

Chronic Kidney Disease and Cognitive Function in Older Adults: Findings from the Chronic Renal Insufficiency Cohort Cognitive Study

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OBJECTIVES: To investigate cognitive impairment in older, ethnically diverse individuals with a broad range of kidney function, to evaluate a spectrum of cognitive domains, and to determine whether the relationship between chronic kidney disease (CKD) and cognitive function is independent of demographic and clinical factors.

DESIGN: Cross-sectional.

SETTING: Chronic Renal Insufficiency Cohort Study.

PARTICIPANTS: Eight hundred twenty-five adults aged 55 and older with CKD.

MEASUREMENTS: Estimated glomerular filtration rate (eGFR, mL/min per 1.73 m²) was estimated using the four-variable Modification of Diet in Renal Disease equation. Cognitive scores on six cognitive tests were compared across eGFR strata using linear regression; multivariable logistic regression was used to examine level of CKD and

clinically significant cognitive impairment (score ≤ 1 standard deviations from the mean).

RESULTS: Mean age of the participants was 64.9, 50.4% were male, and 44.5% were black. After multivariable adjustment, participants with lower eGFR had lower cognitive scores on most cognitive domains ($P < .05$). In addition, participants with advanced CKD (eGFR < 30) were more likely to have clinically significant cognitive impairment on global cognition (adjusted odds ratio (AOR) 2.0, 95% CI = 1.1–3.9), naming (AOR = 1.9, 95% CI = 1.0–3.3), attention (AOR = 2.4, 95% CI = 1.3–4.5), executive function (AOR = 2.5, 95% CI = 1.9–4.4), and delayed memory (AOR = 1.5, 95% CI = 0.9–2.6) but not on category fluency (AOR = 1.1, 95% CI = 0.6–2.0) than those with mild to moderate CKD (eGFR 45–59).

CONCLUSION: In older adults with CKD, lower level of kidney function was associated with lower cognitive function on most domains. These results suggest that older patients with advanced CKD should be screened for cognitive impairment. *J Am Geriatr Soc* 58:338–345, 2010.

Key words: chronic kidney disease; cognitive impairment; cognitive function

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An abstract from this study will be shared at the 2009 International Conference on Alzheimer's disease and Associated Disorders in Vienna, Austria. See Appendix A for a list of the Chronic Renal Insufficiency Cohort Investigators.

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The prevalence of chronic kidney disease (CKD) increases with advancing age. Similarly, cognitive impairment is more common in older adults. Both conditions are associated with greater healthcare use and poorer quality of life and are of increasing public health significance.^{1,2} Whether CKD is associated with accelerated cognitive aging has not been rigorously addressed. There are several potential mechanisms, including cerebrovascular disease,^{3–5} metabolic

dysregulation,⁶ and direct effects of kidney disease^{7–9} that may link CKD with impaired cognitive function.

The few studies that have investigated the association between CKD before kidney failure and cognitive outcomes suggest that older adults with very low levels of kidney function have worse cognitive function than those without CKD,^{10–14} but little is known about the specific cognitive domains affected in CKD, because most of the prior research studies have used global cognitive screening measures rather than tests of specific domains. In addition, they had limited representation of minority subjects and a limited range of kidney function.

The Chronic Renal Insufficiency Cohort (CRIC) Study, a prospective observational cohort study, was established to examine the risk factors and mechanisms of progression of CKD and cardiovascular disease (CVD). The CRIC Cognitive (CRIC COG) Study, an ancillary study to CRIC, provided the opportunity to investigate cognitive impairment in older, ethnically diverse individuals with a broad range of kidney function, to evaluate a spectrum of cognitive domains, and to determine whether the relationship between CKD and cognitive function is independent of demographic and clinical factors.

