

Depressive Symptoms Associate With Race and All-Cause Mortality in Patients With CKD



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Introduction: Depression is common but underrecognized in patients with chronic kidney disease (CKD), especially among racial/ethnic minorities. We examined the association between depressive symptoms and all-cause mortality (including deaths before and after end-stage renal disease [ESRD]) and whether antidepressant use impacts this association, overall, and by race/ethnicity.

Methods: We ascertained whether the presence of depressive symptoms, defined by a Beck Depression Inventory II (BDI) score of >14 at cohort enrollment, was associated with all-cause mortality (before or after ESRD) among study participants of the Chronic Renal Insufficient Cohort (CRIC) overall and by race/ethnicity. Models were adjusted for socioeconomic factors, baseline CKD severity, time-updated comorbid conditions, and time-updated antidepressant use. Confirmatory analyses were performed among African American Study of Kidney Disease and Hypertension (AASK) participants.

Results: Among 3739 CRIC participants, 16.3% had a baseline BDI of >14; 18.2% reported antidepressant use. Crude mortality rate was 3.16 per 100 person-years during 6.8 years of median follow-up. Baseline BDI >14 was independently associated with higher risk of all-cause mortality (adjusted hazard ratio [aHR]: 1.27; 95% confidence interval: 1.07–1.52) without attenuation by antidepressant use. Differences among white and black individuals were noted ($P_{\text{interaction}} = 0.02$) but not among white versus Hispanic individuals ($P_{\text{interaction}} = 0.43$) or black versus Hispanic individuals ($P_{\text{interaction}} = 0.22$). Depressive symptoms were associated with higher mortality among white individuals (aHR: 1.66; 1.21–2.28), but not Hispanic individuals (aHR: 1.47; 0.95–2.28) or black individuals (aHR: 1.06; 0.82–1.37). Similar results were noted among 611 AASK participants (aHR: 0.99; 0.69–1.42).

Conclusions: The presence of depressive symptoms is a risk factor for all-cause mortality among patients with mild-moderate CKD, particularly among white individuals. Further studies are needed to understand the heterogeneity in the response to the presence of depressive symptoms by race.

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KEYWORDS: AASK; chronic kidney disease; CKD; CRIC; depression; mortality

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See Commentary on Page 189

Depression is common among patients with CKD, with reported prevalence between 20% and 30% compared with 2% to 4% in the general population.¹ Similar to the general population, in the CKD

population, depression is more common among women, younger individuals, racial/ethnic minorities, those of lower socioeconomic status, and individuals with more comorbid conditions.² With advancing CKD, the prevalence of depression increases based on either self-report or by interview-based diagnoses,³ with well-recognized higher prevalence of depression among patients with ESRD.⁴ Despite these data, however, depression is frequently underrecognized among patients with earlier stages of kidney disease who often receive nephrology care in primary care settings, and when recognized, it is often undertreated, particularly among racial or ethnic minorities.^{2,5}

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The strength of the association between depression and adverse health outcomes among patients with CKD may not be clear to clinicians who care for most patients with earlier stages of CKD. This may be because most prior studies have examined this issue while considering CKD and ESRD as separate entities, even though CKD and ESRD represent a continuum of kidney disease. For example, among US patients with ESRD, depressive symptoms have been associated with higher risk of cardiovascular events and death, especially if these symptoms are persistent.⁶ Among US patients with CKD, depression has been associated with a higher risk of acute kidney injury,⁷ progression of kidney disease,⁸ and worse cardiovascular outcomes.⁹ Data that associate depression with early mortality among patients with CKD are mixed, however, and there are sparse long-term data that demonstrate how presence of depressive symptoms may associate with adverse outcomes. Although some studies have demonstrated an association between depressive symptoms and a higher risk of death,^{10,11} in others, depressed affect was not associated with all-cause mortality.⁹

It is possible that the presence of depressive symptoms during CKD may more strongly associate with mortality after ESRD onset, because patients with depressive symptoms may have poor outcomes if they go on to require dialysis, a life-changing event. One of the few studies that examined the association between depression during the CKD phase of illness and mortality after ESRD found only a weak association in a cohort of US veterans receiving antidepressive therapy.¹² However, only the most severely depressed patients with CKD are likely diagnosed and treated in the clinical setting, so the results of this study may not be widely generalizable to the CKD population.

