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Cognitive Impairment and Progression of CKD

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Contributions: Research idea and study design: MKT, KY, C-yH, ASG; data acquisition: KY, JC, AO, JD, ASG; data analysis/ interpretation: MKT, KY, C-H, JY, SS, MF, JC, AO, JD, DX, EV, ASG; statistical analysis: JY, DX, EV. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MKT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Abstract

Background—Cognitive impairment is common among patients with chronic kidney disease (CKD); however, its prognostic significance is unclear. We assessed the independent association between cognitive impairment and CKD progression in adults with mild to moderate CKD.

Study Design—Prospective cohort

Setting and Participants—Adults with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC) Study. Mean age of the sample was 57.7 ± 11.0 years and mean estimated glomerular filtration rate (eGFR) was 45.0 ± 16.9 ml/min/1.73m^2.

Predictor—Cognitive function was assessed with the Modified Mini-Mental State Examination (3MS) at study entry. A subset of participants aged 55 years and older received five additional cognitive tests assessing different domains. Cognitive impairment was defined as a score more than 1 SD below the mean score on each test. Covariates included demographics, kidney function, comorbidities and medications.

Outcomes—Incident end-stage renal disease (ESRD) and incident ESRD or 50% decline in baseline eGFR.

Results—In 3883 CRIC participants, 524 (13.5%) had cognitive impairment at baseline. Over a median 6.1 years of follow-up, 813 developed ESRD and 1062 developed ESRD or a ≥50% reduction in eGFR. There was no significant association between cognitive impairment and risk of ESRD (HR, 1.07; 95% CI, 0.87–1.30) or the composite of ESRD or 50% reduction in eGFR (HR, 1.06; 95% CI, 0.89–1.27). Similarly, there was no association between cognitive impairment and the joint outcome of death, ESRD. or 50% reduction in eGFR (HR, 1.06; 95% CI, 0.91–1.23). Among CRIC participants who underwent additional cognitive testing, we found no consistent association between impairment in specific cognitive domains and risk of CKD progression in adjusted analyses.

Limitations—Unmeasured potential confounders, single measure of cognition for younger participants

Conclusions—Among adults with CKD, cognitive impairment is not associated with an excess risk of CKD progression after accounting for traditional risk factors.

Keywords

cognitive impairment; impaired cognitive function; chronic kidney disease (CKD); microvascular disease; Modified Mini-Mental State Exam (3MS); cognitive function testing; concentration; attention; memory; disease progression; end-stage renal disease (ESRD); renal function; CRIC (Chronic Renal Insufficiency Cohort)

The prevalence of cognitive impairment is high among adults with chronic kidney disease (CKD) and the two conditions share several risk factors,[1] suggesting they may share a common pathogenesis. Microvascular injury in the kidney is a prominent feature of the two most common causes of CKD, diabetes mellitus and hypertension. Similarly, neuroimaging markers of microvascular injury in the brain associate with an elevated risk for cognitive decline and dementia.[2,3] These neuroimaging findings are more common among patients

with CKD compared to patients with normal kidney function.[4,5] Furthermore, among patients with diabetes mellitus, brain microvascular disease predicts incident nephropathy and progression to end-stage renal disease (ESRD).[6,7] Thus, the presence of impaired cognitive function may identify patients with systemic microvascular disease who are at risk for the development and progression of CKD. Whereas the assessment of microvascular disease within the kidney requires a biopsy, and the assessment of microvascular disease within the brain requires imaging, cognitive function testing is non-invasive and less costly.

Impaired cognitive function may also predispose patients to progression of kidney disease due to lower use or adherence with CKD risk reduction strategies. For example, treatment of hypertension may be less intensive in patients with cognitive impairment due to fear of precipitating adverse effects. Similarly, concerns about adherence with dietary potassium restriction and compliance with laboratory monitoring may lead to lower use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), resulting in more rapid loss of kidney function. As such, an assessment of cognitive function may be potentially useful for refining prediction of ESRD in at-risk patients.

Using data collected from the prospective, multicenter Chronic Renal Insufficiency Cohort (CRIC) Study, we tested the hypothesis that adults with CKD and cognitive impairment would be at higher risk for progression of CKD. We also tested the hypothesis that selected cognitive domains linked with microvascular disease,[8] such as attention and executive function, would be more strongly linked with CKD progression than language and memory.

