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Risk Factors for ESRD in Individuals With Preserved Estimated GFR With and Without Albuminuria: Results From the Kidney Early Evaluation Program (KEEP)

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Background: Given the increasing costs and poor outcomes of end-stage renal disease (ESRD), we sought to identify risk factors for ESRD in people with preserved estimated glomerular filtration rate (eGFR), with or without albuminuria, who were at high risk of ESRD.

Methods: This cohort study included participants in the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) with eGFR ≥60 mL/min/1.73 m^2 at baseline stratified by the presence or absence of albuminuria. The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR. Urine was tested for albuminuria by semiquantitative dipstick. The outcome was the development of treated chronic kidney failure, defined as initiation of maintenance dialysis therapy or kidney transplantation, determined by linkage to the US Renal Data System. We used a Cox model with the Fine-Gray method to assess risk factors for treated chronic kidney failure while accounting for the competing risk of death.

Results: During a median follow-up of 4.8 years, 126 of 13,923 participants with albuminuria (16/10,000 patient-years) and 56 of 109,135 participants without albuminuria (1.1/10,000 patient-years) developed treated chronic kidney failure. Diabetes was a strong risk factor for developing treated chronic kidney failure in participants with and without albuminuria (adjusted HRs of 9.3 [95% CI, 5.7-15.3] and 7.8 [95% CI, 4.1-14.8], respectively). Black race, lower eGFR, and higher systolic blood pressure also were associated with higher adjusted risks of developing treated chronic kidney failure.

Conclusions: In a diverse high-risk cohort of KEEP participants with preserved eGFR, we showed that diabetes, higher systolic blood pressure, lower eGFR, and black race were risk factors for developing treated chronic kidney failure irrespective of albuminuria status, although the absolute risk of kidney failure in participants without albuminuria was very low. Our findings support testing for kidney disease in high-risk populations, which often have otherwise unrecognized kidney disease.

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INDEX WORDS: Albuminuria; blood pressure; chronic kidney disease; diabetes; dialysis risk factors; end-stage renal disease; public health.

Estimates indicate that by 2020, more than three-quarters of a million people in the United States will have end-stage renal disease (ESRD), leading to increased requirements for dialysis or kidney transplant.[1] Treatment for chronic kidney failure accounted for more than $30 billion, or 8%, of all Medicare expenditures in 2009, yet outcomes remain poor; mortality rates are more than 6 times higher in patients with ESRD than in the non-ESRD population.[1] Therefore, identifying people at high risk of ESRD early in the disease course to allow time for risk-factor modification is important.

Previous observational studies have identified risk factors for developing ESRD, such as black race, hypertension, and diabetes,[2-10] but these studies included people who already had a moderately de-

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creased estimated glomerular filtration rate (eGFR). In contrast, relatively few studies have focused on identifying risk factors for ESRD in people who still have a normal serum creatinine level and a correspondingly preserved eGFR. In one such study of volunteers in a health assessment program, participants were all insured and lived in Northern California, limiting its generalizability.[11] Other population-based cohort studies lacked baseline kidney function measurements,[12-14] precluding identification of participants with underlying kidney disease at the study start.

To address some of the limitations of these previous studies, we conducted a study of participants in the Kidney Early Evaluation Program (KEEP), a nationwide community-based health screening study of people at high risk of kidney disease, with eGFR ≥60 mL/min/1.73 m^2. The primary objective was to identify risk factors for developing treated chronic kidney failure in participants with preserved eGFR. Because risk factors for developing treated chronic kidney failure vary by albuminuria status in patients with moderate to severe decreases in eGFR,[15,16] we conducted all analyses stratified by albuminuria status.

METHODS

Study Population

KEEP is a free community-based voluntary screening program run by the National Kidney Foundation that was launched in August 2000 and is designed to identify individuals at increased risk of kidney disease and encourage follow-up care.[17] KEEP screenings are conducted in urban and rural locations throughout the United States through each state's National Kidney Foundation affiliate. During KEEP screening, participants complete a questionnaire to assess demographic characteristics, personal and family medical history, and health behaviors. Blood pressure, height, and weight are recorded. In this study, we included eligible KEEP participants screened from August 2000 to December 31, 2011. Because we were interested in studying participants with preserved eGFR, we excluded participants with eGFR <60 mL/min/1.73 m^2 and participants with self-reported history of kidney transplantation, leaving 123,058 participants for our analysis. KEEP was approved by the Institutional Review Board at Hennepin County Medical Center, Minneapolis, MN.

