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Prospective Study on Kidney Dysfunction Markers and Risk for Mortality among South Asians

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Introduction: Associations between markers of impaired kidney function and adverse outcomes among South Asians is understudied and could differ from existing data derived mostly from North American or European cohorts.

Methods: We conducted a prospective analysis of 9797 participants from the ongoing cardiometabolic risk reduction study in South Asia, India. We examined the associations between baseline spot urine albumin-to-creatinine (UACR) ratio and creatinine-based estimated glomerular filtration rate (eGFR) estimating equations with all-cause mortality using Cox proportional hazards regression, adjusting for baseline age, sex, diabetes, systolic blood pressure, tobacco, history of cardiovascular disease, and cholesterol. Additionally, we calculated population attributable fraction (PAF) for both markers.

Results: Over a median 7-year follow-up, with 66,909 person-years, 791 deaths occurred. At baseline, the weighted prevalence of UACR $\geq$ 30 mg/g and $eGFR_{CKD\text{-}EPI\ 2009}$ $<$60 ml/min per 1.73 m^2 was 6.6% and 1.6%, respectively. The risk for mortality was increased with higher UACR (10–30 hazard ratio [HR]: 1.6 [1.2–2.1]), 30–300 HR: 2.4 [1.8–3.1]), and $\geq$300 (HR: 6.0 [3.8-9.4] relative to UACR $<$10 mg/g). Risk for mortality was also higher with lower $eGFR_{CKD\text{-}EPI\ 2009}$ (44–30; HR: 4.5 [2.5–8.3] and $<$30 HR: 7.0 [3.7–13.0], relative to 90–104 ml/min per 1.73 m^2). PAF for mortality because of UACR $\geq$30 mg/g and $eGFR_{CKD\text{-}EPI\ 2009}$ $<$45 ml/min per 1.73 m^2 were 24.4% and 13.4%, respectively.

Conclusion: Single-time point assessment of UACR $\geq$30 mg/g or $eGFR_{CKD\text{-}EPI\ 2009}$ $<$45 ml/min per 1.73 m^2 portends higher mortality risk among urban South Asians. Because albuminuria is common and associated with accelerated decline in GFR, screening and targeted efforts to reduce albuminuria are warranted.

Kidney Int Rep (2024) **9,** 2537–2545; https://doi.org/10.1016/j.ekir.2024.05.025
KEYWORDS: albuminuria; glomerular filtration rate; mortality; South Asians

Current thresholds defining chronic kidney disease (CKD) are derived largely from population-based studies from North America and Western Europe.[1] In one of the largest population-based South Asian cohorts, we determined that the prevalence of albuminuria was ~50% higher than contemporary estimates in the USA.[2,3] However, the clinical significance of the relatively higher prevalence of albuminuria among South Asians is uncertain.

South Asians are prone to type 2 diabetes, with a 2- to 3-fold higher prevalence compared with Europeans[4] and lending biological plausibility to the high prevalence of albuminuria observed in our study and others.[5] At the same time, South Asians generally exhibit lower urinary creatinine excretion, which could result in higher spot urine albumin to creatinine ratio (UACR) without high level of urinary albumin

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Received 20 March 2024; revised 10 May 2024; accepted 20 May 2024; published online 29 May 2024

excretion. In an analysis of 24-hour urine creatinine excretion from a Pakistani cohort, Jafar *et al*.[6] found that the mean observed creatinine excretion was 17.5 and 14.1 mg/kg/d in men and women, respectively, compared with age- and sex-matched expected mean values of 19.0 and 16.3 mg/kg/d as derived from Caucasian populations.[6] Twenty five percent of Pakistani women had urine creatinine excretion <10 mg/kg/d. Thus, more South Asians may reach UACR ≥ 30 mg/g; the threshold used to define clinically actionable, moderately increased albuminuria because of lower creatinine excretion, rather than higher albumin excretion.

Similarly, creatinine-based eGFR are reported to over-estimate kidney function among South Asians.[7] Meat intake, a potential contributor to creatinine production, is substantially lower among South Asians compared with many other regions in the world, including other parts of Asia.[8] A study of 130 Indians with GFR measured through urinary inulin clearance assessed bias in eGFR from the CKD Epidemiology Collaboration (CKD-EPI 2009), CKD-EPI (Pakistan), and modification of diet in renal disease equations; all 3 equations overestimated measured GFR.[7]

Only 3 studies evaluate the association between kidney dysfunction markers and outcomes. The existing studies, largely based on elderly South Asians residing in Canada or the UK, present varying results.[9-11] For instance, a study involving ∼40,000 UK South Asians found a weak association between creatinine-based eGFR and mortality in both men and women, in comparison with their White counterparts.[11] Another study reported similarly null to weak association between eGFR and mortality, and a modest association between albuminuria and mortality.[10] Notably, there is an absence of population-based studies from the South Asian region.