Methods

Study Design and Recruitment

The CRIC Study is a prospective observational study designed to evaluate risk factors for progression of CKD among adults with moderate to advanced CKD. The study design and methods have been previously described in detail.[9,10] From June 2003 through May 2008, we recruited persons aged 21–74 years from seven clinical centers across the United States. Participants met age-based estimated glomerular filtration rate (eGFR) criteria: 20–70, 20–60, and 20–50 ml/min/1.73 m^2 for ages 21–44, 45–64, and 65–74 years, respectively. Exclusion criteria included diagnosis of polycystic kidney disease, pregnancy, recent immunosuppression for kidney disease, coexisting disease likely to affect survival (such as metastatic cancer), prior receipt of dialysis or organ transplant, or institutionalization (including residence in nursing homes). Institutional Review Boards at all clinical sites approved the study protocol (University of Pennsylvania: approval nos. 707819, 807882, Johns Hopkins University: NA_00044034, University of Maryland: HCR-HP-00041233-6, University Hospitals of Cleveland: 02-03-04, MetroHealth Medical Center: IRB03-00052, Cleveland Clinic Foundation: 5969, University of Michigan: HUM00073515, St. John Health System: SJ 0403-04, Wayne State University: 071803MP2F, University of Illinois: 2003-0149, Tulane University: H0340, and Kaiser Permanente/UCSF: CN-01AGo-02-H) and all participants signed informed consent.

Assessment of Cognitive Function

We assessed cognitive function in all CRIC participants at study entry with the Modified Mini-Mental State Examination (3MS)[11]. The 3MS is a test of global cognitive function with components for concentration, orientation, language, praxis, and memory. Scores on the 3MS range from 0 to 100, with higher scores denoting better cognitive function. Starting in 2006, we enrolled participants aged 55 years and older from four of the seven CRIC Clinical Centers in an ancillary study in which five additional cognitive tests were administered: The Trail-Making Test, Forms A and B (Trails A and B), Category Fluency, Buschke Selective Reminding Test, and the Boston Naming Test.[12] The Trails A measures attention, visuospatial scanning, and motor speed. The Trails B is primarily a test of executive function.[13] Category Fluency evaluates verbal production, semantic memory, and language.[14] The Buschke Selective Reminding Test measures verbal memory with delayed components.[15] The Boston Naming Test assesses language function by asking participants to name objects presented in pictures.[14] Compared with participants aged 55 years and older who were not enrolled in the cognitive ancillary study, participants who completed additional cognitive testing were one year older and more likely to be female, white, non-Hispanic, and have higher educational attainment (P-value <0.05).

We defined clinically significant cognitive impairment for each test separately. For the 3MS, Category Fluency, Buschke Selective Reminding Test, and the Boston Naming Test we defined impairment as a score 1 standard deviation (SD) or more below the mean.[16] For the Trails A and B where lower scores indicate better function, we defined cognitive impairment as having a score 1 SD above the mean or greater. To assess whether the use of a single cut-point to define cognitive impairment affected the results, we defined impairment as 3MS scores <85, <80, and <75 for participants aged younger than 65, 65–79, and 80 years or older, respectively.

Kidney Disease Progression Outcomes

Serum creatinine concentration and cystatin C concentration were measured annually at a central study laboratory. We calculated the eGFR with the CRIC equation which uses serum creatinine level, serum cystatin C level, age, sex, and race.[17] We assessed two CKD progression outcomes: (1) incidence of ESRD, defined as the initiation of dialysis or receipt of a pre-emptive kidney transplant, and (2) a composite of ESRD incidence or ≥50% reduction from the baseline eGFR.[18,19] We ascertained ESRD and death through semi-annual surveillance by CRIC study personnel, supplemented by crosslinkage with the US Renal Data System and the Social Security Death Master File.[20] In complementary analyses, we assessed the joint outcomes of death or ESRD, and death, ESRD, or ≥50% reduction from the baseline eGFR, to determine whether the competing risk of death materially affected the results.

Covariates

At the baseline visit, participants completed questionnaires ascertaining sociodemographic information, medical and family history, and health behaviors. Height, weight and blood pressure were recorded by trained study personnel. We defined diabetes mellitus as self-report of diabetes mellitus, use of medications for diabetes mellitus, or fasting blood glucose

of ≥126 mg/dL. We defined hypertension as self-report of hypertension, use of medications for high blood pressure, or a seated blood pressure of ≥140/80 mm Hg. We defined coronary heart disease as self-report of a myocardial infarction, angina or coronary revascularization procedure. We defined cerebrovascular disease as self-report of a stroke. We defined peripheral arterial disease as self-report of claudication, amputation, or revascularization procedure of the extremities. We defined smoking as current versus former or no history of smoking cigarettes. We defined alcohol use as current or former use of beer, wine or liquor. Use of ACE inhibitors and ARBs were reviewed and documented at the baseline study visit. Low-density lipoprotein (LDL) cholesterol was categorized as <100, 100–129, 130–159, or ≥160 mg/dL for analysis. Albuminuria, assessed as urine albumin-creatinine ratio measured on spot urine samples, was categorized as < 30, 30–299, or ≥300 mg/g or missing for analysis.

