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Association of normal range of urinary albumin-to-creatinine ratio with all-cause mortality among diabetic adults with preserved kidney function: National Health and Nutrition Examination Survey (NHANES) 2003–2018

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Abstract

Aim: To ascertain the connection between normal-range urinary albumin-to-creatinine ratio (UACR) and all-cause mortality (ACM) among diabetic adults with preserved eGFR.

Methods: We used data from the 2003–2018 National Health and Nutrition Examination Survey. Nationally representative cross-sectional survey data linked with mortality outcomes from the National Death Index. Restricted cubic spline curves (RCS) and multivariable Cox regression models alongside subgroup analyses were utilised for estimating hazard ratios (HRs) and 95% confidence intervals (CIs) for UACR-ACM interplay, adjusting for demographic, socioeconomic, biochemical, medication and medical history factors. The UACR's predictive accuracy for survival outcomes was determined through receiver operating characteristic analysis.

Results: The RCS regression analysis showcased that there was no significant evidence to support a nonlinear relationship between normal-range UACR and ACM ($p = 0.080$ for nonlinearity) in participants with diabetes mellitus (DM). In the model 2 adjusted for multiple confounding variables, the HR for ACM was 1.22 (95% CI, 1.06–1.40) per 10 mg/g raise in continuous UACR and 1.50 (95%CI, 1.18–1.91) for the high UACR tertile compared to the low. Kaplan–Meier analysis showed significantly lower survival rates in the medium and high UACR groups ($p < 0.001$). Subgroup analysis manifested a significant UACR–body mass index (BMI) interaction ($p = 0.033$ for interaction).

Conclusions: In DM adults without overt kidney dysfunction, elevated normal-range UACR was independently related to escalated ACM, particularly in those with normal BMI. To conclude, we underscore the significance of early risk assessment in DM patients with normal-range albuminuria, even without overt kidney dysfunction.

KEYWORDS
mortality, diabetes, NHANES, urinary albumin-to-creatinine ratio

1 | INTRODUCTION

In a global context, diabetes mellitus (DM) constitutes a considerable public health concern,[1] with 40% of patients who have type 2 DM (T2DM) developing diabetic kidney disease (DKD), a significant mortality cause in T2DM patients, contributing to the mortality burden.[2] Traditionally, DKD has been identified as a urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g and/or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.[3]

Recently, DKD classical pattern along with declined eGFR starts after the progressive worsening of albuminuria has been challenged owing to the novel prevailing DKD phenotype that exhibits significant renal malfunction without elevated UACR levels: nonalbuminuric DKD (NA-DKD).[4,5] The frequency of normal-range UACR in diabetes of DM, despite reduced eGFR, is increasing.[6] Prior research has established that UACR ≥30 mg/g and lowered eGFR are independent mortality rate risk factors in T2DM.[7,8] Furthermore, elevated UACR, even within the traditional normal range of <30 mg/g, has been reported to be associated with higher risks of metabolic syndrome, all-cause mortality (ACM).[9–13]

However, there are limited data on whether normal-range UACR is associated with ACM among relatively healthy individuals with diabetes who have preserved kidney function, defined as eGFR ≥60 mL/min/1.73 m^2 and UACR <30 mg/g. Accordingly, our aim was to uncover the connection between normal-range UACR and ACM among DM adults with preserved kidney function using a public database of the National Health and Nutrition Examination Survey (NHANES) representative sample.

2 | METHODS

2.1 | Study population

The study data were obtained from the large cross-sectional program NHANES that evaluates the American populations' health and nutrition status administered by the National Center for Health Statistics. All enrolled individuals provided informed consent. Guang'anmen Hospital China Academy of Chinese Medical Sciences Institutional Review Board came to the conclusion that this study did not require review or informed consent because the study data were available to the public and had been de-identified.

The analysis included 80 312 participants from eight consecutive NHANES cycles (2003–2018), excluding those (1) who were pregnant ($n = 1051$), (2) aged <18 years ($n = 32\,508$), (3) missing mortality data ($n = 131$), (4) without DM ($n = 38\,622$), (5) missing information on urine albumin and creatinine data ($n = 509$), (6) missing information on serum creatinine data ($n = 373$), (7) with eGFR <60 mL/min/1.73 m^2 ($n = 641$), (8) with UACR ≥30 mg/g ($n = 2155$) and (9) with body mass index (BMI; Kg/m^2) <18.5 kg/m^2 ($n = 14$). Eventually, 4308 participants qualified for the analysis (Figure S1).