The objectives of this study were to (i) examine the association between depressive symptoms among patients with CKD and all-cause mortality (including deaths before and after ESRD) in well-characterized cohorts of patients with long-term follow-up, and (ii) determine whether antidepressant use attenuates or strengthens the association between depressive symptoms and death. A secondary objective was to identify whether there are racial or ethnic differences in the association between depression and all-cause mortality given prior evidence that depressive symptoms may associate with outcomes differentially in black and white individuals.^{3,9}

MATERIALS AND METHODS

Study Sample and Design

We conducted a retrospective cohort study associating depressive symptoms with mortality among

participants of the CRIC and the AASK. Between May 2003 and March 2008, CRIC enrolled 3939 adults aged 21 to 74 with mild to moderate CKD (estimated glomerular filtration rate [eGFR] 20–70 ml/min per 1.73 m²). Broadly, exclusion criteria included New York Heart Association class III or IV heart failure, cirrhosis, HIV disease, polycystic kidney disease, prior dialysis therapy or transplant, and current immunosuppressive therapy or chemotherapy. Other inclusion and exclusion criteria have been previously described.¹³ For this study, we included only participants who self-identified as white, black, or Hispanic (and excluded those of other race or ethnicity due to small sample size, $N = 150$). We also excluded participants with missing BDI score at the baseline visit ($n = 50$).

We included participants from the AASK cohort as a secondary cohort of interest to validate our findings from the CRIC study. The AASK was a 2 × 3 factorial randomized controlled trial that examined the impact of strict blood pressure control and different antihypertensive agents on the progression of CKD among black participants with hypertension-attributed CKD. Between 1995 and 2001, 1094 participants between 18 and 70 years of age with GFR 20–65 ml/min per 1.73 m² were enrolled. At trial closure, 691 participants (87% of eligible participants) who had not developed ESRD or died, continued in the cohort phase of the study, which began in 2002 and ended in 2007. We excluded AASK cohort participants without a baseline BDI ($n = 75$) and those missing covariates ($n = 5$).

Primary Predictor

We assessed the presence of depressive symptoms at baseline, defined by a BDI II score of >14 at enrollment.¹⁴ The BDI was administered as either a self- or interviewer-administered questionnaire to all CRIC and AASK cohort participants at their baseline visit. The 21-item BDI is a widely used and validated instrument to assess depressive symptoms in patients with and without CKD.^{15–17} The total score range is 0 to 63, with higher scores reflecting more severe depression. A score of greater than 14 has been shown to have reasonable diagnostic accuracy for a clinical diagnosis of depression in CKD.¹⁶

Outcome Ascertainment

The outcome of interest was all-cause mortality (before or after ESRD). Deaths in CRIC were ascertained by report from next of kin, retrieval of death certificates or obituaries, review of hospital records, and linkage with the Social Security Death Index. Deaths among AASK study participants were ascertained based on a combination of trial and cohort data, and linkage to the

Social Security Death Index after end of the cohort study, as previously described.^{18–20}

Statistical Analyses

In CRIC, unadjusted Cox regression was used to associate baseline depressive symptoms with risk of all-cause mortality (including deaths before or after ESRD). Models were incrementally adjusted for the following potential confounders: sociodemographic factors (age, sex, education [high school graduate yes/no], income, marital status, alcohol, tobacco use) in Model 1; and additional adjustments for baseline eGFR, proteinuria, body mass index, diabetes, and self-reported time-updated comorbid conditions, including cardiovascular disease (myocardial infarction or revascularization), peripheral vascular disease, heart failure, stroke, and hypertension in Model 2; and finally adjustment for self-reported antidepressant use as a time-dependent covariate (Model 3). [Supplementary Table S1](#) lists the antidepressant medications included in this analysis.