We investigated whether the potential sources of variation in kidney function markers, unrelated to intrinsic kidney function, among South Asians alter risk stratification implied in the current Kidney Disease: Improving Global Outcomes cutpoints for eGFR and UACR.[1] We tested the associations of spot UACR and creatinine-based eGFR equations with mortality in the center for cardiometabolic risk reduction in South Asia (CARRS) cohort.[2] Using measures of explained variation in mortality, we additionally compared the performance of four creatinine-based equations: CKD-EPI 2009, CKD-EPI PK coefficient, CKD-EPI (race free) 2021, and the European Kidney Function Consortium (EKFC) equations. The CARRS cohort is a population-representative cohort from Delhi and Chennai, and thus we also estimated population-attributable risks of impaired kidney function for mortality among South Asians.

METHODS

The CARRS Cohort

With baseline assessments conducted from 2010 to 2011, the CARRS study representatively sampled 12,270 participants from Delhi and Chennai, using multi-stage cluster sampling.[12-14] Participants have since been followed at an annual or biannual cadence. The cohort has been well-retained.[15] The study received approval for research on human subjects from the Ethics Committees of the Public Health Foundation of India and All India Institute of Medical Sciences (Delhi), Madras Diabetes Research Foundation (Chennai), and Emory University (Atlanta). The CARRS cohort has demonstrated high retention rates (70%–85% at each follow-up and >95% have at least one follow-up or assessment of vital status).[15] Furthermore, analysis of the cohort follow-up indicates high retention and minimal bias because of loss of follow-up. Research assistants undertook in-person interviews during each follow-up and collected biospecimens during the second and fourth follow-up visits. If a participant was identified as deceased during an in-person home visit, date of death was determined either by hospital records, or if none were available, by next-of-kin, whose contact information was obtained at study entry. At the time of this analyses, each participant had the opportunity for a total of 5 follow-up visits (detailed data on cohort profile and follow up are published elsewhere).[12-14] The earliest baseline and latest follow-up dates were in 2010 and 2018, respectively.

Kidney Function Assessment

Creatinine-based eGFR was calculated using CKD-EPI 2009,[16] CKD-EPI 2021,[17] and EKFC[18] equations using the nephro (version 1.4) package in R.[19] CKD-EPI (PK) was computed using the formula: $0.686 \times \text{eGFR}_{\text{CKD-EPI 2009}}^{1.059}$.[6] Baseline eGFR (ml/min per 1.73 m^2) levels were categorized based on the Kidney Disease: Improving Global Outcomes guidelines[20]: ≥105; eGFR 90 to 104 (optimal); 89 to 75; eGFR 74 to 60; 59 to 45; 44 to 30; and G4-5, <30. Baseline UACR (mg/g) levels was categorized into 4 groups: <10 (optimal); 10 to 30 (mild); 30 to 300 (moderate); and UACR >300 (severe).[21] The category with eGFR 90 to 104 ml/min per 1.73 m^2 and the lowest albuminuria (<10 mg/g), was used as the reference group.

Potential Association Confounders and Modifiers

Following the protocols outlined by the CKD prognosis consortium to examine the association of kidney function markers with mortality[22] and end-stage kidney disease,[23] we included as potential confounders

baseline age (continuous), sex (male/female), city (Delhi/Chennai), tobacco use , history of cardiovascular disease (yes/no), diabetes (yes/no), baseline systolic blood pressure (continuous), serum total cholesterol (continuous) concentration. We categorized tobacco use as never used, previously used, and currently using. We defined cardiovascular disease as self-report of myocardial infarction or stroke, and diabetes as fasting glucose ≥126 mg/dl or glycosylated hemoglobin A1c ≥ 6.5%, or self-reported diabetes or use of glucose-lowering medications.[24] We used continuous measures of baseline systolic blood pressure (average of 2 readings) and serum total cholesterol concentration.

Additionally, we tested the interaction of baseline city, sex, diabetes status, hypertension, cardiovascular disease, diet and lean body mass, UACR and eGFR categories with mortality. We categorized diet status as vegetarian and nonvegetarian based on the self-reported food frequency questionnaire. Finally, we used bioimpedance body composition analysis (Tanita BC-418) to calculate the lean body mass percentage (defined as total body mass [%] − fat mass [%]).