2.2 | DM and UACR definitions

The existence of one or more of these criteria was used to define DM: (1) fasting plasma glucose ≥7.0 mmol/L or 2-h oral glucose tolerance test level ≥11.1 mmol/L; (2) glycated haemoglobin A1c (HbA1c) ≥6.5%; (3) casual blood glucose level ≥11.1 mmol/L; (4) self-reported doctor DM diagnosis; and (5) usage of DM medication or insulin.

The urinary albumin concentration (a solid-phase fluorescent immunoassay, mg/dL) was divided by the urine creatinine concentration (the Jaffe reaction in 2003–2006 and the enzymatic method in 2007–2018, mg/L) in order to calculate UACR. Therefore, to adjust the 2003–2006 urine creatinine levels, the NHANES-recommended equation was employed. Besides considering UACR as a continuous outcome variable, we further categorised the normal-range UACRs into low (<6.1 mg/g), medium (6.1–11.08 mg/g) and high (11.08 to <30 mg/g) tertiles.

2.3 | Outcomes and covariates

ACM served as our outcome, with mortality data obtained from the National Death Index (NDI). Calculating each participant's follow-up duration started from the study enrolment date to either the death date or 31 December 2019 (the most recent NDI database update). Demographic data (age, sex, race and family income-to-poverty ratio [PIR]), examination data (serum creatinine [Scr], triglyceride [TG], total cholesterol [TC], high-density lipoprotein [HDL] and low-density lipoprotein [LDL] all expressed in μmol/L and HbA1c [%]) and health questionnaires (smoking status, body mass index [BMI], eGFR, hypertension [HPT], cardiovascular disease [CVD], renin–angiotensin–aldosterone system [RAAS] inhibitors use) were adopted. Age (years), BMI, Scr, TG, TC, HDL, LDL, eGFR and HbA1c were continuous variables. Race (non-Hispanic Black/White and Mexican American, among others), sex (male/female), PIR, smoking status, BMI status, HPT (yes/no), RAAS inhibitors use (yes/no) and CVDs (yes/no) were categorical variables. The PIR was categorised into <1.0%, 1.0%–3.0% and >3.0% groups. Smoking status categorisation was as follows: never (<100 cigarettes in a lifetime), former (>100 cigarettes but not currently) and current (>100 cigarettes and actively). HPT was determined as a self-reported HPT history, an average systolic ≥140 and/or diastolic blood pressure ≥90 mmHg and antihypertensive drug usage. The BMI status (weight [kg]/height [m^2]) was divided into three groups: normal (18.5 ≤ BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2) and obesity (≥30 kg/m^2). CVD was determined on the basis of a self-reported stroke, angina, congestive heart failure, heart attack or coronary artery disease history. The eGFR (mL/min/1.73 m^2) calculation was performed by the 2021 Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation.[14]

2.4 | Statistical analysis

Data analysis was carried out from 1 June to 30 September 2024, and accounted for sampling weights and complex sampling designs.

Sampling weight calculation: the 16-year fasting subsample Mobile Examination Center weight is derived by dividing the 2-year fasting subsample Mobile Examination Center weight by 8. Continuous variables were reported as weighted means with their respective standard deviations (SDs) while categorical variables were reported as weighted percentages. In order to assess baseline characteristics across UACR groups, the chi-square test was used for categorical variables and the ANOVA was used for continuous variables.

We applied a weighted three-knotted restricted cubic spline for exploring the potential nonlinear interconnection between the UACR and ACM. Aiming at examining UACR and mortality interplay as a continuous (per 10 mg/g increase) and category variable (UACR tertiles), multivariable Cox regression models were deployed for calculating HRs with 95% CIs. We estimated two models: age, sex, race, BMI, smoking status and PIR were adjusted in model 1, while Scr, eGFR, HbA1c, TG, RAAS inhibitors use, hypertension and CVD history were additionally adjusted in model 2. Survival probabilities were ascertained by the K–M method, conducting comparisons by the log-rank test.

In subgroup analyses, we examined whether the potential correlation of UACR values with mortality was moderated by age (<65 vs. ≥65 years), sex, race, smoking status, BMI, RAAS inhibitors use, HPT and CVD history. Through interaction terms as well as likelihood ratio tests, p values for interaction were assessed and evaluated. In addition, we successively excluded individuals with CVD and HPT history or those aged >80, as these groups already have a higher mortality risk, which could potentially obscure the independent effect of UACR on ACM. Receiver operating characteristic (ROC) analysis[15] was performed via the 'timeROC' package to assess UACR predictive accuracy for survival outcomes at various time points. Statistical significance was determined by a two-tailed $p < 0.05$ using R Statistical Software version 4.4.1 (http://www.r-project.org).