For analysis focused on racial differences in mortality among those with and without depressive symptoms, we first tested for interaction between race and ethnicity (categorized as white, black, and Hispanic) and depressive symptoms in the fully adjusted model (Model 2). We identified presence of interaction between white and black participants ($P_{\text{interaction black vs. white}} = 0.02$) but not white and Hispanic participants ($P_{\text{interaction Hispanic vs. white}} = 0.43$) or black and Hispanic participants ($P_{\text{interaction Hispanic vs. black}} = 0.22$). Analyses were then stratified by race/ethnicity. No interaction was identified in Model 3, examining impact of antidepressant use on the relationship between baseline depressive symptoms and mortality. Sensitivity analyses were performed with a baseline BDI > 16 indicating the presence of more severe depressive symptoms. Additional *post hoc* analyses censored participants at ESRD onset to examine consistency in the association between depression and mortality before and after ESRD.

As confirmatory analysis, we used Cox regression to associate baseline depressive symptoms with risk of all-cause mortality (including deaths before or after ESRD) in AASK. Models were incrementally adjusted for similar potential cofounders as described in Model 1, additionally adjusted for baseline eGFR, baseline proteinuria, cardiovascular disease by self-report, body mass index, cancer, diabetes, and prior randomization assignment (blood pressure target and drug arm) in Model 2, and finally adjusted for baseline antidepressant use (Model 3). Sensitivity analysis was performed using a baseline BDI score of > 16, indicating the presence of more severe depressive symptoms.²¹

STATA 14 (StataCorp LP, College Station, TX) was used for all statistical analyses and verified by a separate analyst in SAS version 9.4 (SAS Institute, Inc., Cary, NC). De-identified National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository data were used for analyses. The University of California San Francisco Institutional Review Board considers this study exempt human subjects research.

RESULTS

Participant Characteristics

Among the 3739 CRIC participants eligible for this study, mean age was 58 (± 11) years. Approximately 45% were women and the study population was racially and ethnically diverse (43% white, 43% black, 13% Hispanic). Most CRIC participants had prevalent hypertension, approximately one-half had diabetes, and nearly one-third had cardiovascular disease. Mean eGFR at enrollment was 44 ml/min per 1.73 m² (SD = 15). Individuals with baseline depressive symptoms defined by a BDI > 14 were likely to be younger, female, of nonwhite race/ethnicity, have lower household income, and have more comorbid conditions compared with individuals without depressive symptoms ([Table 1](#)). Participants with depressive symptoms were also more likely to have a lower eGFR and proteinuria > 1g/g at baseline. There was no difference in the percentage of participants who progressed to ESRD among those with depressive symptoms ($n = 173$, 28.2%) and without depressive symptoms ($n = 736$, 23.5%) at baseline.

Among 611 eligible AASK study participants, mean age was 60 (SD = 10) years. Approximately 38% of participants were women and most had an annual income of less than \$40,000. Fewer than 10% of the cohort had diabetes (onset post study entry), although nearly two-thirds had cardiovascular disease. Mean eGFR at enrollment was 39 ml/min per 1.73 m² (SD = 15). Compared with those without depressive symptoms, AASK participants with baseline depressive symptoms were younger, had lower annual household incomes, and were more likely to consume alcohol or be uninsured ([Table 2](#)). There was no difference in the percentage of participants who progressed to ESRD in those with ($n = 54$, 34.6%) and without ($n = 135$, 30.0%) depressive symptoms at baseline. Compared with black CRIC participants, AASK participants were slightly older, less likely to have health insurance, more likely to have cardiovascular disease but less likely to have diabetes, and self-reported less alcohol use but more tobacco use. Mean eGFR among AASK participants was slightly lower than black CRIC participants (39.2 [± 16.2] vs. 43.6 [± 15.9], $P < 0.001$) but