METHODS

Study Design

The CRIC Study is a prospective cohort study designed to evaluate the risk factors and mechanisms of progression of CKD and CVD in adults with mild to moderate CKD. A total of 3,612 participants (47.0% with diabetes mellitus (DM)) were enrolled at seven clinical centers from May 2003 to March 2007 and are being followed annually until death or withdrawal of informed consent. The study design and methods have been published previously.¹⁵

The present study of cognitive function, called the CRIC COG Study, is ancillary to the parent CRIC Study. Similar to its parent study, the CRIC COG is a prospective observational cohort study that recruited study participants from four of the seven clinical CRIC centers located in Philadelphia, Pennsylvania; Cleveland, Ohio; Oakland, California; and Chicago, Illinois. Only persons enrolled in the CRIC Study and who were aged 55 and older were eligible for the cognitive function study. At their next scheduled in-clinic visit, eligible participants were enrolled in the CRIC COG Study and administered a cognitive battery. This served as the baseline visit for the study but may not have coincided with the baseline visit for the parent study. Thus “baseline” in this report is the participants’ first visit as part of CRIC COG Study.

Institutional review boards at each of the participating sites and at the University of California at San Francisco approved the CRIC COG Study, and all participants gave written informed consent.

Study Population

To be enrolled in the CRIC Study, participants must be aged 21 to 74 and have an estimated glomerular filtration rate (eGFR) of 20 to 70 mL/min per 1.73 m² if aged 21 to 44, 20 to 60 mL/min per 1.73 m² if aged 45 to 64, and 20 to 50 mL/min per 1.73 m² if aged 65 to 74. They were not eligible if

they were institutionalized, did not provide informed consent, had previously undergone dialysis for longer than 1 month, were diagnosed with polycystic kidney disease, had received a prior organ or bone marrow transplant, were taking immunosuppressive drugs for kidney disease in the past 6 months, or were currently participating in a clinical trial or the African American Study of Kidney Disease and Hypertension, an ongoing cohort study at some of the centers. Other exclusions included New York Heart Association Class III or IV heart failure, cirrhosis, human immunodeficiency virus infection or acquired immunodeficiency syndrome, chemotherapy for cancer within 2 years, multiple myeloma, or renal cell carcinoma.¹⁵ The CRIC COG Study required that participants be enrolled in the CRIC Study and be aged 55 and older. This minimum age requirement was established to increase the likelihood of observing clinically significant cognitive decline in the sample. The target sample size was 720, with equal recruitment from the four clinical centers.

Predictor Variable

The primary predictor of interest was level of kidney function. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) estimating equation.¹⁶ Whenever possible, the eGFR value determined at the CRIC visit coinciding with the CRIC COG baseline visit was used. In cases ($n = 8$; 0.9%) in which visits did not coincide or when eGFR was missing, the most recent eGFR value was used (mean interval of 1.4 years).

Cognitive Function Measures

Six cognitive function tests (with 7 scores) were administered in the CRIC COG Study: the Modified Mini-Mental State Examination (3MS), the Trail Making Test Parts A and B (Trails A and B), Category (verbal) Fluency, Buschke Selective Reminding Test (immediate and delayed memory), and Boston Naming. The 3MS is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory, with scores ranging from 0 to 100, higher scores indicating better function.¹⁷ Trails A and B measure visuospatial scanning, motor speed, executive function, and attention.¹⁸ Trails B is primarily a test of executive function, and Trails A is predominantly a test of attention. The scores are based on the time to complete a particular task, and therefore, lower scores indicate higher function. Category (verbal) Fluency measures verbal production, semantic memory, and language, with higher scores indicating better performance.¹⁹ Category Fluency and Trails B are typically impaired in the context of subcortical vascular disease.²⁰ The Buschke Selective Reminding Test is a well-established test of verbal memory, with immediate and delayed components.²¹ Verbal memory is one of the earliest cognitive domains to be affected in Alzheimer’s disease (AD) and is a hallmark feature of all dementias.²² Higher scores indicate higher function. The Modified Boston Naming test is a 15-item test of language function that requires the participant to name objects presented in pictures.¹⁹ Language deficits, such as those found with naming, are a hallmark feature of early AD. Higher scores indicate higher function.