3 | RESULTS

According to the inclusion criteria, 4308 adults out of 8000 DM patients were included (Figure S1), accounting for 54% (mean [SD] age, 56.46 [13.49] years; 2207 male [51.9%]) (Table 1). The maximum UACR value was 29.88 mg/g, and the minimum was 0.54 mg/g. Relying upon weighted UACR levels, the population was divided into low (<6.1 mg/g), medium (6.1–11.08 mg/g) and high (11.08–30 mg/g) tertiles. The high UACR tertile participants tended to be older and displayed escalated HbA1c, TG and Scr levels, decreased PIR, as well as CVD, HPT and RAAS inhibitors use histories. The eGFR values were significantly similar across UACR tertiles, differing by only 1.83 mL/min/1.73 m^2 ($p > 0.05$). Table 1 presents the population's detailed features.

TABLE 1 Baseline characteristics of diabetic participants with normal range of UACR and eGFR ≥60 mL/min/1.73 m^2 in NHANES (2003–2018).[a]

	Participants, No. (weighted %)				
		UACR, mg/g[b]			
Characteristic	Total ($n = 4308$)	Low ($n = 1303$)	Medium ($n = 1470$)	High ($n = 1535$)	p-Value
Age, mean (SD), years	56.46 (13.49)	53.90 (12.86)	57.70 (12.93)	57.75 (14.35)	<0.001
Sex					
Male	2207 (51.9)	728 (56.5)	712 (48.8)	767 (50.4)	0.011
Female	2101 (48.1)	575 (43.5)	758 (51.2)	768 (49.6)	
Race					
Non-Hispanic Black	964 (12.7)	353 (14.4)	302 (11.7)	309 (12.1)	0.014
Non-Hispanic White	1518 (63.1)	459 (64.5)	515 (62.9)	544 (61.9)	
Mexican American	876 (9.8)	223 (7.9)	314 (10.8)	339 (10.8)	
Other[c]	950 (14.3)	268 (13.2)	339 (14.7)	343 (15.3)	
BMI, mean (SD)	32.84 (7.38)	32.78 (7.28)	32.91 (7.55)	32.73 (7.40)	0.886
BMI status					
Normal weight	547 (11.0)	148 (10.9)	182 (11.1)	217 (11.1)	0.952
Overweight	1323 (28.5)	408 (29.5)	439 (27.9)	476 (28.2)	
Obesity	2384 (60.4)	733 (59.6)	832 (61.0)	819 (60.7)	
Smoking status					
Never	2251 (51.2)	696 (52.9)	768 (50.1)	787 (50.4)	0.810
Former	1334 (32.4)	389 (31.5)	454 (32.6)	491 (33.0)	
Current	710 (16.5)	212 (15.7)	245 (17.3)	253 (16.6)	

TABLE 1 (Continued)

Characteristic	Participants, No. (weighted %)				
	Total	UACR, mg/g[b]			
		Low	Medium	High	
	(*n* = 4308)	(*n* = 1303)	(*n* = 1470)	(*n* = 1535)	*p*-Value
Hypertension					
No	1806 (42.6)	617 (48.9)	594 (40.7)	595 (38.2)	<0.001
Yes	2502 (57.4)	686 (51.1)	876 (59.3)	940 (61.8)	
Scr, μmol/L	74.58 (16.29)	78.02 (15.65)	73.32 (16.17)	72.37 (16.46)	<0.001
eGFR, ml/min/1.73m^2	93.09 (16.66)	92.23 (16.43)	93.02 (16.24)	94.06 (17.26)	0.097
HbA1c, %	6.95 (1.50)	6.69 (1.31)	6.93 (1.50)	7.21 (1.64)	<0.001
HDL, mmol/L	1.24 (0.36)	1.24 (0.35)	1.25 (0.38)	1.22 (0.36)	0.127
LDL, mmol/L	2.78 (0.96)	2.74 (0.97)	2.81 (0.97)	2.79 (0.93)	0.602
TG, mmol/L	2.15 (2.03)	1.96 (1.50)	2.13 (1.83)	2.35 (2.58)	<0.001
TC, mmol/L	4.87 (1.21)	4.80 (1.15)	4.89 (1.16)	4.91 (1.30)	0.182
RAAS inhibitors					
No	2280 (53.5)	741 (58.2)	777 (52.7)	762 (49.8)	0.004
Yes	2028 (46.5)	562 (41.8)	693 (47.3)	773 (50.2)	
CVD history					
No	3527 (82.1)	1104 (85.0)	1205 (81.7)	1218 (79.6)	0.023
Yes	781 (17.9)	199 (15.0)	265 (18.3)	317 (20.4)	
Family income poverty ratio, mean (SD), %					
<1.0	894 (13.9)	248 (12.3)	311 (14.2)	335 (15.3)	0.002
1.0–3.0	1723 (35.9)	480 (32.2)	607 (36.9)	636 (38.6)	
>3.0	1294 (42.9)	464 (49.1)	405 (40.5)	425 (39.0)	
Not recorded	397 (7.3)	111 (6.4)	147 (8.4)	139 (7.1)	
Cardiovascular death					
No	4176 (97.5)	1278 (98.8)	1428 (97.2)	1470 (96.5)	0.002
Yes	132 (2.5)	25 (1.2)	42 (2.8)	65 (3.5)	
Malignant neoplasms death					
No	4152 (96.9)	1263 (97.8)	1415 (96.8)	1474 (96.0)	0.053
Yes	156 (3.1)	40 (2.2)	55 (3.2)	61 (4.0)	