Estimation of Kidney Function

Blood and urine specimens were collected for determination of serum creatinine level and albuminuria. Serum creatinine was measured by Satellite Laboratory Services (Redwood City, CA) using the Olympus 5431 (Olympus Optical) and by Consolidated Laboratory Services, Van Nuys, CA, using the Abbott Architect c8000 (Abbott Laboratories) and calibrated to the Cleveland Clinic. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[18] was used to calculate eGFR in milliliters per minute per 1.73 m^2.

Measurements of albuminuria were obtained using Micral Strips (Roche) from August 2000 to September 2001 and were considered positive for microalbuminuria if albumin excretion was >20 mg/dL. From September 2001 to April 2002, albuminuria was measured using Clinitek Microalbumin Urinalysis Strips (Bayer), and albumin values >30 mg/L were considered positive for microalbuminuria. From April 2002 to the present, urine albumin-creatinine ratio also was measured and reported as <30, 30-300, or >300 mg/g. For the present analysis, participants were categorized as having albuminuria if they had a positive urine dipstick for albumin using either assay or albumin-creatinine ratio of 30-300 or >300 mg/g.

Outcome

The primary outcome was incident ESRD defined as initiation of dialysis therapy or kidney transplant. We ascertained ESRD by linking KEEP with the US Renal Data Systems database, which includes >90% of patients with incident ESRD.[1] We followed up participants until December 31, 2011, or time of death as reported by the National Death Index.

Risk Factors for ESRD

Demographic information for age, sex, and race/ethnicity was recorded at the screening session. Education was categorized as fewer than 12 or 12 or more years. Current smoking status and health insurance status were categorized as yes or no. Diabetes mellitus was defined by self-report, self-reported use of medications for diabetes, fasting glucose values ≥126 mg/dL, or nonfasting glucose levels ≥200 mg/dL. Cardiovascular disease was defined as self-report of cardiac angioplasty, cardiac bypass surgery, heart attack, heart failure, abnormal heart rhythm, stroke, or peripheral vascular disease. Hypertension was defined by self-report or self-reported use of antihypertensive medications. Hyperlipidemia was defined by self-report, self-reported use of lipid-lowering medications, or fasting total cholesterol level >200 mg/dL. Family history of kidney disease and diabetes also was ascertained.

Body mass index was calculated from the recorded height and weight. Blood pressure was measured with the participant seated after at least 5 minutes of rest. If the first systolic blood pressure (SBP) reading was ≥140 mm Hg or the first diastolic blood pressure reading was ≥90 mm Hg, the participant rested for an additional 5 minutes and blood pressure was measured again on the same arm.

Statistical Analysis

We conducted all analyses after stratifying by baseline albuminuria status. Baseline characteristics were described using proportions or mean ± standard deviation, as appropriate. Because death is a competing risk for the development of ESRD, we estimated the subdistribution hazard ratio (HR) using the Fine-Gray[19] method, which accounts for competing events and allows for multivariable adjustment. We examined the following demographic and comorbid conditions: age (per 10 years older), sex, race/ethnicity, current smoking status, education, health insurance, diabetes mellitus, cardiovascular disease, hyperlipidemia, family history of kidney disease, family history of diabetes, eGFR (per–10 mL/min/1.73m^2 lower), SBP (per 10–mm Hg higher), and body mass index (per 5–kg/m^2 higher). To avoid collinearity, self-reported hypertension and diastolic blood pressure were not included in the multivariable models. We created a missing category for variables with missing data. Except for hyperlipidemia (for which data were available only after 2005), missing data constituted <6% for all variables. We considered 2-tailed $P < 0.05$ statistically significant. All analyses were conducted with SAS, version 9.2 (SAS Institute Inc).