Laboratory Measurements

Accredited site laboratories in Delhi and Chennai processed the participants' fasting blood and urine samples. These laboratories participated in the External Quality Assurance program of Randox International Quality Assessment Scheme. We used the immunoturbidimetric assay to measure urine albumin, and the kinetic Jaffe method with IDMS traceable assays to measure urine and serum creatinine (Roche Diagnostics GmbH, Manheim, Germany). We measured venous fasting plasma glucose using hexokinase/kinetic methods and hemoglobin A1c using high performance liquid chromatography standardized to the National Glycohemoglobin Standardization Program.

Statistical Analyses

We present continuous data as means (± SD) and categorical data as proportions. We present median follow-up, number of events, and mortality rates (calculated as number of events/total person-years) with 95% confidence intervals by UACR and CKD-EPI (2009) eGFR using previously established cutpoints.[1]

Cox proportional hazards regression methods that accounted for the survey weights were used to estimate the association of UACR and $eGFR_{CKD\text{-}EPI\ 2009}$ categories with mortality, accounting for all confounders including UACR and $eGFR_{CKD\text{-}EPI\ 2009}$ as appropriate.[22] Follow-up time was calculated as the duration from baseline to either the occurrence of death or the end of latest follow-up period, whichever occurred first. We then replicated our analysis for each eGFR equation. We checked the proportional hazards assumption using the Schoenfeld residuals.[25] We computed Harrell's C statistic, a measure of discrimination comparable to the area under a receiver operating characteristic curve but accounting for the censored nature of the data.[26] Additionally, we calculated R^2_{pm} values (where higher values correspond to greater proportion of explained variation in time to all-cause mortality explained by the model),[27,28] and D statistic, another measure of discrimination was also considered,[29] with greater values indicating better discrimination. These analyses permitted us to compare models among the four creatinine-based eGFR equations.

We also present estimates for all-cause mortality in models using UACR ≥ 30 mg/g and $eGFR_{CKD\text{-}EPI\ 2009}$ <45 ml/min per1.73 m^2 cutpoints, and testing for association interaction by city, sex, diabetes, hypertension, cardiovascular disease, vegetarian diet, and lean body mass. We used the following formula to compute the PAF: PD (HR − 1) / HR for all-cause mortality associated with the baseline UACR and eGFR categories, where PD represents the proportion of total cases in the population arising from the cases exposed to a specific risk factor.[30]

All analyses accounted for the complex survey structure of the data (strata, clusters, and weights) among participants with available baseline data on kidney function markers (n = 9797, 80% of all participants). We have previously shown that the age, sex, occupation, and educational distribution of this group was similar to the entire CARRS cohort from Delhi and Chennai.[2] We performed all statistical analyses in R (version 4.1.1., R Foundation for Statistical Computing), following the STROBE guidelines.

RESULTS

Table 1 delineates characteristics of the weighted cohort with available kidney function markers at baseline. The majority of participants (65%) were 20 to 44 years of age, and 23% had diabetes at baseline. There were 791 deaths over 66,909 participant-years of follow-up with a median follow-up of 7.0 years per participant. Baseline characteristics stratified by eGFR and ACR categories are presented in Supplementary Table S1 and S2).

Adjusted Risks by Albuminuria and eGFR Categories

Table 2 shows follow up times and mortality events by UACR cut points. Unadjusted incidence rates for mortality, adjusted HR, and PAF were higher in higher albuminuria categories, starting at UACR ≥ 10 mg/g.

Table 1. Weighted baseline characteristics of Participants in the study cohort with available data on kidney function markers[a]

Characteristics	Chennai	Delhi	Total
Demographics			
Age (yr)	40.0 (12.1)	42.5 (11.8)	41.1 (12.0)
Age categories			
20–44 yr	68.6	59.2	64.4
45–59	23.3	31.9	27.1
≥60	8.2	8.9	8.5
Male	43.7	49.1	46.1
Vegetarian	4.8	40.0	20.5
Tobacco use (ever)	1.8	1.9	1.8
Tobacco use (current)	19.4	22.0	20.5
Medical history			
Diabetes[b]	22.1	30.2	25.7
Self-report	11.9	10.5	11.3
Missing	0.2	0.8	0.5
Cardiovascular disease	2.1	3.3	2.6
Measurements			
Lean body mass (kg/m^2)	17.7 (0.2)	17.1 (0.2)	17.5 (0.1)
Missing	29.5	38.9	33.6
Systolic blood pressure (mm Hg)	120 (17.8)	125.4 (19.3)	122.4 (18.7)
Missing	7.1	0.5	3.3
Diastolic blood pressure (mm Hg)	80.1 (11.1)	83.5 (11.7)	81.6 (11.5)
Missing	7.1	0.5	3.3
Fasting glucose (mg/dl)	107.1 (40.9)	112.4 (43.8)	109.43 (42.28)
Missing	NA	0.1	0.04
Hemoglobin A1c	6.2 (1.5)	6.3 (1.5)	6.24 (1.48)
Missing	0.3	1.0	0.59
Kidney disease measures			
Urine albumin to creatinine ratio (mg/g)[c]	4.07 (2.65, 7.29)	0.00 (0.00, 3.83)	2.96 (0.00, 6.34)
<10	82.0	84.7	83.2
10–30	12.1	7.9	10.2
30–300	5.6	6.0	5.8
≥300	0.3	1.4	0.8
CKD-EPI eGFR (ml/min per 1.73 m^2)[c]	112.8 (102.7, 121.0)	108.0 (95.8, 117.6)	110.43 (99.2, 119.8)
>105	69.3	56.1	63.5
104–90	21.1	26.2	23.4
89–75	6.6	10.9	8.5
74–60	1.9	4.4	3.1
59–45	0.6	1.3	1.0
44–30	0.2	0.7	0.4
<30	0.2	0.3	0.2

CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration.
[a]Data from 9797 participants are weighted to reflect population-representative design and presented as percent or mean ± SD, unless indicated otherwise.
[b]Diabetes defined as self-report of diabetes, use of antiglycemic medications, fasting glucose ≥126 mg/dl or glycosolated hemoglobin (Hb) A1c ≥6.5%.
[c]median (25th–75th percentile); to convert UACR in mg/g to mg/mmol, divide by 8.84.

Unadjusted incidence rates for mortality also increased with lower $eGFR_{CKD\text{-}EPI\ 2009}$ categories (Table 3). Adjusted HR for mortality increased starting at $eGFR_{CKD\ EPI\text{-}2009}$ 30 to 45 ml/min per 1.73 m^2 category.

For the remainder of the analysis, we dichotomized the UACR (<30 mg/g vs. ≥ 30 mg/g) and $eGFR_{CKD\text{-}EPI\ 2009}$ (>45 vs. <45 ml/min per 1.73 m^2 categories). The PAF for UACR ≥ 30 mg/g (vs. lower) was 24.4% (95% confidence intervals: 17.1%–57.7%) and $eGFR_{CKD\text{-}EPI\ 2009}$ <45 ml/min per 1.73 m^2 (vs. higher) was 13.4% (95% confidence intervals: 7.7%–21.2%).

Differences by Sex, Diabetes, Lean Body Mass, and Diet

Associations between UACR ≥ 30 mg/g and mortality were similar by city, sex, diabetes, and vegetarian diet (Figure 1). Notably UACR ≥ 30 mg/g was associated with higher mortality among persons with and without diabetes. Although the risk for mortality was higher for participants with albuminuria, regardless of whether they had above (≥41) or below (<41) median lean body mass%, those with below median lean body mass % exhibited comparatively lower risks.

Diabetes, hypertension, cardiovascular disease, city, and lean body mass % did not substantially alter the association between $eGFR_{CKD\text{-}EPI\ 2009}$ ml/min per 1.73 m^2 and mortality. Risks of mortality among female and vegetarian participants were higher relative to male and nonvegetarian participants, respectively. The results did not change when we tested interaction between eGFR and lean body mass across the range of both measures (*P*-value for interaction 0.49 using continuous eGFR and lean body mass).

Comparisons of Creatinine-based eGFR Equations

The distributions of eGFR differed depending on the formula applied (Figure 2). Compared with $eGFR_{CKD\text{-}EPI\ 2009}$, the $eGFR_{CKD\text{-}EPI\ 2021}$, and $eGFR_{EKFC}$ equations had a higher mean but left- skewed distribution. Accordingly, more participants were classified as having eGFR <60 ml/min per 1.73 m^2 when applying the CKD-EPI 2021 and EKFC equations; however, the higher risk for mortality by eGFR categories was observed only for those with eGFR<30 ml/min per 1.73 m^2 (Table 4). Since the $eGFR_{CKD\text{-}EPI\ PK}$ equation applies a constant coefficient to CKD-EPI 2009, the distribution of the $eGFR_{CKD\text{-}EPI\ PK}$ equation was similar but systematically shifted to a lower value (Figure 2). There was a higher risk for mortality among participants with eGFR <60 or >105 ml/min per 1.73 m^2 (compared with eGFR 90–105 ml/min per 1.73 m^2) when applying CKD-EPI PK equation (Table 4). When we compared the 4 creatinine-based equations, their performance was similar according to measures of explained variation, with the $eGFR_{CKD\text{-}EPI\ PK}$ and $eGFR_{CKD\text{-}EPI\ 2009}$ equations having slightly better explanatory power (Supplementary Table S3).