Table 1. Baseline characteristics of Chronic Renal Insufficiency Cohort (CRIC) participants

	No baseline depression, BDI ≤ 14	Baseline depression, BDI > 14	P
	n = 3126	n = 613	
Age, mean (SD)	58.1 (11.1)	55.8 (10.2)	<0.001
Female sex, n (%)	1358 (43.4)	326 (53.2)	<0.001
Race/ethnicity, n (%)			<0.001
Non-Hispanic white	1429 (45.7)	199 (32.5)	
Non-Hispanic black	1353 (43.3)	263 (42.9)	
Hispanic	344 (11.0)	151 (24.6)	
Annual household income, n (%)			<0.001
<\$20,000	868 (27.8)	329 (53.7)	
\$20,001–\$50,000	788 (25.2)	124 (20.2)	
\$50,001–\$100,000	638 (20.4)	49 (8.0)	
>\$100,000	351 (11.2)	18 (2.9)	
Refuse to answer	481 (15.4)	93 (15.2)	
Educational attainment, n (%)			<0.001
Less than high school	591 (18.9)	216 (35.2)	
High school graduate or more	2535 (81.1)	397 (64.8)	
Health insurance, ^a n (%)	2622 (93.0)	456 (88.7)	<0.001
Medical history, n (%)			
Hypertension	2687 (86.0)	541 (88.3)	0.13
Congestive heart failure	289 (9.3)	77 (12.6)	0.01
MI or coronary vascularization	677 (21.7)	143 (23.5)	0.32
Cerebrovascular disease	293 (9.4)	85 (13.9)	<0.001
Peripheral arterial disease	197 (6.3)	59 (9.6)	0.003
Diabetes	1457 (46.6)	359 (58.6)	<0.001
Alcohol use, n (%)	830 (26.6)	119 (19.4)	<0.001
Tobacco use, n (%)	372 (11.9)	121 (19.7)	<0.001
BMI category, n (%)			0.003
Underweight, BMI < 25	477 (15.3)	98 (16.0)	
Overweight, BMI 25 to < 30	917 (29.4)	138 (22.6)	
Obese, BMI ≥ 30	1725 (55.3)	375 (61.4)	
eGFR, mean (SD)	44.5 (14.9)	42.7 (15.1)	0.006
Urinary PCR ratio ≥ 1 g/g, n (%)	627 (20.7)	158 (25.8)	<0.001

BMI, body mass index; BDI, Beck Depression Inventory; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCR, protein-to-creatinine ratio.

^aMissing in n = 453.

fewer had proteinuria > 1 g/g (Supplementary Table S2).

Prevalence of Depressive Symptoms and Use of Antidepressants

More than 16% (n = 613) of CRIC participants had a baseline BDI > 14. Prevalence of depressive symptoms was greater among Hispanic participants (30.5%) and black participants (16.3%) compared with white participants (12.2%) (P ≤ 0.01). Overall, 18.3% of CRIC participants reported antidepressant use, with a higher percentage among white (23.5%) compared with black individuals (14.2%) and Hispanic individuals (13.5%)

Table 2. Baseline characteristics of African American Study of Kidney Disease and Hypertension (AASK) Cohort participants