RESULTS

Participants with preserved eGFR with albuminuria were older and more often were black or current

Table 1. Baseline Characteristics of the KEEP Study Cohort With eGFR ≥60 mL/min/1.73 m^2 With and Without Albuminuria

	Albuminuria (n = 13,923)	No Albuminuria (n = 109,135)	*P*
Age (y)	54.0 ± 15.1	52.9 ± 14.5	<0.001
Female sex	66.7	68.1	0.001
Race/ethnicity			<0.001
Non-Hispanic white	35.0	43.7	
Non-Hispanic black	40.0	32.5	
Non-Hispanic other	12.3	10.4	
Hispanic	12.7	13.4	
Current smoker	14.0	11.1	<0.001
Education ≥12 y	82.9	86.7	<0.001
No health insurance	23.7	22.1	<0.001
Diabetes mellitus	42.8	28.8	<0.001
Cardiovascular disease	20.9	18.6	<0.001
Hypertension	62.5	51.8	<0.001
Hyperlipidemia	50.0	46.4	<0.001
Family history			
Kidney disease	21.6	19.0	<0.001
Diabetes	63.6	59.5	<0.001
eGFR (mL/min/1.73 m^2)	90.3 ± 18.9	90.6 ± 17.8	0.05
eGFR category			<0.001
60-74.9 mL/min/1.73 m^2	24.8	22.0	
75-89.9 mL/min/1.73 m^2	27.8	29.4	
90-104.9 mL/min/1.73 m^2	25.0	27.0	
≥105 mL/min/1.73 m^2	22.4	21.6	
BMI (kg/m^2)	31.4 ± 7.6	30.2 ± 6.8	<0.001
SBP (mm Hg)	138.6 ± 22.2	131.7 ± 18.6	<0.001
DBP (mm Hg)	82.2 ± 12.7	79.5 ± 11.1	<0.001

Note: Values for categorical variables given as percentage; values for continuous variables given as mean ± standard deviation.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; KEEP, Kidney Early Evaluation Program; SBP, systolic blood pressure.

smokers, with a higher prevalence of diabetes mellitus, cardiovascular disease, and hypertension compared with participants with preserved eGFR without albuminuria (Table 1). During an overall median of 4.8 years of follow-up (interquartile range, 4.1 years), 126 participants with albuminuria developed treated chronic kidney failure (16/10,000 patient-years), compared with 56 participants without albuminuria (1.1/10,000 patient-years); 866 participants with albuminuria (11.0/10,000 patient-years) and 2,556 participants without albuminuria (4.9/10,000 patient-years) died before developing treated chronic kidney failure.

The crude incidence of ESRD was approximately 10- to 20-fold higher for participants with albuminuria than for participants without albuminuria in each subgroup (Table 2). For example, for all participants with diabetes mellitus, the crude incidence of ESRD was 8.6 events per 10,000 patient-years. However, for the subset of participants with both diabetes mellitus and albuminuria, the crude incidence of ESRD was 35.1 events per 10,000 patient-years, compared with 3.0 events per 10,000 patient-years for the subset with diabetes mellitus without albuminuria. The crude incidence of ESRD for participants with neither diabetes mellitus nor albuminuria was only 0.4 events per 10,000 patient-years.

In univariate analysis, risk factors for ESRD in participants with and without albuminuria were similar (Table 3). For example, diabetes mellitus was associated with an 8.2-fold (95% confidence interval [CI], 5.2-13.0) higher risk of developing ESRD in participants with albuminuria and an 8.1-fold (95% CI, 4.5-14.8) higher risk in participants without albuminuria. One exception was for non-Hispanic other race, which was associated with a higher risk of treated chronic kidney failure in participants with albuminuria only (Table 3).

After multivariable adjustment, black race, diabetes mellitus, and lower eGFR remained significantly associated with developing treated chronic kidney failure irrespective of albuminuria status (Fig 1). Higher SBP and non-Hispanic other race remained

Table 2. Prevalence of Albuminuria and Development of ESRD for Selected KEEP Subgroups