DISCUSSION

In our population-representative cohort from urban India, a single-time point assessment of UACR ≥ 30 mg/g and CKD-EPI 2009 eGFR <45 ml/min per 1.73 m^2 was associated with higher risk of mortality. Because

Table 2. Risk of mortality by kidney function markers (albuminuria categories)

	Albuminuria categories (mg/g)			
Outcome	**<10**	**10–30**	**≥30–300**	**≥300**
n	8102	1011	596	88
No. of events/PYs at risk	494/55722	130/6831	125/3845	42/511
Mortality rate (per 1000 person-yr)	8.9 (8.1, 9.7)	19.0 (15.9, 22.6)	32.5 (27.1, 38.7)	82.1 (59.2, 111.1)
HR (95% CI)[a]	Ref	1.6 (1.2, 2.1)	2.4 (1.8, 3.1)	6.0 (3.8, 9.4)
PAF (95% CI) %		8.7 (3.2, 15.0)	17.7 (11.1, 25.0)	20.9 (12.9, 30.8)

PAF, Population attributable fraction;PY, person-year; UACR, urine albumin to creatinine ratio.
[a]Adjusted for age categories (20–44/45–59/≥60 years), city (Chennai/Delhi), sex (male/female), tobacco status (no/previous/current), self-reported CVD (no/yes), diabetes (no/yes), systolic blood pressure, total cholesterol, and UACR or eGFR as appropriate.

moderately increased albuminuria is more common among South Asians, the PAF for mortality for albuminuria exceeded that for reduced eGFR. We also found that choice of creatinine-based equations applied to estimate GFR creates substantial heterogeneity in individual-level classification of CKD. Additionally, associations with mortality were attenuated when using categories generated from the $eGFR_{CKD\text{-}EPI\ 2021}$ and $eGFR_{EKFC}$ equations, compared with $eGFR_{CKD\text{-}EPI\ 2009}$ and $eGFR_{CKD\text{-}EPI\ PK}$ equations.

A meta-analysis evaluating the associations of UACR with mortality and other cardiovascular outcomes from 14 pooled studies with a total of >100,000 participants concluded that UACR ≥10 mg/g was associated with higher risk for mortality.[22] At UACR of 30 mg/g, the HR for mortality was 1.6 (1.5–1.8).[31] We had considered whether the generally lower rates of creatinine excretion (owing to differences in diet and body composition) might alter the relationship between albuminuria and mortality in South Asians relative to populations in Europe and North America. In the CARRS population, we found that the conventional cut point of UACR ≥ 30 mg/g doubles the risk for mortality among South Asians, even among persons without diabetes, persons with a below median lean body mass %, and persons eating a vegetarian diet.

Our findings of similar relative risk by diabetes status confirm other studies where persons with euglycemia nonetheless experience higher risk for mortality in the presence of UACR ≥ 30 mg/g.[32] The pathophysiology of albuminuria because of diabetes is well-established, linked to changes in glomerular basement membrane and mesangial matrix expansion in the presence of hyperglycemia.[33,34] Diabetes was the most common comorbid condition in our study participants with albuminuria. However, even among persons without diabetes, experts theorize that albuminuria reflects endovascular dysfunction,[35] and is jointly associated with risks for progressive loss of kidney function and cardiovascular events.[36] Similarly, prior studies have established that low eGFR carries similarly higher risk for mortality among persons with and without diabetes, compared with higher eGFR categories.[32]

Determining whether UACR ≥30 mg/g can identify a high-risk population in whom to target public health efforts carries significant import, since its current prevalence, when extrapolated only to the urban Indian population in 2018, means that 10 million urban adults have albuminuria in India. Similar or higher prevalence is reported in South Asians living in the USA, in whom the concomitant disproportionately high rates of diabetes and accelerated cardiovascular disease prompted a special statement from the American Heart Association.[37] Use of renin-angiotensin inhibitors, sodium glucose transporter 2 inhibitors, and selective mineralocorticoid inhibitors can lead to substantial reduction in albuminuria and kidney function protection over time. Emerging therapeutics including aldosterone synthase inhibitors hold promise, with a

Table 3. Risk of mortality by kidney function markers (eGFR categories)