Clinically significant impairment was defined as having a score 1 standard deviation (SD) below the mean or lower, except for the Trails A and B, in which case impairment was a score at least 1 SD above the mean.

Covariates

Covariates included additional data collected as part of the CRIC Study, including sociodemographic characteristics, relevant medical history (diabetes mellitus, diagnosed hypertension; self-reported at each annual clinic visit if a doctor told them they had that condition), body mass index (BMI; measured as weight (kg) divided by the square of height (m)), and resting blood pressure (systolic and diastolic; mean of three seated measurements, 30 seconds apart), each measured or updated annually. The Beck Depression Inventory (BDI) was collected biannually and moderate to severe depression was defined as a score greater than 14.²³

Statistical Methods

Baseline characteristics were compared across eGFR categories (≥ 60 , 45–59, 30–44, and < 30 mL/min per 1.73 m^2) using analysis of variance for normally distributed continuous data, Kruskal-Wallis test for nonnormally distributed continuous data, and chi-square tests for categorical data. Tests for trend were performed using the Cochran-Armitage Trend Test on categorical variables and orthogonal polynomial contrasts within the general linear models for continuous variables. The outcome variables of interest are the six cognitive function tests, resulting in seven scores. The primary analysis was a comparison of each score across category of eGFR level using a linear regression model, so an association between kidney function and cognitive function could be tested for. Adjustment was made for the following possible confounding variables based on their association ($P < .10$) with CKD and cognitive function: age, education, sex, BMI, diabetes mellitus, hypertension, and depression. Additionally, adjustment was made for race based on prior published studies showing separate associations between race and CKD^{9–11} and between race and cognitive function.^{24,25}

Differences in likelihood of clinically significant cognitive impairment were further tested for across eGFR strata using logistic regression models, with adjustment for age, race, education, sex, BMI, diabetes mellitus, hypertension, and depression score. For these analyses, the reference group was the subgroup of participants with eGFR of 45 to 59 mL/min per 1.73 m^2 . (The 80 participants with eGFR ≥ 60 mL/min per 1.73 m^2 were not chosen to be the reference, because they had demonstrated lower levels of kidney function at the time of screening several months before and did not seem to appropriately represent older adults with eGFR ≥ 60 .) Results are summarized with odds ratios (ORs) and 95% confidence intervals (CIs). Models were run with and without adjustment for possible confounders. All analyses were done using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 825 participants were recruited into the CRIC COG Study (of those who were eligible; 983 were asked to participate). This cohort had a mean age \pm SD of 64.9 ± 5.6 and was 50.4% male and 44.5% black. Site enrollment in-

cluded 205 participants from the University of Pennsylvania center, 223 participants from the Case Western Reserve center, 196 from the University of Illinois at Chicago center, and 201 from the Kaiser Permanente of Northern California/University of California San Francisco center. At the time of cognitive testing, mean eGFR was 41.0 ± 14.3 mL/min per 1.73 m^2 , with 80 participants having an eGFR of 60 mL/min per 1.73 m^2 or greater (mean 61 mL/min per 1.73 m^2), 289 with an eGFR of 45 to 59 mL/min per 1.73 m^2 (mean 49 mL/min per 1.73 m^2), 299 with an eGFR of 30 to 44 mL/min per 1.73 m^2 (mean 37 mL/min per 1.73 m^2), and 157 with an eGFR of less than 30 (mean 24) mL/min per 1.73 m^2 . The characteristics of the CRIC COG participants were compared across eGFR categories (Table 1). Participants with lower eGFR tended to be older and have less educational attainment and greater comorbidity burden, including diabetes mellitus and hypertension.