	No. at Risk	Percent	No. Developing ESRD	Crude ESRD Incidence[a]
All	123,058		182	3.0
Albuminuria	13,923	11.3	126	16.0
No albuminuria	109,135	88.7	56	1.1
White race	52,519		45	1.8
Albuminuria	4,872	9.3	27	10.5
No albuminuria	47,647	90.7	18	0.8
Black race	41,082		91	4.4
Albuminuria	5,568	13.6	60	17.9
No albuminuria	35,514	86.4	31	1.8
Current smoker	13,464		39	5.6
Albuminuria	1,866	13.9	28	25.7
No albuminuria	11,598	86.1	11	1.9
Not current smoker	109,594		143	2.7
Albuminuria	12,057	11.0	98	14.5
No albuminuria	97,537	89.0	45	1.0
Diabetes mellitus	37,384		145	8.6
Albuminuria	5,954	15.9	104	35.1
No albuminuria	31,430	84.1	41	3.0
No diabetes mellitus	85,674		37	0.9
Albuminuria	7,969	9.3	22	4.5
No albuminuria	77,705	90.7	15	0.4
Hypertension	64,753		131	4.3
Albuminuria	8,659	13.4	96	20.9
No albuminuria	56,094	86.6	35	1.4
No hypertension	58,305		51	1.7
Albuminuria	5,264	9.0	30	9.2
No albuminuria	53,041	91.0	21	0.8
Hyperlipidemia	41,026		28	2.2
Albuminuria	4,060	9.9	19	15.2
No albuminuria	36,966	90.1	9	0.8
No hyperlipidemia	46,685		26	1.4
Albuminuria	4,059	8.7	17	11.0
No albuminuria	42,626	91.3	9	0.5
CVD	23,084		41	4.5
Albuminuria	2,898	12.6	29	24.1
No albuminuria	20,186	87.4	12	1.5
No CVD	99,974		141	2.8
Albuminuria	11,025	11.0	97	14.6
No albuminuria	88,949	89.0	44	1.0
eGFR = 60-74.9 mL/min/1.73 m^2	27,444		64	5.1
Albuminuria	3,451	12.6	50	28.3
No albuminuria	23,993	87.4	14	1.3
eGFR = 75-89.9 mL/min/1.73 m^2	35,973		51	3.0
Albuminuria	3,870	10.8	32	15.1
No albuminuria	32,103	89.2	19	1.3
eGFR = 90-104.9 mL/min/1.73 m^2	32,995		33	2.1
Albuminuria	3,484	10.6	21	10.5
No albuminuria	29,511	89.4	12	0.9
eGFR ≥105 mL/min/1.73 m^2	26,646		34	2.4
Albuminuria	3,118	11.7	23	11.7
No albuminuria	23,528	88.3	11	0.9

Note: Number at risk does not always sum to 123,058 due to missing values.

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KEEP, Kidney Early Evaluation Program.

[a]Per 10,000 patient-years.

Table 3. Unadjusted Associations of Specified Risk Factors With Developing ESRD

Characteristic	Albuminuria	No Albuminuria
Age (per 10-y older)	0.98 (0.87-1.10)	1.13 (0.94-1.36)
Female sex	0.68 (0.47-0.97)	0.77 (0.44-1.34)
Race/ethnicity		
Non-Hispanic white	1.00 (reference)	1.00 (reference)
Non-Hispanic black	1.61 (1.02-2.54)	2.08 (1.16-3.72)
Non-Hispanic other	2.47 (1.45-4.21)	0.62 (0.18-2.12)
Hispanic	0.93 (0.44-1.97)	0.42 (0.10-1.79)
Current smoker	1.69 (1.09-2.61)	1.63 (0.82-3.25)
Education ≥12 y	0.69 (0.45-1.06)	0.65 (0.33-1.29)
No health insurance	1.48 (0.99-2.21)	1.22 (0.62-2.38)
Diabetes mellitus	8.18 (5.15-13.00)	8.14 (4.48-14.78)
Cardiovascular disease	1.94 (1.27-2.98)	2.22 (1.15-4.29)
Hyperlipidemia	1.67 (0.87-3.23)	1.69 (0.67-4.28)
Family history of		
Kidney disease	1.27 (0.85-1.90)	0.84 (0.41-1.74)
Diabetes	2.02 (1.28-3.18)	2.01 (1.03-3.93)
eGFR (per 10-mL/min/1.73 m^2 lower)	1.24 (1.13-1.38)	1.16 (0.99-1.35)
SBP (per 10–mm Hg higher)	1.18 (1.10-1.27)	1.19 (1.05-1.34)
DBP (per 10–mm Hg higher)	1.21 (1.06-1.38)	0.96 (0.75-1.22)
BMI (per 5-kg/m^2 higher)	1.09 (0.97-1.22)	1.27 (1.08-1.50)

Note: Values are given as hazard ratio (95% confidence interval).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SBP, systolic blood pressure.

significantly associated with developing treated chronic kidney failure in participants with albuminuria. Older age (per 10 years older) was associated with a lower risk of developing treated chronic kidney failure, a finding likely explained because older age was associated significantly with a higher risk of death before developing treated chronic kidney failure in patients with (adjusted HR, 2.0; 95% CI, 1.8-2.1) and without (adjusted HR, 2.3; 95% CI, 2.2-2.4) albuminuria.