Abbreviations: BMI status, body mass index status; CVD history, cardiovascular disease history; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; RAAS inhibitors, renin–angiotensin–aldosterone system inhibitors; Scr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglyceride; UACR, urinary albumin-to-creatinine ratio.

[a]Data were weighted to account for complex survey designs.

[b]Grouped by tertiles into low (<6.1 mg/g), medium (6.1–11.08 mg/g) and high (11.08 to <30 mg/g).

[c]Other included American Indian or Alaska Native, Asian, Native Hawaiian Pacific Islander, multiple races or unknown.

3.1 | Relationship between UACR and ACM

Throughout a 7-year median follow-up (IQR, 3.8–10.8) from 2003 to 2018, the ACM incidence rate was 15.28/1000 person-years. In terms of mortality causes, the high UACR tertile showed significantly higher cardiovascular mortality than the low tertile ($p = 0.002$) and the proportion of deaths due to malignant neoplasms (156 [3.1%]) exceeded that of cardiovascular disease (132 [2.5%]) (Table 1). The restricted cubic spline modelling showcased that there is no significant evidence to support a nonlinear relationship between the normal UACR range and the ACM ($p = 0.080$ for nonlinearity) (Figure 1). After adjustment for multiple confounding variables in model 2, all participants demonstrated an escalated ACM risk (HR: 1.22, 95% CI, 1.06–1.40) per 10 mg/g increase in continuous UACR (Table 2). Similar results were also found when we converted normal-range UACR into categorical variables for piecewise multivariate Cox regression, the adjusted HR of the high UACR group in model 2 was 1.50 (95%CI, 1.18–1.91), with a significant trajectory test between UACR tertiles and ACM (for trend $p < 0.001$). The result showed an elevated ACM risk in the higher UACR group. Kaplan–Meier analysis confirmed significantly

lower survival rates in groups with medium and high UACR ($p < 0.001$) (Figure S2).

3.2 | Subgroup and sensitivity analyses

The outcomes of subgroup analyses by age, sex, race, smoking status, BMI, RAAS inhibitors use, HPT and CVD history showcased that the relation between continuous UACR measurements and ACM remained statistically significant in all subgroups (Figure 2). The continuous UACR did not significantly interact with any of the aforementioned characteristics ($p < 0.01$ for interaction), with the exception of populations with different BMI ($p = 0.033$ for interaction). Notably, normal-weight individuals exhibited the highest ACM risk associated with UACR.

The sensitivity analysis results were inconsistent for relatively healthy participants without HPT or those aged <80 years when UACR was treated as a continuous variable (Tables S1 and S2). But when UACR was treated as a categorical variable, the finding that the high UACR group had the highest risk of ACM remained consistent for participants without CVD (HR, 1.66; 95% CI, 1.19–2.30), hypertension (HR, 1.74; 95% CI, 1.05–2.89) and those aged <80 years (HR, 1.55; 95% CI, 1.19–2.01) (Table 3, Tables S1 and S2). The sensitivity analysis results revealed a significant trend across UACR tertiles and ACM among participants aged <80 and with no CVD history, respectively ($p < 0.01$ for trend).