	CKD-EPI 2009 eGFR categories (ml/min per 1.73 m^2)						
Outcome	**>105**	**104–90**	**89–75**	**74–60**	**59–45**	**44–30**	**<30**
n	5926	2409	882	372	134	49	25
No. of events/PYs at risk	227/48637	252/19317	143/6978	91/2882	45/947	21/311	12/167
Mortality rate (per 1000 person-yr)	4.7 (4.1; 5.3)	13.0 (11.5; 14.8)	20.5 (17.2; 24.1)	31.6 (25.4; 38.8)	47.5 (34.66; 63.58)	67.52 (41.80; 103.2)	71.86 (37.13; 125.52)
HR (95% CI)[a]	1.0 (0.8; 1.3)	Ref	1.1 (1.0; 1.5)	1.4 (0.9; 1.9)	1.3 (0.7; 2.2)	4.5 (2.5; 8.3)	7.0 (3.7; 13.1)
PAF (95% CI) %						8.5 (3.7; 16.7)	8.3 (4.0; 15.5)

PAF, Population attributable fraction; Ref, reference category; UACR, urine albumin to creatinine ratio.
[a]Adjusted for age categories (20–44/45–59/≥60 years), city (Chennai/Delhi), sex (male/female), tobacco status (no/previous/current), self-reported CVD (no/yes), diabetes (no/yes), systolic blood pressure, total cholesterol, and UACR or eGFR as appropriate.

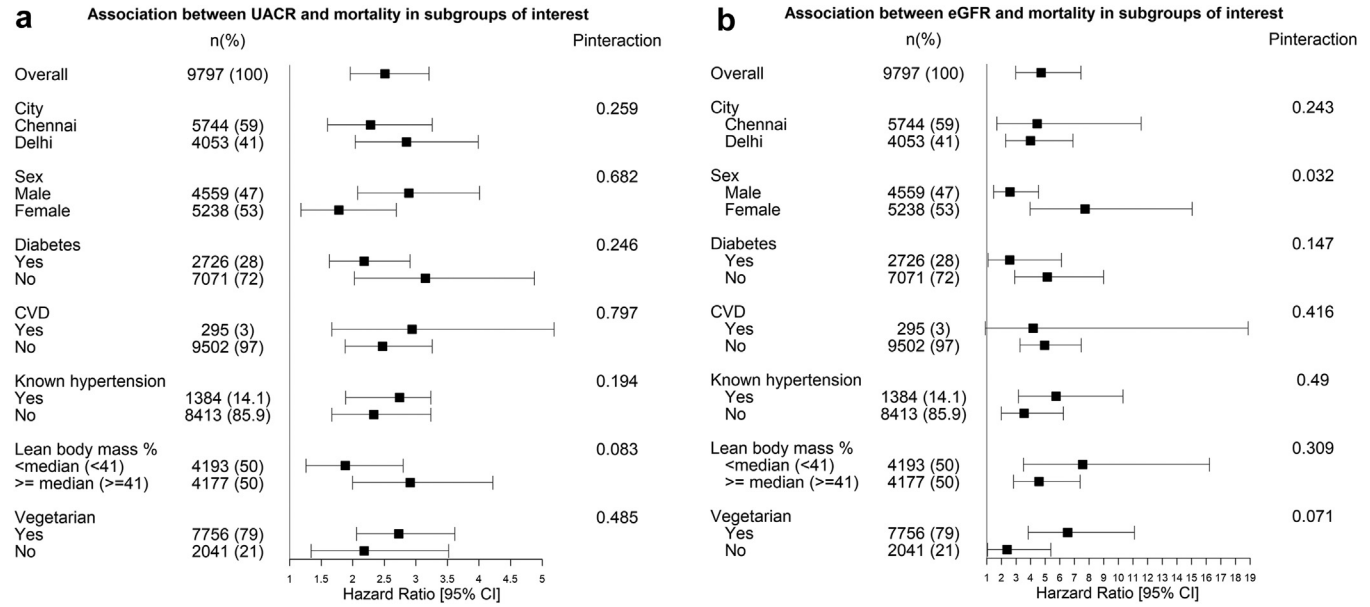

Figure 1. Association between kidney function and mortality in subgroups of interest (a) for UACR (<30 mg/g vs. ≥ 30 mg/g), (b) for $eGFR_{CKD\text{-}EPI\ 2009}$ (>45 vs. <45 ml/min per 1.73 m^2).

recent phase 2 study demonstrating ∼40% further reduction in albuminuria.[38] However >10% of the CARRS cohort with CKD had received renin-angiotensin inhibitors.[39] Use of recently introduced therapeutics is likely rare. Programmatic approaches to detecting and treating albuminuria are urgently needed among urban Indians.[40]