DISCUSSION

We sought to identify risk factors for developing treated chronic kidney failure in people with preserved eGFR with and without albuminuria, a population for which relatively little information currently is available. We show that in a diverse high-risk cohort of KEEP participants with eGFR ≥60 mL/min/1.73 m^2, black race, diabetes mellitus, lower eGFR, and higher SBP are associated with developing treated chronic kidney failure. Moreover, crude rates of ESRD for participants with one of these risk factors and albuminuria were 10- to 20-fold higher than for participants with one of these risk factors but without albuminuria. Our results support the recommendations made by national societies that advocate testing for kidney disease in patients with diabetes mellitus and cardiovascular disease risk factors.[20-22] However, actual rates of testing for kidney disease in clinical practice remain low. An audit of patients with diabetes mellitus and hypertension showed that only 53% had serum creatinine checked in the prior 24 months and 29% had urine tested for proteinuria in the prior 12 months.[23] Similarly, in the ADD-CKD (Awareness, Detection, and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease) Study, only 12.1% of participants with kidney disease were identified correctly as such by their providers.[24]

We found an increased risk of developing treated ESRD with higher SBP in participants with and without albuminuria, although the association was attenuated and no longer statistically significant in participants without albuminuria after multivariable adjustment. Our study complements our recent report of KEEP participants with eGFR <60 mL/min/1.73 m^2, which also demonstrated an increased risk of developing ESRD with SBP ≥150 mm Hg after adjustment for other factors.[25] In a cohort of insured residents of Northern California with preserved eGFR but no albuminuria, Hsu et al[11] found a 2.6- and 3.8-fold higher adjusted risk of developing ESRD with SBP of 140-159 and 160-179 mm Hg, respectively, and our results extend those findings to the more geographically and socioeconomically diverse KEEP cohort. However, in the African American Study of Kidney Disease and Hypertension (AASK), one of the few clinical trials to evaluate blood pressure treatment targets in chronic kidney disease,[16] randomization to more intensive treatment of hypertension (target mean arterial pressure <92 mm Hg) did not reduce the rate of kidney disease progression compared with participants in the standard group (target mean arterial pressure of 102-107 mm Hg). However, because all participants in AASK had established nondiabetic kidney disease (measured GFR of 20-65 mL/min/1.73 m^2), whether those results are applicable to people with preserved eGFR is not known.

Although all participants in the present analysis had eGFR ≥60 mL/min/1.73 m^2, each 10-mL/min/1.73 m^2 lower level in baseline eGFR was associated with a 20%-40% higher risk of developing treated chronic kidney failure irrespective of albuminuria status. Our results are consistent with several previous studies indicating that even slight decrements in eGFR are associated with higher risk of developing ESRD.[9,15,26] For example, the Atherosclerosis Risk in Communities (ARIC) Study[9] examined 15,324 white