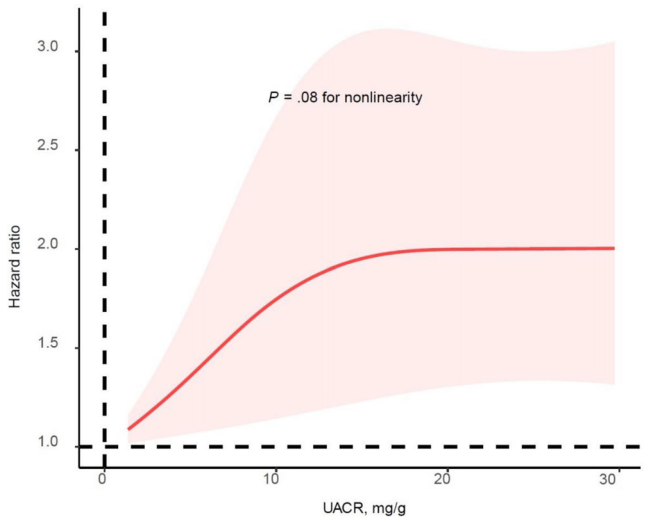

FIGURE 1 Association of urinary albumin-to-creatinine ratio and all-cause mortality among diabetic adults with preserved kidney function in the National Health and Nutrition Examination Survey (2003–2018) using restricted cubic spline models. Hazard ratio (red line) and 95% confidence interval (shaded area) were adjusted for age, sex, race, body mass index status, smoking status and family income-to-poverty ratio, serum creatinine, estimated glomerular filtration rate, glycated haemoglobin A1c, triglyceride, renin–angiotensin–aldosterone system inhibitors use, hypertension and cardiovascular disease history.

3.3 | ROC analysis of UACR predictive value for ACM in DM

The ROC analysis results demonstrated the UACR prognostic value for ACM. The AUC of the UACR for 1-, 3-, 5- and 10-year ACM reached 0.78 (95% CI, 0.69–0.87), 0.80 (95% CI, 0.76–0.84), 0.81 (95% CI, 0.78–0.84) and 0.82 (95% CI, 0.79–0.84), respectively (Figure S3a,b). The findings suggested that UACR appears to have valid predictive value for ACM over both short and long durations.

4 | DISCUSSION

This prospective cohort study with a 7-year median follow-up of 4308 DM adults evaluated that there was no statistically significant nonlinear relationship between normal-range UACR and ACM

TABLE 2 Hazard ratios of ACM by UACR levels among adults with diabetes in NHANES (2003–2018).

		HR (95% CI), *p*-value					
Characteristic	**Incidence rate[a]**	**Crude model[b]**		**Model 1[c]**		**Model 2[d]**	
UACR (per 10 mg/g increment)	15.28	1.57 (1.39–1.77)	<0.001	1.28 (1.11–1.47)	<0.001	1.22 (1.06–1.40)	<0.01
UACR category (mg/g median [range])							
Low UACR (4.94 [<6.1])	9.07	1 [Reference]		1 [Reference]		1 [Reference]	
Medium UACR (8.65 [6.1–11.08])	14.82	1.64 (1.26–2.15)	<0.001	1.27 (0.96–1.67)	>0.05	1.23 (0.93–1.63)	>0.05
High UACR (17.41 [11.08 to <30])	22.40	2.51 (1.93–3.27)	<0.001	1.63 (1.27–2.08)	<0.001	1.50 (1.18–1.91)	<0.001
p-Value for trend		<0.00001		<0.001		<0.001	

Abbreviations: ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; UACR, urinary albumin-to-creatinine ratio.

[a]Calculated as *per 1000 Person-Years*.

[b]No covariates were adjusted.

[c]Adjusted for age, sex, race, body mass index status, smoking status and family income-to-poverty ratio.

[d]Adjusted for age, sex, race, body mass index status, smoking status and family income-to-poverty ratio, serum creatinine, estimated glomerular filtration rate; glycated haemoglobin A_{1c}; triglyceride; renin–angiotensin–aldosterone system inhibitors use, hypertension and cardiovascular disease history.