Statistical Analysis

Continuous variables were expressed as means ± standard deviations and compared using t-tests. Categorical variables were expressed as proportions and compared using the chi-squared test. We used Cox proportional hazards models to estimate the hazard ratio (HR) and 95% confidence interval (CI) for ESRD incidence and the composite outcome ESRD incidence or ≥50% reduction in eGFR for the exposure cognitive impairment, defined by performance on the 3MS. We examined −log(log) plots and Schoenfeld residuals to rule out violation of proportionality assumptions.

For each of the CKD progression outcomes, we adjusted for the following set of baseline covariates: (1) age; (2) other demographic characteristics; sex, race, ethnicity, education; (3) kidney function: eGFR and UACR; and (4) comorbidities: diabetes, coronary artery disease, peripheral arterial disease, stroke, smoking status, alcohol use, systolic blood pressure, body mass index, LDL cholesterol, and use of ACE inhibitors and ARBs. We adjusted for CRIC Clinical Center as a stratum variable. We also constructed models which omitted eGFR and urine albumin-creatinine ratio, as the baseline level of kidney function may reflect the same factors which affect cognitive function.

Next, we examined the association between cognitive impairment in specific domains and kidney outcomes. These analyses were limited to CRIC participants aged 55 years or older who underwent additional cognitive assessments. The same analyses as described above were performed with the exception that models were adjusted for age and eGFR corresponding to the most recent cognitive testing visit. Proportionality assumptions were violated for the Category Fluency test; therefore, we used piecewise regression to estimate the hazard for ESRD or 50% reduction in eGFR between baseline and one year, and after one year, based on examination of the Kaplan-Meier plots.

Results

Of the 3939 participants enrolled in the CRIC Study, 28 were missing baseline 3MS scores and an additional 28 were missing covariates, leaving a final analytic cohort of 3883 participants. Mean age of the sample was 57.7 ± 11.0 years and mean eGFR was 45.0 ± 16.9 ml/min/1.73m^2. Participant characteristics stratified by the presence of cognitive impairment

on the 3MS are shown in Table 1. Participants with cognitive impairment were older, and had lower mean eGFR and higher levels of albuminuria. Traditional ESRD risk factors were more prevalent in those with cognitive impairment, including diabetes mellitus, hypertension, and cardiovascular disease.

During a median follow-up of 6.1 (interquartile range, 4.1–7.4) years, 813 participants developed ESRD and 1062 participants developed the composite outcome ESRD or a ≥50% reduction in eGFR.

In unadjusted analyses, cognitive impairment was associated with a 41% increased risk of ESRD and a 50% increased risk of ESRD or 50% reduction in eGFR (Table 2). We constructed sequentially adjusted models to determine which factors might attenuate the association between cognitive impairment and CKD progression. Perhaps surprisingly, adjustment for age slightly strengthened the association between cognitive impairment and CKD progression. Demographic factors other than age—sex, race, ethnicity and education—explained the majority of the association between cognitive impairment and ESRD, and between cognitive impairment and the outcome ESRD or 50% reduction in eGFR. The addition of kidney function and comorbidities to the model further attenuated the results. In the fully adjusted models, there was no significant association between cognitive impairment and ESRD or the joint outcome of ESRD or 50% reduction in eGFR (Table 2). The results were similar when eGFR and albuminuria were omitted from the models. In sensitivity analyses utilizing different 3MS cut-points to define impairment for different age groups, the results were also similar. For example, in the fully adjusted model, the HR for ESRD was 1.11 (95% CI, 0.92–1.35) and the HR for ESRD or 50% reduction in eGFR was 1.07 (95% CI, 0.90–1.27).

The findings were comparable when we modeled the joint outcome of death or ESRD, and the joint outcome of death, ESRD or 50% reduction in eGFR (Table 3). In the fully adjusted models, there was no significant association between cognitive impairment with either outcome.