In unadjusted analyses, for each of the cognitive tests, a consistent pattern of worse cognitive scores in participants with greater CKD severity was observed. For example, for the 3MS, participants with an eGFR of 60 mL/min per 1.73 m^2 or greater had a mean score of 95.2 ± 5.0 , those with an eGFR of 45 to 59 mL/min per 1.73 m^2 had a score of 94.0 ± 7.6 , those with an eGFR of 30 to 44 mL/min per 1.73 m^2 had a score of 92.1 ± 7.1 , and those with an eGFR less than 30 mL/min per 1.73 m^2 had a score of 91.4 ± 7.8 ($P < .001$ for trend). For the Trails B test, mean scores were 115.7 ± 70.3 , 126.1 ± 70.1 , 150.9 ± 83.0 , and 163.9 ± 85.1 , respectively ($P < .001$ for trend). A similar pattern emerged for the other four cognitive tests (5 subscores). Multivariable adjustment for age, sex, race, education, BMI, diabetes mellitus, hypertension, and depression did not alter the findings, with the exception of the Category Fluency and Buschke tests (Table 2).

The association between severity of CKD and clinically significant cognitive impairment, defined as a score 1 SD or more more severe from the mean, was next determined (Table 3). Participants with more-severe CKD had higher prevalence of cognitive impairment on global cognition (21.7% for eGFR < 30 mL/min per 1.73 m^2 , 14.1% for eGFR 30–44 mL/min per 1.73 m^2 , 9.7% for eGFR 45–59 mL/min per 1.73 m^2 , 5.0% for eGFR ≥ 60 mL/min per 1.73 m^2 , $P < .001$ for trend), attention (20.4%, 16.5%, 8.7%, 3.8%, respectively, $P < .001$), executive function (28.0%, 23.2%, 12.2%, 11.3%, respectively, $P < .001$), naming (23.6%, 20.1%, 12.5%, 7.5%, respectively, $P < .001$), category fluency (16.6%, 15.2%, 12.5%, 5.0%, respectively, $P = .02$), and delayed memory (19.1%, 17.4%, 13.3%, 5.0%, respectively, $P = .003$). Although this pattern was also evident for the test of immediate memory (22.3%, 22.1%, 17.0%, 18.8%, respectively, $P = .16$), the differences were not statistically significant. After multivariable adjustment for age, sex, race, education, hypertension, depression, BMI, and diabetes mellitus, participants with more-severe CKD continued to demonstrate greater likelihood of cognitive impairment on most tests (Figure 1). Participants with advanced CKD (eGFR < 30) were more likely to have cognitive impairment on tests of global cognition (adjusted odds ratio (AOR) = 2.0, 95% CI = 1.1–3.9), naming (AOR = 1.9, 95% CI = 1.0–3.3), attention (AOR = 2.4, 95% CI = 1.3–4.5), executive function (AOR = 2.5, 95% CI = 1.9–4.4) and delayed

Table 1. Characteristics of the 825 Participants Enrolled in the Chronic Renal Insufficiency Cohort Cognitive Function Study