The assessment of kidney function has two primary roles: (i) to estimate glomerular filtration rate and facilitate drug dosing, and (ii) to prognosticate the risk for kidney dysfunction and other complications. Our current markers, whether creatinine-based alone, or combining creatinine with cystatin C, tend to have a substantial margin of error around estimating true GFR. For example, the proportion of eGFR within 30% of measured GFR using CKD-EPI 2021 Creatinine based formula was 87% among White persons.[17] A few drugs (e.g., carboplatin) require high precision around drug dosing, but for the majority, a conservative estimate suffices. The prognostic function of classifying a person as being at risk for adverse outcomes, including mortality, forms the basis for clinical referral, counseling, treatment targets for blood pressure, and preparation for dialysis. Among 3 prior analyses relying on electronic health data from South Asians living in the UK or Canada, one reported a clear association between creatinine-based eGFR and mortality among South Asians, with the other 2 reporting weak or no associations.[9-11]

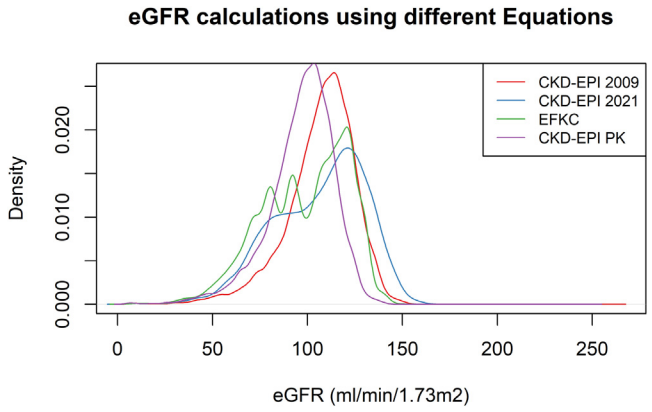

Figure 2. eGFR distributions according to 4 creatinine-based formulae. CKD-EPI, CKD Epidemiology Collaboration; EFKC,European Kidney Function Consortium; PK,Pakistan

Our data suggest that women and vegetarians may experience higher risk for mortality for given eGFR value <45 ml/min per 1.73 m^2 relative to men and nonvegetarian persons, respectively. Given the small sample sizes, these findings are preliminary but may fit our *a priori* hypotheses that diet and body composition may amplify the over eGFR and that risk for mortality may begin to accrue at higher eGFR cut points among these subgroups. As we accumulate additional follow up data, and we continue follow up in a second and related (CARRS-2) cohort drawn from the same 2 cities, we may be able to address these hypotheses definitively. Nonetheless, we find that all subgroups experienced significantly higher risks of death at CKD-EPI 2009 eGFR <45 ml/min per 1.73 m^2.

We found that among 4 creatinine-based equations, the expected and consistent trends by Kidney Disease: Improving Global Outcomes CKD categories are observed with $eGFR_{CKD\text{-}EPI\ 2009}$ and $eGFR_{CKD\text{-}EPI\ PK}$ equations in this urban Indian population. The 'U'

Table 4. Risk of mortality by eGFR categories using alternative GFR estimating equations

	eGFR categories						
Outcome	**>105**	**104–90**	**89–75**	**74–60**	**59–45**	**44–30**	**<30**
CKD-EPI 2021 (CKD-EPI NEW)							
n	1588	5583	1478	789	252	77	30
No. of events/PYs at risk	244/38577	176/10748	139/10061	114/5291	71/1589	33/470	14/173
Mortality rate (per 1000 person-yr)	16.4 (14.0; 18.9)	6.3 (5.6; 7.2)	13.8 (11.6; 16.3)	21.5 (17.8; 25.9)	44.7 (34.9; 56.4)	70.2 (48.3; 98.6)	80.9 (44.2; 135.8)
HR (95% CI)[a]	1.11 (0.80; 1.53)	Ref	0.87 (0.64; 1.17)	0.85 (0.61; 1.18)	1.39 (0.92; 2.10)	1.17 (0.54; 2.52)	4.72 (2.67; 8.33)
CKD-EPI PK							
n	3624	3310	1852	659	226	89	37
No. of events/PYs at risk	101/22919	201/24979	256/12477	113/4374	66/1405	35/547	19/206
Mortality rate (per 1000 person-yr)	4.4 (3.6; 5.4)	8.0 (7.0; 9.2)	20.5 (18.1; 23.2)	25.8 (21.3; 31.1)	47.0 (36.3; 59.8)	64.0 (44.6; 89.0)	92.2 (55.3; 144.0)
HR (95% CI)[a]	1.64 (1.14; 2.36)	Ref	1.29 (0.99; 1.68)	1.35 (0.96; 1.90)	1.60 (1.08; 2.35)	2.48 (1.17; 5.27)	8.17 (4.78; 13.97)
EKFC							
n	4715	1783	1607	1148	409	99	36
No. of events/PYs at risk	145/32690	163/12158	172/10904	142/7752	110/2603	41/594	18/205
Mortality rate (per 1000 person-yr)	4.4 (3.7; 5.2)	13.4 (11.4; 15.6)	15.8 (13.5; 18.3)	18.2 (15.4; 21.6)	42.2 (34.7; 50.9)	69.0 (49.5; 93.6)	87.8 (52.0; 138.8)
HR (95% CI)[a]	0.9 (0.7; 1.3)	Ref	0.9 (0.6; 1.2)	0.9 (0.6; 1.2)	1.2 (0.7; 1.8)	1.2 (0.6; 2.5)	4.18 (2.4; 7.4)