	No baseline depression, BDI ≤ 14	Baseline depression, BDI > 14	P
	n = 455	n = 156	
Age, mean (SD)	60.3 (10.0)	57.9 (9.9)	0.01
Female sex, n (%)	165 (36.3)	66 (42.3)	0.18
Annual household income, n (%)			<0.001
<\$15,000	204 (44.8)	102 (65.4)	
\$15,000–\$39,999	115 (25.3)	21 (13.5)	
≥\$40,000	135 (29.6)	33 (21.1)	
Health insurance	373 (82.0)	113 (72.4)	0.01
Medical history, n (%)			
CV disease	145 (31.9)	65 (41.7)	0.04
Diabetes	43 (9.5)	16 (10.3)	0.77
Alcohol use, n (%)	67 (14.7)	24 (15.9)	0.84
Tobacco use, n (%)	188 (41.3)	59 (37.8)	0.44
BMI category, ^a n (%)			0.56
Underweight, BMI < 25	77 (16.9)	23 (14.7)	
Overweight, BMI 25 to < 30	136 (29.9)	46 (29.5)	
Obese, BMI ≥ 30	231 (50.8)	80 (51.3)	
Baseline eGFR, mean (SD)	38.3 (15.0)	39.6 (17.0)	0.40
Urinary PCR ratio ≥ 1 g/g, ^b n (%)	43 (9.5)	14 (9.0)	0.73
Drug arm assignment, n (%)			0.09
ACE inhibitor	179 (39.3)	77 (49.4)	
Beta-blocker	197 (43.3)	56 (35.9)	
Calcium channel blocker	79 (17.4)	23 (14.7)	
Strict BP arm assignment, n (%)	217 (47.7)	85 (54.5)	0.14

ACE, angiotensin converting enzyme; BDI, Beck Depression Inventory; BMI, body mass index; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; PCR, protein-to-creatinine ratio

^aMissing in n = 18.

^bMissing in n = 57.

(P < 0.01). More than one-fourth of AASK participants had BDI > 14 and 5.2% self-reported antidepressant use at baseline (Figure 1).

Association of Depressive Symptoms and Mortality

Among all CRIC participants, crude mortality rate was 3.16 per 100 person-years during 6.8 years of median follow-up. Of those who died, nearly 66% (n = 534) died before developing ESRD. Baseline BDI > 14 was associated with higher risk of all-cause mortality before or after ESRD onset (aHR: 1.27; 95% confidence interval 1.07–1.52), even after accounting for socio-demographic variables and comorbid conditions (Model 2, Table 3). Results were similar in the sensitivity analysis using BDI > 16 as a marker of more severe depressive symptoms (aHR: 1.38; 1.15–1.67; Supplementary Table S3) and the analysis that censored individuals at ESRD onset (aHR: 1.29; 1.09–1.54). In all analyses, the relationship between baseline depression and mortality was not attenuated by antidepressant use (Table 3 and Supplementary Table S3).

Baseline BDI > 14 was associated with higher risk of death among white participants (aHR: 1.66; 1.21–2.28),