Characteristic	eGFR (mL/min per 1.73 m ²)				P-Value*
	≥60 (n = 80)	45–59 (n = 289)	30–44 (n = 299)	<30 (n = 157)	
Age, mean ± SD	61.5 ± 3.5	64.8 ± 5.6	65.5 ± 5.7	65.6 ± 5.7	<.001
Male, n (%)	44 (55.0)	162 (56.1)	139 (46.5)	71 (45.2)	.05
Race, n (%)					.70
White	42 (52.5)	144 (49.8)	145 (48.5)	70 (44.6)	
Black	33 (41.3)	120 (41.5)	138 (46.2)	76 (48.4)	
Other	5 (6.3)	20 (6.9)	14 (4.7)	11 (7.0)	
Hispanic ethnicity	2 (2.5)	11(3.8)	6 (2.0)	3 (1.9)	.51
Education ≤high school, n (%)	22 (27.5)	82 (28.4)	124 (41.5)	67 (42.7)	<.001
Married or domestic partner, n (%)	50 (62.5)	165 (57.1)	151 (50.5)	83 (52.9)	.18
Diabetes mellitus, n (%)	32 (40.0)	125 (43.3)	176 (58.9)	88 (56.1)	<.001
Current smoker, n (%)	10 (12.5)	27 (9.3)	40 (13.4)	14 (8.9)	.33
Hypertension, n (%)	62 (77.5)	251 (86.9)	289 (96.7)	150 (95.5)	<.001
Stroke, n (%)	5 (6.3)	30 (10.4)	37 (12.4)	20 (13.4)	.40
Depression, n (%)	13 (16.3)	31 (10.7)	59 (19.7)	21 (13.4)	.02
Body mass index, kg/m ² , mean ± SD	31.0 ± 5.9	31.3 ± 7.8	32.9 ± 7.8	32.1 ± 8.5	.06
Systolic blood pressure, mean ± SD	119.3 ± 14.3	126.5 ± 21.2	129.9 ± 24.2	130.9 ± 22.3	<.001
Diastolic blood pressure, mean ± SD	68.7 ± 11.8	67.6 ± 12.2	67.1 ± 12.5	65.7 ± 11.5	.28

* P-value is for test of differences across levels of estimated glomerular filtration rate (eGFR).
SD = standard deviation.

memory (AOR = 1.5, 95% CI = 0.9–2.6) but not on category fluency (AOR = 1.1, 95% CI = 0.6–2.0) or immediate memory (AOR = 1.2, 95% CI = 0.7–2.1) than those with mild or moderate CKD (eGFR 45–59).

In subgroup analyses defined a priori according to a diagnosis of diabetes mellitus, race (black vs white) and sex, consistent interactions for these strata (*P* > .10 for all) and the association between level of eGFR and cognitive function were not observed. The cohort was also stratified according to age (55–64, 65–74, and ≥75), and it was found that the prevalence of global cognitive impairment (defined according to the 3MS) was 9.1%, 18.4%, and 13.3%, respectively, but

there was no interaction according to age on the association between CKD severity and cognitive function.

DISCUSSION

In the CRIC COG Study, it was found that baseline cognitive function measured across multiple domains was worse in participants with more-severe kidney disease, even after adjustment for several potential confounders, including demographic characteristics and relevant comorbidities. The proportion of participants with clinically meaningful cognitive impairment was much greater for those with

Table 2. Adjusted Mean Cognitive Function Score According to Baseline Level of Estimated Glomerular Filtration Rate (eGFR)

Cognitive Test	N	eGFR (mL/min per 1.73 m ²) Mean (Standard Error)				P-Value*
		≥60	45–59	30–44	<30	
Modified Mini-Mental State Examination (range 0–100)	813	92.8 (0.82)	92.2 (0.61)	91.2 (0.62)	91.0 (0.70)	.01
Trail Making Test (range 0–300)						
Part A	810	49.3 (4.44)	53.7 (3.30)	62.9 (3.37)	68.0 (3.77)	<.001
Part B	809	143.3 (8.58)	148.1 (6.38)	161.2 (6.50)	170.0 (7.28)	<.001
Boston Naming (range 0–15)	811	13.6 (0.18)	13.5 (0.11)	13.3 (0.11)	13.2 (0.13)	.02
Category Fluency (range 0–45)	811	17.7 (0.61)	16.4 (0.46)	16.5 (0.46)	16.6 (0.52)	.11
Buschke Selective Reminding Test						
Immediate Recall (range 0–12)	813	6.4 (0.24)	6.3 (0.18)	6.1 (0.18)	6.1 (0.20)	.14
Delayed Recall (range 0–12)	804	7.9 (0.37)	7.4 (0.28)	7.4 (0.28)	7.3 (0.32)	.12

Adjusted for age, race, education, sex, diabetes mellitus, hypertension, body mass index, and depression.
Higher scores indicate higher function for all tests except for Trails A and B, on which lower scores are better.
* P-value for test of trend.