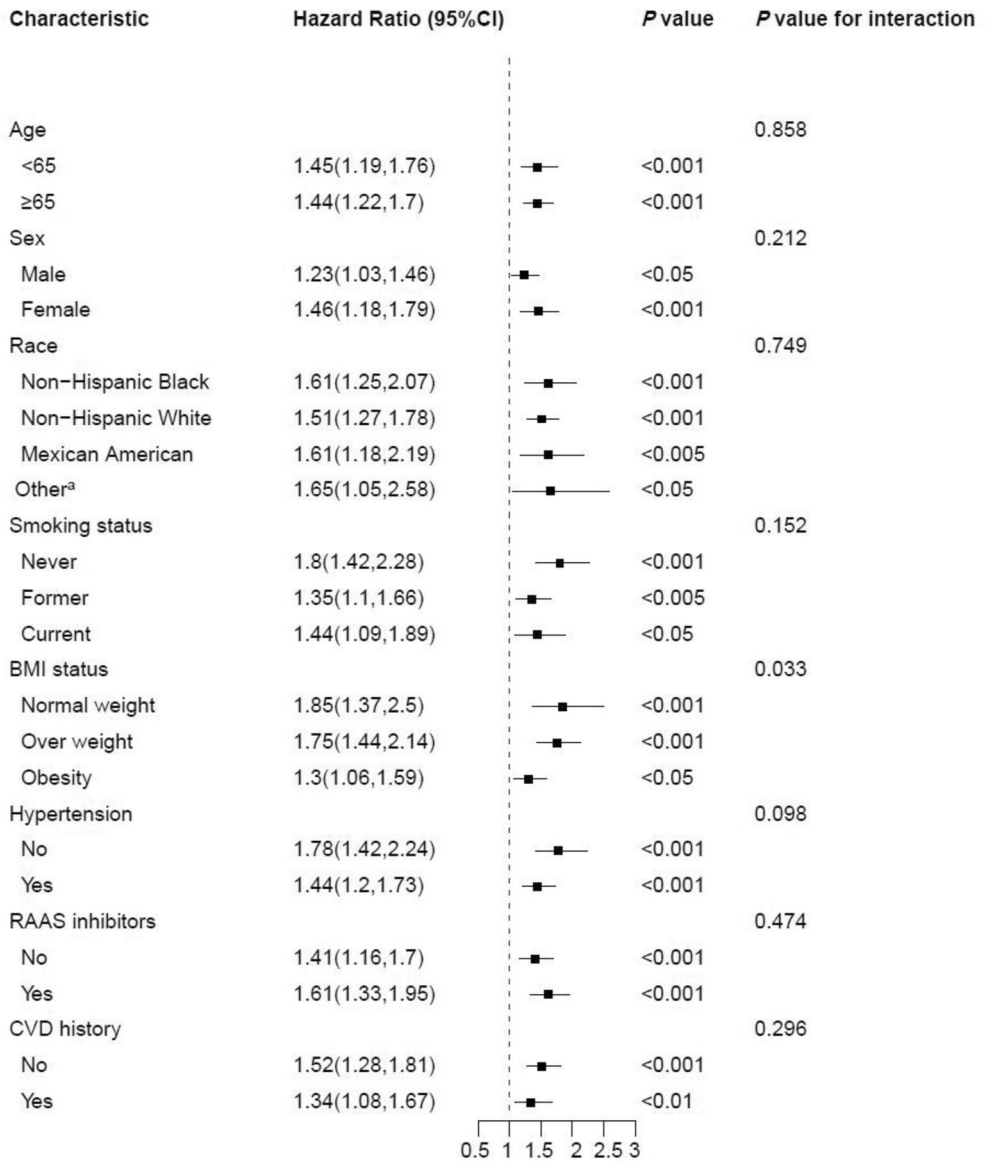

FIGURE 2 Subgroup analysis of the association of urinary albumin-to-creatinine ratio and all-cause mortality among diabetic adults with preserved kidney function. [a]Other included American Indian or Alaska Native, Asian, Native Hawaiian Pacific Islander, multiple races or unknown. Hazard ratios and 95% CIs were adjusted for family income-to-poverty ratio, serum creatinine, estimated glomerular filtration rate, glycated haemoglobin A1c, triglyceride and triglyceride. BMI, body mass index; CI, confidence interval; CVD history, cardiovascular disease history; RAAS inhibitors, renin–angiotensin–aldosterone system inhibitors.

TABLE 3 Hazard ratios of ACM by UACR levels among diabetic adults without CVD in NHANES (2003–2018).