In the subset of CRIC participants aged 55 years or older who underwent more extensive cognitive testing, impairment on the Category Fluency test was not associated with the composite outcome ESRD or 50% decline in eGFR between baseline and one year, but was associated with a 70% increased relative hazard thereafter in adjusted analyses (Table 4). There was no association between impairment on the Buschke Selective Reminding Test, Boston Naming Test, Trails A or Trails B with ESRD or 50% decline in eGFR in analyses adjusted for demographics, kidney function and comorbidities.

Discussion

In a large cohort of adults with CKD prospectively followed up for a median >6 years, we found no significant association between global cognitive impairment and risk for progression of CKD after accounting for traditional ESRD risk factors. There was also no consistent association between impairment in specific cognitive domains with increased risk

for CKD progression. These findings suggest assessment of cognitive function does not add information for ESRD risk prediction beyond that reflected in traditional ESRD risk factors.

Among adults with normal baseline kidney function, several studies have demonstrated that changes in albuminuria or eGFR parallel declines in cognitive function, supporting the idea that microvascular disease may link the two conditions. For example, among 28,384 adults with vascular disease or diabetes mellitus and mean eGFR of 73 ml/min/1.73 m^2, incident albuminuria was associated with an increased risk for cognitive decline.[21] Similar associations between progressive increases in albuminuria and increased risk for cognitive decline have been demonstrated among middle-aged adults with type 2 diabetes mellitus and mean eGFR 90 ml/min/1.73 m^2, and among younger (<48 years) but not older Dutch adults with mean eGFR of 84 ml/min/1.73m^2.[22,23] Among 7839 adults aged 65 years or older with mean eGFR of 75 ml/min/1.73m^2, annualized eGFR decline > 4 ml/min/1.73m^2 was associated with a higher incidence of vascular dementia.[24] Another study of 2968 adults aged 65 years or older found that increased eGFR variability, but not eGFR trajectory, was associated with an increased risk for dementia.[25] Thus, the existing literature supports the hypothesis that changes in cognitive function parallel changes in markers of kidney function.

There are several possible reasons why cognitive impairment was not independently associated with progression of CKD in our study population. First, the pathogenesis of cognitive impairment may reflect several processes in addition to microvascular disease which are unrelated to or even protective from CKD progression. For example, carriers of apolipoprotein E (*APOE*) €4 allele are at increased risk for cognitive impairment and Alzheimer's disease[26] but may be at lower risk for CKD and ESRD.[27,28] Unfortunately, we lacked information on *APOE* €4 status, so we were unable to account for this potential confounder.

Second, cognitive impairment may be predictive of kidney outcomes in populations with a lower risk of ESRD, but not in a population who are already at high risk for ESRD. In lower risk populations, albuminuria and especially low eGFR may reflect several factors other than microvascular injury, such as aging or acute illness. In this setting, it is plausible that the added finding of cognitive impairment would support an underlying microvascular cause and identify individuals at risk for kidney disease progression. This may explain why studies in patients with preserved kidney function found positive correlations between kidney function decline and cognitive decline. Conversely, in high risk patients such as CRIC participants, cognitive impairment may not add ESRD risk information beyond that already reflected in eGFR and albuminuria. Individuals with cognitive impairment and CKD may also be at increased risk for earlier death, which would preclude being at risk for future kidney outcomes. However, a high competing risk of death did not appear to explain the mostly null findings in this study.

We hypothesized that impairment in the domain of executive function would be more strongly associated with CKD progression than other cognitive domains because impairment in executive function is linked with vascular risk factors.[8] We found no association between the Trails B, a test of executive function, and CKD progression. However, we found that poor performance on the Category Fluency test was associated with an increased risk for

CKD progression after one year. Category Fluency is a test which assesses semantic memory and also taps executive function. The absence of consistency between these two tests may suggest a false positive finding, or that the two tests capture different aspects of executive function. Further study is needed to determine the significance.

This study has several limitations. First, the participants recruited for CRIC may not be fully representative of all CKD patients. For example, volunteer kidney research participants may be at higher risk for progression to ESRD and lower risk for cognitive impairment than the broader population with CKD. Second, for the majority of study participants, we assessed baseline cognitive function with a single global measure, rather than a comprehensive battery. However, we found generally similar results when we used tests of specific cognitive domains rather than a global measure. Third, we lacked information on selected potential confounders or mediators, such as *APOE* €4 status and neuroimaging measures of microvascular disease, respectively. Our study also has several important strengths, including the large diverse population with prospective follow-up, repeated assessments of kidney function and the use of clinically important CKD progression outcomes.