Table 3. Prevalence and Unadjusted Odds Ratios of Clinically Significant Cognitive Impairment, According to Estimated Glomerular Filtration Rate (eGFR) Group

Cognitive Test	eGFR Rate (mL/min per 1.73 m ²) %; Odds Ratio (95% Confidence Interval)			
	≥60	45–59	30–44	<30
Modified Mini-Mental State Examination	5.0; 0.5 (0.2–1.4)	9.7; Reference	14.1; 1.5 (0.9–2.5)	21.7; 2.6 (1.5–4.4)
Trail Making Test				
Part A	3.8; 0.4 (0.1–1.4)	8.7; Reference	16.5; 2.1 (1.2–3.5)	20.4; 2.7 (1.5–4.7)
Part B	11.3; 0.9 (0.4–2.0)	12.2; Reference	23.2; 2.2 (1.4–3.4)	28.0; 2.8 (1.7–4.6)
Boston Naming	7.5; 0.6 (0.2–1.4)	12.5; Reference	20.1; 1.8 (1.1–2.8)	23.6; 2.2 (1.3–3.6)
Category Fluency	5.0; 0.4 (0.1–1.1)	12.5; Reference	15.2; 1.3 (0.8–2.0)	16.6; 1.4 (0.8–2.4)
Buschke Selective Reminding Test				
Immediate Recall	18.8; 1.1 (0.6–2.1)	17.0; Reference	22.1; 1.4 (0.9–2.1)	22.3; 1.4 (0.9–2.3)
Delayed Recall	5.0; 0.3 (0.1–1.0)	13.3; Reference	17.4; 1.4 (0.9–2.2)	19.1; 1.5 (0.9–2.6)

more-severe CKD as well. This pattern was observed for most of the cognitive domains, including global cognition, verbal memory, attention, naming, and executive function, but not for verbal fluency. Similar findings were observed for participants with and without diabetes mellitus, men and women, and blacks and whites.

These findings support and extend the findings observed by several published cross-sectional studies. Of 1,015 postmenopausal women with CVD, for every 10 mL/min per 1.73 m² reduction in GFR, there was a 27% increase in likelihood of global cognitive impairment. In more than 20,000 U.S. adults, lower levels of kidney function were found to be associated with greater prevalence of cognitive impairment.¹³ Level of eGFR was associated with

cognitive impairment on executive function, memory, and language measures.²⁶ In other studies, subjects with CKD had significantly poorer performance on tests of executive function, verbal memory, and global performance.^{27,28} Similarly, patients with CKD performed significantly worse on executive and memory measures than controls in a small clinical sample.¹⁴ The few longitudinal studies that have been conducted on CKD and cognition also support the current study's observations. Of more than 3,000 older adults, those with CKD (defined as an eGFR < 60 mL/min per 1.73 m²) had greater 3MS score decline over 4 years than those without CKD, although there were few participants with severe CKD.¹⁰ One of the only studies to investigate the association between CKD and dementia reported a high risk of incident dementia in elderly subjects with CKD participating in the Cardiovascular Health Cognition Study,¹¹ although another longitudinal study did not find an association between kidney function and global cognitive impairment or risk in cognitive decline.¹² This may be due to differences in study populations, because that study cohort comprised older community-dwelling men primarily without CKD.¹²

There are several mechanisms that might link CKD with cognitive impairment. Individuals with CKD have a greater prevalence of established CVD and cardiovascular risk factors, and these same risk factors increase the risk of developing dementia, including AD and vascular dementia.³ CKD is also associated with a number of other factors that also may induce cognitive impairment, including anemia, high levels of inflammatory cytokines, oxidative stress, and alterations in lipid and homocysteine metabolism.^{29–33}