		HR (95% CI), *p*-value					
Characteristic	**Incidence rate[a]**	**Crude model[b]**		**Model 1[c]**		**Model 2[d]**	
UACR (per 10 mg/g increment)	15.15	1.54 (1.31–1.81)	<0.001	1.34 (1.13–1.60)	<0.001	1.32 (1.10–1.58)	<0.01
UACR category (mg/g, median [range])							
Low UACR (4.93 [<6.1])	6.96	1 [Reference]		1 [Reference]		1 [Reference]	
Medium UACR (8.79 [6.1–11.08])	11.22	1.61 (1.15–2.28)	<0.01	1.30 (0.92–1.83)	>0.05	1.26 (0.90–1.77)	>0.05
High UACR (17.75 [11.08 to <30])	15.46	2.24 (1.59–3.15)	<0.001	1.72 (1.23–2.42)	<0.01	1.66 (1.19–2.30)	<0.001
p-Value for trend		<0.001		<0.001		<0.01	

Abbreviations: ACM, all-cause mortality; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; UACR, urinary albumin-to-creatinine ratio.

[a]Calculated as *per 1000 Person-Years*.

[b]No covariates were adjusted.

[c]Adjusted for age, sex, race, body mass index status, smoking status and family income-to-poverty ratio.

[d]Adjusted for age, sex, race, body mass index status, smoking status, family income-to-poverty ratio, serum creatinine, estimated glomerular filtration rate; glycated haemoglobin A1c, triglyceride, renin–angiotensin–aldosterone system inhibitors use and hypertension.

($p = 0.080$ for nonlinearity). However, a potential nonlinear trend cannot be entirely ruled out. Further studies are needed to validate this trend. The eGFR only varied by 1.83 mL/min/1.73 m^2 across UACR tertiles, and HRs for the interconnection between higher UACR and ACM were not affected by eGFR adjustment in the regression models. The consistent results that higher normal-range UACR was associated with the highest ACM in diabetic participants without CVD, HPT or aged <80 years further demonstrate that our findings are robust. Our study underscores the significance of early monitoring of normal UACR and risk assessment in DM patients, particularly with normal BMI, even in the absence of overt kidney dysfunction.

Several studies have manifested that normal-range UACR (< 30 mg/g) is related to a significantly escalated ACM risk.[9–13] A retrospective meta-analysis with over 27 million adults has reported that UACR of 10 mg/g to <30 mg/g was significantly associated with an increased ACM risk among individuals exhibiting an eGFR of 90–104 mL/min/1.73 m^2, in comparison with those in the UACR <10 mg/g with the same eGFR level group, with an HR of 1.30.[16] However, prior studies were conducted in the general population, which included individuals with DM, but did not specifically focus on this group. Among people with DM, hyperglycaemia-induced inflammation and oxidative stress often lead to a high prevalence of albuminuria, which eventually leads to kidney damage[17]; the evidence regarding normal UACR status and ACM is limited and mixed. An earlier study, using 1988–2006 NHANES data, reported increasing mortality rates for US DM adults with a normal range of UACR and an eGFR <60 mL/min/1.73 m^2 from 35 deaths/1000 person-years during 1988–1994 to 51 mortalities during 2003–2006.[6] In China, another multicentre prospective cohort study of T2DM individuals also found that patients with reduced eGFR but without albuminuria exhibited an increased ACM risk (HR: 1.59, 95% CI: 1.04–2.44) relative to those without DKD.[18] Nevertheless, among Japanese individuals with T2DM, the Japan Diabetes Clinical Data Management Study found no significantly higher mortality risk in those with NA-DKD, unlike those with normal kidney function.[19] Proteinuria and eGFR are independent risk factors for ACM in DM,[7,8] even the traditional normal-range UACR correlates with an increased mortality risk.[9] These studies did not consider the association between normal UACR and ACM and overlooked the risk assessment. In contrast, the current study concentrated on DM patients with a normal-range UACR alongside an eGFR ≥60 mL/min/1.73 m^2. Employing 2003–2018 NHANES data, we highlighted a promising finding that ACM risk remained elevated in DM individuals with high-normal UACR levels, even among those who have an eGFR ≥60 mL/min/1.73 m^2, following the potential confounder adjustment. The adjusted HRs of the high UACR category were 1.63 (95%CI, 1.27–2.08) and 1.50 (95% CI, 1.18–1.91) in models 1 and 2, respectively, and remained the highest even after three sensitivity analyses.