PAF, Population attributable fraction; UACR, urine albumin to creatinine ratio.
[a]Adjusted for age categories (20–44/45–59/≥60 years), city (Chennai/Delhi), sex (male/female), tobacco status (no/previous/current), self-reported CVD (no/yes), diabetes (no/yes), systolic blood pressure, total cholesterol, and UACR level.

shaped relationship observed with $eGFR_{CKD\text{-}EPI\ PK}$ may reflect sarcopenia or hyperfiltration among persons with eGFR >105 ml/min per 1.73 m^2, as has been previously described.[41] Although more persons were classified as having CKD using the (race free) $eGFR_{CKD\text{-}EPI\ 2021}$ and $eGFR_{EKFC}$ equations, the attenuation of an association with mortality may indicate a larger bias between measured and eGFR when using these equations among urban Indians.

The strengths of our analysis include the prospective study design, large sample size, long duration of follow-up, and the evaluation of an understudied yet highly affected South Asian population with available baseline data on anthropometry, blood pressure, and glycemic status. All laboratory samples were processed at a central accredited laboratory.

We also acknowledge several limitations in our work. First, the population is derived from 2 major cities in South Asia. The results may not be generalizable to other regions or different settings within South Asia, because rural populations may have differing trajectories and associated risk factors. Because this is a population-based analysis, the number of persons with CKD is limited, relative to a cohort of persons with established CKD. Given the smaller proportion of individuals within progressive eGFR and UACR categories, we have dichotomized the analysis, using a threshold of >30 for UACR and <45 for eGFR, when conducting subgroup analysis, owing to the relatively lower prevalence of high-risk ACR (30–300: 6.1%; ≥300: 0.9%) and eGFR categories (44–30: 0.4%; <30: 0.2%) observed within this cohort. Furthermore, we currently lack data on medication use and cause of death. There were too few end-stage kidney disease events to determine relative risks associated with UACR and eGFR categories in this population. The accrual of additional events and other (e.g., cardiovascular) events over time may allow us to better understand the public health risks of albuminuria and impaired kidney function in South Asia.

Associations of kidney function markers with clinically significant outcomes should be evaluated in diverse cohorts which should become more feasible as an increasing number of countries prioritize chronic diseases. Herein, we confirm that UACR ≥ 30 mg/g and $eGFR_{CKD\text{-}EPI\ 2009}$ <45 ml/min per 1.73 m^2 confers higher risk for all-cause mortality in the South Asian population. Because albuminuria is common, underdiagnosed at the population level, and its evidence-based management can delay the CKD progression, public health efforts and clinical programming should target early detection and management of albuminuria in South Asia.

DISCLOSURES

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The authors are grateful to the study participants, and the dedicated research assistants who undertook outreach and follow-up, despite difficult study conditions, and deeply cared for the health and wellbeing of our study participants. The CARRS study has been funded with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, under Contract No. HHSN2682009900026C and P01HL154996. Anand was supported by NIDDK K23DK101826.

DATA AVAILABILITY STATEMENT

Data supporting this study's findings are available to the corresponding authors (JR: ram.jagannathan@emory.edu or SA: sanand2@stanford.edu) upon reasonable request. The R codes and the R notebook for the reproducible analysis is available to interested readers upon contacting: ram.jagannathan@emory.edu.

AUTHOR CONTRIBUTIONS

RJ and SA conceptualized the study. JR performed formal analysis. SA supervised data analysis. DK performed data curation. DK, RG, and SM performed project administration. DP, NT, VM, KMVN, and MKA acquired funding. SA and RJ prepared original draft of manuscript. DK, JH, MMR, MKA, SAP, KS, RS, RMA, RG, SM, GMC, VM, KMV, and DP critically reviewed and edited the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Baseline demographic and clinical characteristics of the study cohort by UACR categories.

Table S2. Baseline demographic and clinical characteristics of the study cohort by eGFR categories.

Table S3. Validation statistics for the different eGFR equations in predicting mortality.

STROBE Statement (PDF)

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