In summary, among adults with CKD, cognitive impairment was not significantly associated with a higher risk of progression of CKD after accounting for traditional risk factors.

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Table 1

Baseline characteristics of CRIC Study participants overall and stratified by cognitive impairment based on 3MS

Characteristics	Overall (N=3883)	Cognitive Impairment (n=524)	No cognitive Impairment (n=3359)	P
Age				<0.001
21–49 y	796 (20.5)	66 (12.6)	730 (21.7)	
50–59 y	1151 (29.6)	144 (27.5)	1007 (30.0)	
60–69 y	1418 (36.5)	212 (40.5)	1206 (35.9)	
70–79 y	518 (13.3)	102 (19.5)	416 (12.4)	
Sex				0.3
Female	1753 (45.1)	225 (42.9)	1528 (45.5)	
Male	2130 (54.9)	299 (57.1)	1831 (54.5)	
Race				<0.001
White	1814 (46.7)	104 (19.8)	1710 (50.9)	
Black	1627 (41.9)	299 (57.1)	1328 (39.5)	
Other/Unknown	442 (11.4)	121 (23.1)	321 (9.6)	
Hispanic Ethnicity				<0.001
Hispanic	484 (12.5)	180 (34.4)	304 (9.1)	
Other/Unknown	3399 (87.5)	344 (65.6)	3055 (90.9)	
Educational attainment				<0.001
< High School	810 (20.9)	325 (62.0)	485 (14.4)	
High School Graduate	731 (18.8)	104 (19.8)	627 (18.7)	
Some College	2342 (60.3)	95 (18.1)	2247 (66.9)	
Diabetes Mellitus	1875 (48.3)	335 (63.9)	1540 (45.8)	<0.001
Hypertension	3344 (86.1)	497 (94.8)	2847 (84.8)	<0.001
Prior Coronary Heart Disease	845 (21.8)	136 (26.0)	709 (21.1)	<0.05
Prior Peripheral Arterial Disease	253 (6.5)	48 (9.2)	205 (6.1)	<0.01
Prior Stroke	385 (9.9)	84 (16.0)	301 (9.0)	<0.001
Current Smoker	507 (13.1)	84 (16.0)	423 (12.6)	<0.05
Current or Former Use of Alcohol	2445 (63.0)	212 (40.5)	2233 (66.5)	<0.001
Receiving ACE inhibitors and/or ARBs	2649 (68.2)	351 (67.0)	2298 (68.4)	0.5
Systolic blood pressure, mmHg	128.5 ±22.2	138.2 ±24.5	126.9 ±21.4	<0.001
Diastolic blood pressure, mm Hg	71.6 ±12.8	72.0 ±13.3	71.5 ±12.7	0.4
Body mass index				0.7
<18.5 kg/m2	27 (0.7)	5 (1.0)	22 (0.7)	
18.5–24.9 kg/m2	593 (15.3)	79 (15.1)	514 (15.3)	
25–29.9 kg/m2	1117 (28.8)	158 (30.2)	959 (28.6)	
≥30 kg/m2	2146 (55.3)	282 (53.8)	1864 (55.5)	
LDL cholesterol				<0.05

Characteristics	Overall (N=3883)	Cognitive Impairment (n=524)	No cognitive Impairment (n=3359)	P
<100 mg/dL	1991 (51.3)	274 (52.3)	1717 (51.1)	
100–129 mg/dL	1093 (28.1)	146 (27.9)	947 (28.2)	
130–159 mg/dL	539 (13.9)	57 (10.9)	482 (14.3)	
≥160 mg/dL	260 (6.7)	47 (9.0)	213 (6.3)	
eGFR, mL/min/1.73m^2				
Mean	45.0 ±16.9	37.3 ±13.4	46.2 ±17.0	<0.001
Median	43.1 [32.4–55.4]	36.4 [26.6–46.0]	44.5 [33.4–56.9]	<0.001
Albuminuria				<0.001
<30 mg/d	1493 (38.4)	136 (26.0)	1357 (40.4)	
30–299 mg/d	1004 (25.9)	138 (26.3)	866 (25.8)	
300–999 mg/d	569 (14.7)	86 (16.4)	483 (14.4)	
>999 mg/d	645 (16.6)	125 (23.9)	520 (15.5)	
Unknown	172 (4.4)	39 (7.4)	133 (4.0)	

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factor for cholesterol in mg/dL to mmol/L, ×0.02586.