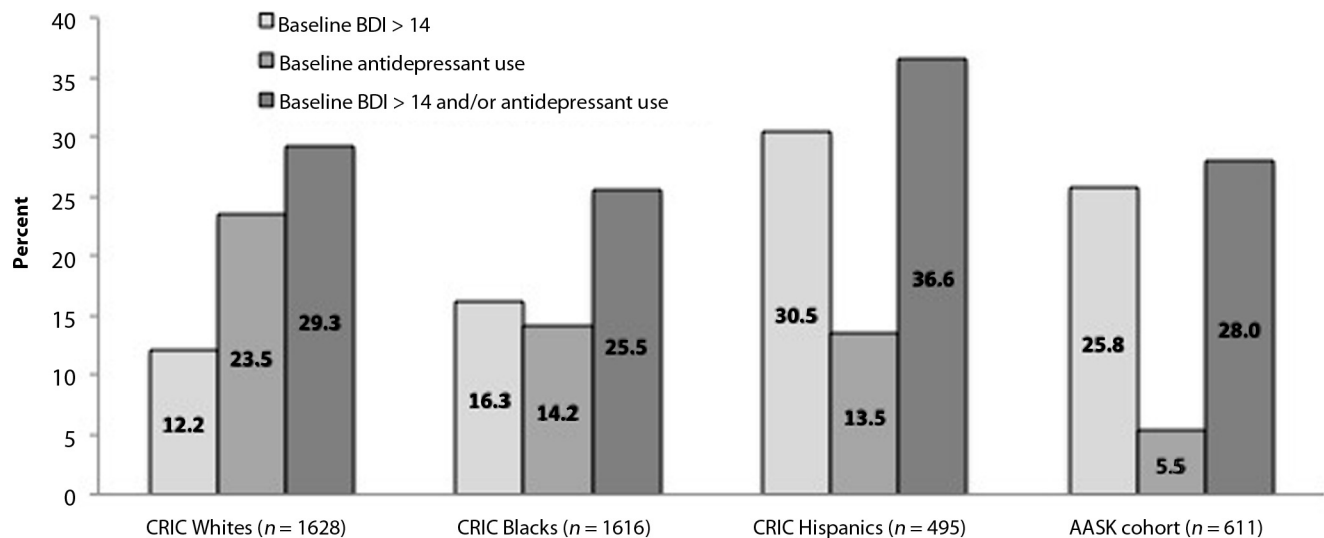


Figure 1. Prevalence of depression symptoms and antidepressant use among Chronic Renal Insufficiency Cohort (CRIC) and African American Study of Kidney Disease and Hypertension Cohort (AASK) participants, by race/ethnicity. BDI, Beck Depression Inventory.

a non-statistically significant tendency toward higher mortality risk among Hispanic participants (aHR: 1.47; 0.95–2.29), and was not associated with all-cause mortality among black participants (aHR: 1.06; 0.82–1.37). Similar results were noted when BDI > 16 was used to define the presence of more severe depressive symptoms (Supplementary Table S3). Results were again similar when individuals were censored at ESRD onset, except that presence of depressive symptoms was more strongly associated with higher mortality risk among Hispanic participants (whites individual: aHR: 1.72, 1.29–2.44; Hispanic individuals: aHR: 1.72, 1.10–2.68; black individuals: aHR: 1.04, 0.81–1.34). Adjustment for antidepressant use did not substantially change results in any of the analyses (Table 3 and Supplementary Table S3).

Results of black CRIC study participants were consistent with findings from AASK study participants. AASK participants experienced a crude mortality rate of 3.82 per 100 person-years over a median of 5.1 years of follow-up. Baseline BDI > 14 was not independently associated with greater risk of all-cause mortality (aHR: 0.99; 0.69–1.42), and use of antidepressants at AASK cohort baseline enrollment did not substantially change this association (Table 3). Similar results were noted with BDI > 16 (Supplementary Table S3).

DISCUSSION

Depression has been consistently associated with all-cause mortality, adverse cardiovascular health outcomes, and poor quality of life among ESRD populations. This has led to the inclusion of depression screening and follow-up planning in the Centers for

Medicare and Medicaid Services ESRD Medicare Quality Incentive Program.²² Despite studies that have suggested an equally high prevalence of depression among patients with CKD,²³ identification and management of this condition is suboptimal. Although depression among patients with CKD has been associated with worse quality of life²³ and adverse cardiovascular health outcomes,⁹ its association with all-cause mortality is still unclear. With this study leveraging long-term follow-up, we provide additional evidence that depressive symptoms among patients with CKD are associated with increased risk of all-cause mortality, including deaths before and after progression to ESRD, and that use of antidepressant medication does not attenuate that risk. This provides additional evidence for the importance of depression identification and new strategies to manage depression among adults with CKD.

