg/g to be clinically meaningful albuminuria (9). In this study, we found that albuminuria in the normoalbuminuria category (ACR <30 mg/g) was associated with all-cause and CV mortality. Risks of all-cause mortality were prominent in the non-DM, nonhypertensive, and non-CKD groups.

A previous study showed that, even in the normoalbuminuria category (ACR <30 mg/g), the prevalence of low eGFR (<60 ml/min per 1.73 m^2) and increased urine α1-microglobulin–creatinine ratio, an indicator of renal tubular dysfunction, was high in the elderly Chinese population (26). This study suggested the possibility that renal damage may have already occurred in normoalbuminuria. However, the degree of renal injury was not analyzed by subdividing the normoalbuminuria category in that study. In another study, the condition of patients with DM and renal dysfunction (eGFR <60 ml/min per 1.73 m^2) but without albuminuria was even named normoalbuminuric DKD

because the prevalence of renal dysfunction could not be ignored, ranging from 21% to 63% (21,27). Another study showed that low-grade albuminuria (8.1–29.6 mg/g in males and 11.8–28.9 mg/g in females) was associated with left ventricular hypertrophy and left ventricular dysfunction in patients with hypertension (19). Collectively, these studies considered normoalbuminuria a pathologic state and suggested a need for monitoring. However, these studies analyzed <1000 subjects and, of these, few patients were in the normoalbuminuria category. In addition, it was difficult to generalize the results of these studies because they were limited to patients with diseases such as DM (21) or hypertension (19). Moreover, there were studies that showed the association between albuminuria within normoalbuminuria and poor clinical outcome in the general population. The Reasons for Geographic and Racial Differences in Stroke study showed that low-grade albuminuria (ACR 10–30 mg/g) increased the risk of all-cause mortality (28), and the ARIC study showed that low-grade albuminuria (ACR 10–30 mg/g) increased the risks of CV events and all-cause mortality in the elderly population (mean age, 63 years) (18). However, these studies used ACR <10 mg/g as a reference, and the relationship between albuminuria and mortality was not analyzed in categories with ACR <10 mg/g. The prevention of Renal and Vascular End Stage Disease study, which analyzed 40,548 subjects, showed that albuminuria was a predictor of all-cause mortality in the general population (29). However, that study analyzed >40,000 subjects with microalbuminuria, macroalbuminuria, and normoalbuminuria, and the enrollment period of subjects was shorter than that in our study. In addition, subjects were limited to the city of Groningen, The Netherlands, and various races were not analyzed. On the other hand, it was also shown that low-grade albuminuria and mortality were associated in the group with low CV risks. In a nondiabetic, normotensive, Japanese group, low-grade albuminuria (ACR ≥9.6 mg/g for men, ≥12.0 mg/g for women) was associated with CV disease and all-cause mortality (30). In addition, an ARIC study showed

that intermediate normal albuminuria (ACR 5–9 mg/g) was associated with incident heart failure, defined as heart failure–related hospitalization or death in participants with low CV risks (20). These studies suggested that the association between albuminuria and CV mortality did not necessarily mediate CV diseases because this association was significant even in participants with low CV risks. These results were confirmed in this study using a US nationally representative study population.

The risk of all-cause mortality was higher in low-grade albuminuria (ACR ≥6.211 mg/g) than in the reference group (ACR <4.171 mg/g). Similar patterns were observed between low-grade albuminuria and CV mortality. It is suggested that albuminuria should be carefully monitored for individuals with an ACR of <10 mg/g and those with an ACR of 10–30 mg/g. Albuminuria has been associated with hypertension (31), DM (8), dyslipidemia (32), obesity (33,34), CKD (9), and activation of the renin-angiotensin-aldosterone system (35), which are traditional risk factors for CV disease. Low-grade albuminuria was also associated with other risk factors for CV disease, such as frailty in the elderly (36), pulmonary arterial hypertension (37), and left ventricular hypertrophy (19). Collectively, these risk factors could contribute to all-cause and CV mortality. Moreover, non-CV mortality could also contribute to all-cause mortality. Cancer mortality is the main cause of death worldwide and in the United States (38,39). In our data, the main causes of death were malignant neoplasms and heart disease. Indeed, albuminuria was associated with cancer incidence (40). Albuminuria was also associated with inflammation, which is a risk factor for cancer, and is also considered a manifestation of paraneoplastic syndrome (40). Therefore, albuminuria could affect the incidence of malignant neoplasms and subsequently increase the risk of all-cause mortality.

In the groups with few risk factors, such as the non-DM, nonhypertensive, and non-CKD groups (eGFR ≥60 ml/min per 1.73 m^2), low-grade albuminuria (ACR ≥10.010 mg/g) was associated with the risk of all-cause mortality. We also confirmed the results from previous studies that showed that low-grade albuminuria was associated with mortality in non-DM groups (20,30). Furthermore, low-grade albuminuria was reported to be associated with the risk of developing nonalcoholic fatty liver disease and liver fibrosis, especially in non-DM groups (41). Albumin leakage through the vessel wall might induce an inflammatory response (42), which induces nonalcoholic fatty liver disease and liver fibrosis (43). In our study, subgroup analyses showed that the patients in the non-CKD group had a higher risk of mortality than the patients in the CKD group. The proportions of patients with high-risk factors, such as old age, DM, hypertension, and CV disease, were higher in the CKD group compared with the non-CKD group. The very high prevalence of such risk factors obscures the effect of albuminuria, an indicator for endothelial damage, on mortality, even with statistical adjustments. Endothelial damage was also observed in the non-CKD group. It has been reported that subnormal renal function (eGFR 61–90 ml/min per 1.73 m^2) could predict CV events in the diabetic group with normoalbuminuria (44). Collectively, these findings suggest that, even in individuals with few CV risks that have not yet been screened for albuminuria, it is necessary to carefully monitor for the occurrence of low-grade albuminuria.

The strengths of this study include the use of the United States nationally representative, large-scale study population. Nevertheless, this study has several limitations. By measuring baseline ACR only once, each albuminuria status could be misclassified. Because it is an observational study, there were limitations in concluding causal relationships.

In conclusion, low-grade albuminuria is associated with an increased risk of all-cause and CV mortality. In particular, risk was most pronounced in the non-DM, nonhypertensive, and non-CKD groups. Our findings suggest that low-grade albuminuria is associated with mortality and should be monitored even in groups with low CV risks.

Author Contributions

E. Bae, M. Kang, D. K. Kim, E.Y. Kim, Y.C. Kim, S. Kwon, J. Lee, J.P. Lee, C.S. Lim, and J.I. Shin were responsible for methodology; E. Bae, M. Kang, D.K. Kim, E.Y. Kim, S. Kwon, J. Lee, J.P. Lee, C.S. Lim, and J.Y. Park were responsible for formal analysis; J.P. Lee were responsible for funding acquisition; M. Kang, Y.C. Kim, J.P. Lee, and J.I. Shin reviewed and edited the manuscript; M. Kang wrote the original draft and were responsible for data curation and visualization; M. Kang, S. Kwon, and J.P. Lee conceptualized the study; J.P. Lee provided supervision; J.Y. Park was responsible for investigation; and all authors read and approved the final manuscript.

Data Sharing Statement

All data is included in the manuscript and/or supporting information.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0003912021/-/DCSupplemental.

Supplemental Figure 1. Flow diagram of study cohort.

Supplemental Figure 2. Subgroup associations of urine albumin creatine ratio with all-cause mortality.

Supplemental Figure 3. The relationship between the urine albumin-creatinine ratio and mortality.

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