A collaborative meta-analysis observed that in the general population, a higher normal albuminuria level (UACR 10 mg/g) represented an independent mortality risk predictor. With UACR at 5 mg/g and eGFR at 95 mL/min/1.73 m^2 as reference points, HRs for ACM were 1.20 (95%CI, 1.15–1.26) at UACR 10 mg/g and 1.63 (95%, 1.50–1.77) at UACR 30 mg/g.[20] Our study found that when the weighted mean eGFR was 93.09 mL/min/1.73 m^2 (SD,16.66) and weighted mean UACR was 4.94 mg/g (UACR <6.1 mg/g) were treated as reference points, the HRs for ACM at weighted mean UACR 8.65 mg/g in the middle UACR tertile and 17.41 mg/g in the high UACR tertile were 1.23 (95%CI, 0.93–1.63) and 1.50 (95%, 1.18–1.91) in model 2 with DM patients (Table 2). The reason why the risk of the high UACR tertile among DM participants in this study was lower than in the general population may be that the meta-analysis used better kidney function as reference points. Additionally, the study population's median age in the meta-analysis was higher (61 years) compared to the average age of 56.45 years in our study.

Obesity is correlated with a higher mortality risk with DM,[21,22] whereas a cohort study of 2625 adults with incident DM elucidated that normal-weight adults have higher mortality than overweight or obese adults.[23] All those studies did not report renal function data and UACR status at baseline and disregarded CKD in their discussion. In our study, we included relatively healthy DM participants with no evidence of CKD by eGFR and albuminuria; the subgroup analysis manifested HRs of, respectively, 1.85 (95% CI, 1.37–2.5), 1.75 (95% CI, 1.44–2.14) and 1.3 (95% CI, 1.06–1.59) for ACM in normal weight, overweight and obesity BMI groups with a significant interaction impact between normal-range UACR level and ACM ($p = 0.033$ for interaction). Normal-weight DM individuals who have an eGFR ≥60 mL/min/1.73 m^2 and normal-range UACR levels had the highest risk of ACM than those who are overweight or obese. This finding further supported the obesity paradox, indicating that obesity, compared to normal weight, is linked to lower mortality in DM patients[23,24] and emphasised the need for risk assessment of normal UACR in DM patients, particularly in individuals with normal weight.

Cardiovascular and malignant neoplasm deaths are major causes of mortality among individuals with diabetes, and cancers become the leading contributor to death rates in individuals with diabetes as the large decline in vascular disease death rates.[25] Our study also found that the proportion of deaths mainly attributed to malignant neoplasms. A prospective cohort study of 8592 individuals indicated that higher albuminuria is connected to a higher cancer mortality risk, independent of baseline eGFR.[26] The mechanisms link may be albuminuria can result from endothelial malfunction or abnormal renin–angiotensin system activation that is linked with pro-cancerous anti-immune microenvironment along with tumour vasculature formation.[27,28]

The potential biological mechanism behind the interplay between normal UACR in DM and mortality risk is still unclear. Oxidative stress,[29] hemodynamic abnormalities,[30–32] mitochondrial dysfunction[33] and lipotoxicity[34] contribute to the central mechanism of proteinuria in DM nephropathy: podocyte injury.[35,36] More mechanistic studies should elucidate the involvement of UACR levels in the long-term health of DM individuals.

5 | STRENGTHS AND LIMITATIONS

Our strengths included the inclusion of more confounders related to the disease status and medication use. However, several limitations

need to be addressed. First, NHANES evaluated only one spot of urinary albumin excretion. Despite the fact that repeat samples or 24-h urinary albumin excretion are clinically suggested, the Australasian Proteinuria Consensus Working Group concluded that a random spot urine specimen for UACR in patients with DM is also appropriate.[37] Second, we were unable to analyse the medication status of sodium–glucose cotransporter 2 inhibitors as well as glucagon-like peptide-1 receptor agonists because relatively few people administrate them throughout the current follow-up period.[38] Third, given the small number of cardiovascular death cases ($n = 132$), cardiovascular mortality was not explored in our outcome.

6 | CONCLUSIONS

Among DM adults without overt kidney disfunction, raised normal-range UACR exhibited a significant relation to an escalated ACM risk, particularly among those with normal BMI. These outcomes underscore the significance of early diagnosis and thorough assessment of high-risk DM in persons with normal UACR and adequate renal function.

AUTHOR CONTRIBUTIONS

Drs S. Li and Rao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: S. Li. Acquisition, analysis or interpretation of data: Pang, Dan, H. Li and Lin. Drafting of the manuscript: Pang. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis and administrative, technical or material support: Pang and Dan. Obtained funding and supervision: S. Li and Rao.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data of National Health and Nutrition Examination Survey (NHANES) can be downloaded from the website:https://www.cdc.gov/nchs/nhanes/index.html.

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