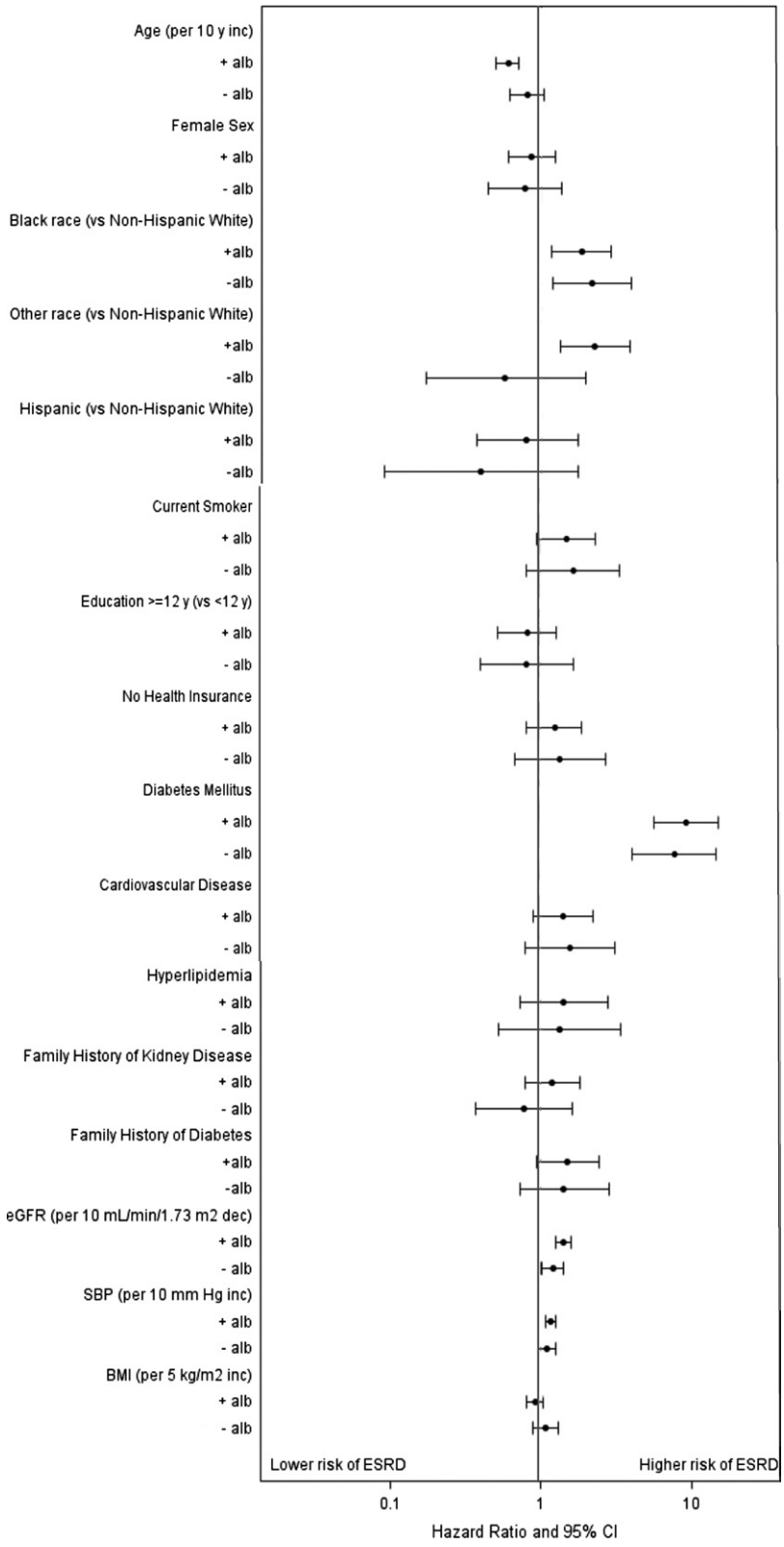

Figure 1. Forest plot shows adjusted hazard ratios associated with specified factors and the development of treated end-stage renal disease (ESRD) in KEEP (Kidney Early Evaluation Program) participants with (+alb) and without (-alb) albuminuria. Abbreviations: BMI, body mass index; dec, decrease; eGFR, estimated glomerular filtration rate; inc, increase; SBP, systolic blood pressure.

and African American participants with cardiovascular risk factors and found that eGFR of 75-90 mL/min/1.73 m^2 was associated with a 2-fold higher risk, and eGFR of 60-75 mL/min/1.73 m^2, with a 3.7-fold higher risk of developing ESRD compared with participants with eGFR of 90-120 mL/min/1.73 m^2.

We found a significant 19%-40% lower risk of developing treated ESRD for each 10-year-older age

in adjusted models, consistent with other observational studies.[10,26,27] These results likely are explained because each 10-year increase in age was associated with a 2-fold higher risk of death before developing treated ESRD. Moreover, we examined treated ESRD as the primary end point and were unable to identify participants who may have chosen not to undergo renal replacement therapy despite a low eGFR, a decision made more commonly by older patients.[28]

Although our study has several strengths, it also has several limitations. First, we relied on a single measurement of serum creatinine and albuminuria, possibly leading to misclassification of some participants. However, as a screening tool to identify people at high risk of developing ESRD, a single measurement may be appropriate. Second, we did not have information for medications, specifically angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which can slow the development of ESRD.[29,30] Finally, our median follow-up time was relatively short, yet we still found an incidence rate of ESRD approximately twice that reported by studies based on general unselected cohorts.[12,26] The relatively rapid development of ESRD in our cohort, all of whom started the study with eGFR $\geq$60 mL/min/1.73 m^2, may have been precipitated by episodes of acute kidney injury from hospitalization, use of nephrotoxic medications, or other acute events that we were unable to identify.

In conclusion, we identified several risk factors for developing ESRD in participants with preserved eGFR with and without albuminuria, including diabetes mellitus, higher SBP, black race, and lower eGFR. Our findings have important clinical implications because they help identify high-risk people who may benefit from kidney disease screening.

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