The association between depression and mortality among individuals with CKD appears to be stronger among white compared with black or Hispanic individuals (although sample size for the Hispanic subgroup was relatively small, and analyses may be limited in power). We did not find any association between depressive symptoms and all-cause mortality among AASK participants, which is consistent with prior literature. Although depression (defined by either diagnostic codes or having a prescription of an antidepressant medication) was previously found to be strongly associated with increased risk of death among a cohort of white and black patients with CKD, the strength of that association was substantially weaker among black patients.¹¹ Similarly, no statistically significant association was found between the presence of depressive symptoms (defined by BDI > 14) and

Table 3. Association between baseline BDI > 14 and all-cause mortality, overall and by race

	Number of deaths	Crude mortality rate, per 100 person-years	Association between baseline BDI > 14 and all-cause mortality			
			Unadjusted HR	Model 1	Model 2	Model 2 + antidepressant use
CRIC cohort, <i>n</i> = 3739	815	3.16	1.64 (1.39–1.94)	1.47 (1.24–1.75)	1.27 (1.07–1.52)	1.27 (1.07–1.51)
White individuals, <i>n</i> = 1628	301	2.58	1.82 (1.36–2.43)	1.89 (1.38–2.60)	1.66 (1.21–2.28)	1.67 (1.21–2.30)
Hispanic individuals, <i>n</i> = 495	105	3.61	1.83 (1.24–2.71)	1.53 (1.00–2.34)	1.47 (0.95–2.28)	1.53 (0.99–2.39)
Black individuals, <i>n</i> = 1616	409	3.64	1.37 (1.08–1.74)	1.28 (0.99–1.65)	1.06 [‡] (0.82–1.37)	1.00 (0.77–1.30)
AASK cohort, <i>n</i> = 611	196	3.82	1.06 (0.77–1.46)	1.06 (0.75–1.48)	0.99 (0.68–1.41)	0.97 (0.67–1.40)

Model 1 adjusted for age, race/ethnicity, gender, income, marital status, baseline smoking, baseline alcohol (and education in CRIC only).

Model 2 adjusted for model 1 + body mass index category, time-updated comorbid conditions (cardiovascular disease in both cohorts; and congestive heart failure, peripheral vascular disease, stroke, and hypertension in CRIC only) baseline eGFR, baseline proteinuria, baseline diabetes.

AASK models are adjusted also for BP and drug arm assignment.

Associations that are statistically significant with a *P* value < 0.05 are in bold.

AASK, African American Study of Kidney Disease and Hypertension; BDI, Beck Depression Inventory; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

[‡]Statistically significant interaction using white as reference group.

all-cause mortality among AASK cohort participants with CKD during short-term follow-up, although presence of depressive symptoms were associated with a higher risk of cardiovascular events and hospitalizations.⁹ In our study, despite additional years of follow-up and enhanced power due to the accrual of a larger number of deaths over this time period, we found BDI > 14 among AASK cohort participants was still not associated with deaths before or after ESRD. Overall, these studies suggest that depressive symptoms are a strong, independent risk factor for mortality among patients with CKD in whites that is not explained by demographic, socioeconomic, or medical factors. In contrast, depressive symptoms do not appear to independently associate with all-cause mortality among blacks with CKD.

Suboptimal understanding of the behavioral and biological mechanisms that explain the link between depression and adverse outcomes (including mortality) may contribute to suboptimal awareness, recognition, and treatment of depression among patients with CKD. Prior proposed mechanisms include the increased self-care demands among patients with multimorbidity (such as those with CKD and ESRD),²⁴ functional and cognitive impairment that may result from chronic illness,^{25,26} and physical symptoms and biological mechanisms directly related to chronic disease progression and treatments, such as inflammation.²⁷ None of these mechanisms are known to explain racial/ethnic differences in response to depression, however. Group differences in self-regulatory, stress-coping strategies known to impact health outcomes, such as prayer, social support, exercise, and overeating, could have influenced our findings, but a recent analysis of a subset of 1354 participants in the Health and Retirement Study (mean age = 67) did not find any differences in these behaviors by race/ethnicity.²⁸ Similarly, nondepressive psychosocial factors were not associated with incident CKD or CKD decline among 3990 participants of the Jackson Heart Study, although mortality

was not assessed.²⁹ Higher of 2 stress resilience genes, glutathione-S-transferase-m1³⁰ or GSTM1 and the G allele of FOXO3³¹ in black individuals could account in part for the lack of association between depressive symptoms and mortality among black individuals with CKD, but this remains speculation. Finally, there could be racial/ethnic biases in the depression survey itself. An analysis of college students found no evidence of racial bias in the BDI II survey that was used in this study,³² but to our knowledge has not been tested among older adult populations with chronic disease and greater racial diversity.