Abbreviations: 3MS, Modified Mini-Mental State Examination; ACE – angiotensin-converting enzyme, ARB, angiotensin II receptor blocker; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein

Table 2

Association of cognitive impairment based on 3MS with progression of CKD in CRIC Study participants.

	ESRD (N=3,883)	ESRD or 50% eGFR decline (n=3,622)
No. (%) with outcome	813 (20.9)	1062 (29.3)
Unadjusted	1.41 (1.17–1.70)	1.50 (1.28–1.76)
Models *		
1: Age adjusted	1.53 (1.27–1.85)	1.59 (1.35–1.87)
2: Demographics adjusted	1.18 (0.96–1.43)	1.24 (1.05–1.47)
3: Demographics and kidney function adjusted	1.11 (0.91–1.35)	1.13 (0.95–1.34)
4: Fully adjusted	1.07 (0.87–1.30)	1.06 (0.89–1.27)
5: Fully adjusted model minus kidney function	1.07 (0.87–1.31)	1.12 (0.94–1.33)

Note: Unless otherwise indicated, values are given as hazard ratio (95% confidence interval).

3MS, Modified Mini-Mental State Examination; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate

* Model 1 is adjusted for age;
Model 2 is adjusted for age, sex, race, Hispanic ethnicity, and educational attainment; Model 3 is adjusted as in model 2 plus eGFR and albuminuria; Model 4 is adjusted as in model 3 plus diabetes mellitus, coronary artery disease, peripheral vascular disease, stroke, smoking status, alcohol use, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and CRIC center as a stratum variable;. Model 5 includes all covariates except eGFR and albuminuria

Table 3

Association of cognitive impairment based on 3MS with joint outcome of death or progression of CKD in CRIC Study participants.

	Death or ESRD (N=3,883)	Death or ESRD or 50% eGFR decline (n=3,622)
% with outcome	33.5	38.6
Unadjusted	1.58 (1.37–1.82)	1.34 (1.16–1.54)
Models *		
1: Age adjusted	1.56 (1.35–1.80)	1.30 (1.13–1.50)
2: Demographics adjusted	1.23 (1.05–1.44)	1.12 (0.97–1.31)
3: Demographics and kidney function adjusted	1.15 (0.99–1.35)	1.10 (0.94–1.28)
4: Fully adjusted	1.11 (0.95–1.30)	1.06 (0.91–1.23)
5: Fully adjusted model minus kidney function	1.13 (0.96–1.32)	1.08 (0.92–1.25)

Note: Unless otherwise indicated, values are given as hazard ratio (95% confidence interval).

3MS, Modified Mini-Mental State Examination; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate

* Model 1 is adjusted for age; Model 2 is adjusted for age, sex, race, Hispanic ethnicity, and educational attainment; Model 3 is adjusted as in model 2 plus eGFR and albuminuria; Model 4 is adjusted as in model 3 plus diabetes mellitus, coronary artery disease, peripheral vascular disease, stroke, smoking status, alcohol use, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and CRIC center as a stratum variable;
Model 5 includes all covariates except eGFR and albuminuria

Table 4

Adjusted association of cognitive impairment in different cognitive domains with ESRD or 50% decline in eGFR among CRIC Cognitive Study participants

Category Fluency	ESRD or 50% eGFR decline (n=773; 19.2% of CRIC Cognitive Study participants)	
	Demographics adjusted*	Fully Adjusted**
Category Fluency Baseline to year 1^ After year 1^	1.30 (0.48–3.53) 2.14 (1.37–3.33)	0.84 (0.28–2.53) 1.70 (1.02–2.83)
Buschke Selective Reminding Test	1.01 (0.65–1.56)	0.98 (0.62–1.56)
Boston Naming Test	0.73 (0.46–1.14)	1.13 (0.68–1.87)
Trails A	1.03 (0.66–1.63)	0.88 (0.53–1.45)
Trails B	1.07 (0.69–1.67)	0.72 (0.43–1.22)

Note: Unless otherwise indicated, values are given as hazard ratio (95% confidence interval).

3MS, Modified Mini-Mental State Examination; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate

^ piecewise regression

* Demographics adjusted model is adjusted for age, sex, race, Hispanic ethnicity, and educational attainment.

** Fully adjusted model includes age, sex, race, Hispanic ethnicity, educational attainment, eGFR, albuminuria, diabetes mellitus, coronary artery disease, peripheral vascular disease, stroke, smoking status, alcohol use, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and CRIC center as a stratum variable.