This study is an important step in advancing understanding of the important role that kidney function may play in cognitive aging. Strengths of this study are its recruitment of patients from the ongoing CRIC Study, which includes a large number of patients with a range of CKD severity, allowing the association between severity of CKD and cognitive function to be explored; the administration of sensitive cognitive tests that evaluate a range of cognitive domains; and the ability to adjust for differences across levels of kidney function in important possible confounders to determine whether the association between CKD and

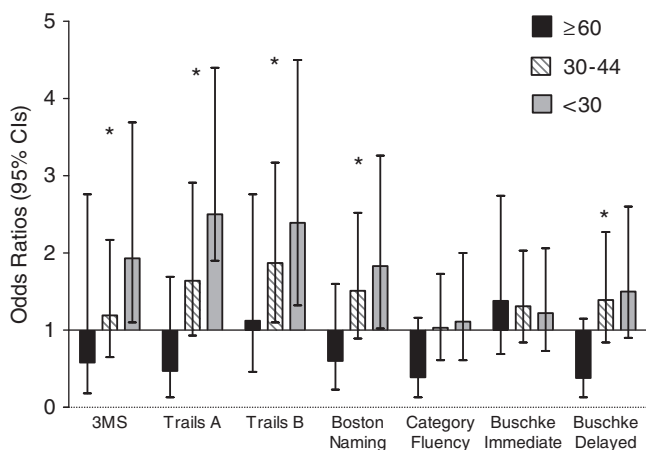


Figure 1. The likelihood of cognitive impairment (adjusted odds ratios and 95% confidence intervals) across estimated glomerular filtration rate (eGFR) category (reference group is 45–59 mL/min per 1.73 m²). Models were adjusted for age, sex, race, education, diabetes, hypertension, body mass index, and depression. **P*-value for trend test < .05. Modified Mini-Mental State Examination (3MS) scores range from 0 to 100; Trail Making Test Parts A and B (Trails A and B) scores range from 0 to 300; Boston Naming scores range from 0 to 15; Category Fluency scores range from 0 to 45; Buschke Immediate and Delayed Recall scores range from 0 to 12; higher scores indicate higher function for all tests except for Trails A and B in which lower scores are better.

cognitive function was independent of demographics and comorbidities.

Some limitations of the study deserve mention. As a cross-sectional analysis, the ability to draw causal conclusions between level of eGFR and cognitive function is limited. The pattern of cognitive deficits is more suggestive of subcortical vascular disease involvement than underlying AD, but without structural brain imaging results, the etiology of clinically significant cognitive impairment cannot be determined. Despite the large, diverse sample of patients with CKD, these results may not be fully generalizable to the broader population with CKD in the United States, and CRIC participants with an eGFR of 60 mL/min per 1.73 m² or greater most certainly are not reflective of people with better kidney function, because they at one time had an eGFR less than 60 mL/min per 1.73 m². Finally, although the effect sizes may seem small for some of the cognitive tests (e.g., 3MS), similar effect sizes have been found in studies investigating better-studied risk factors for cognitive impairment, such as hypertension or dyslipidemia.^{34,35}

In summary, this study found that lower levels of eGFR were independently associated with impaired cognitive functioning across multiple different domains, especially related to tests of executive function, even after adjustment for sociodemographic and clinical factors. These results suggest that screening older patients with advanced CKD for cognitive impairment might be important, but future research is needed to determine the appropriate screening tools and the sensitivity and specificity of various cut-points for screening. It is hoped that the ongoing longitudinal assessments of the CRIC COG Study will facilitate better understanding of the clinical importance, etiology, and mechanisms explaining the association between CKD severity and cognition.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Author Contributions: Study concept and design: KY, MKT, JWK, ASG. Acquisition of subjects and data analysis: KY, ASG. Interpretation of data: KY, LA, MKT, JWK, ARS, ASG. Preparation of manuscript: KY, PLB, JWK, ARS, DC, CA, LA, KD, AO, SS, NR, GM.

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