Given the apparent heterogeneity in pathophysiology, consistent and successful treatment of depression to mitigate adverse health outcomes will likely require a comprehensive, multifaceted and multidisciplinary approach.³³ Treatment of depression with antidepressants among patients with chronic illnesses (not CKD) has been shown to improve depressive symptoms and functional status in some studies^{34,35} but not others.^{36,37} The impact of antidepressant use on cardiovascular health and mortality has also been mixed,^{38,39} although evidence for the treatment of depression immediately following a cardiovascular event⁴⁰ or as part of a multidisciplinary approach that includes pharmacologic therapy is stronger.⁴¹ Recent trial data suggest that short-term antidepressant use among patients with CKD does not decrease depressive symptoms.⁴² Similarly, in our study, exposure to antidepressant use did not attenuate the mortality risk associated with depressive symptoms among white, black, or Hispanic participants. Recent evidence suggests a benefit of cognitive behavioral interventions on depressive symptoms, quality of life, and prescription adherence among patients with ESRD.^{43,44} Studies investigating the impact of a more comprehensive approach (outside of antidepressant medications) to depression treatment, including psychotherapy, among patients with earlier stages of kidney disease are warranted.

The strength of our study includes the use of a well-characterized cohort that is racially and ethnically diverse. In addition, CRIC provides more than a decade of follow-up of participants and granular data on comorbid conditions, medication use, and laboratory data. The detailed and routine ascertainment of time-updated antidepressant medication use in the CRIC cohort is also a strength. Limitations to our study include its observational nature and reliance on a single measure of depressive symptoms at baseline. We chose not to use time-updated BDI scores due to a large percentage of missing BDI data in later years, potentially contributing to informative censoring. The sample size of Hispanic CRIC participants was relatively small, and thus may be limited in power. In addition, we cannot rule out the presence of residual confounding. We are unable to capture any non-pharmacologic therapy that may have been delivered for treatment of depressive symptoms or depression. We also acknowledge the possibility that use of antidepressants among CRIC participants is a marker of greater attentiveness by providers and/or the provision of more comprehensive cardiovascular care or higher patient vigilance. However, antidepressant use did not attenuate mortality risk in this study.

In conclusion, we found that the presence of depression symptoms strongly associates with mortality risk, both before and after ESRD, particularly in white populations with mild to moderate kidney disease. This adds data about the long-term implications of depression in CKD to existing literature that associates depression with shorter-term adverse outcomes, such as poor quality of life, and underscores the importance of recognizing depressive symptoms and investigating new strategies to manage depression among adults with CKD. Further studies are needed to understand the heterogeneity in the response to the presence of depressive symptoms by race and ethnicity.

DISCLOSURE

All the authors declared no competing interests.

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data from the CRIC study reported here were supplied by the NIDDK Central Repositories. This article was not prepared in collaboration with investigators of the CRIC study and does not necessarily reflect the opinions or views of the CRIC study, the NIDDK Central Repositories, or the NIDDK. The interpretation and reporting of the data presented here are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

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Author contributions: Research idea and study design: DST, EK; data analysis/interpretation: DST, KN, EK; statistical analysis: FL, EK; manuscript drafting: DST, KN, EK. Each author contributed intellectual content during manuscript drafting or revision and accepts accountability for the work.

SUPPLEMENTARY MATERIAL

Table S1. Self-reported antidepressant medication use in CRIC.

Table S2. Baseline characteristics of black participants in the African American Study of Kidney Disease (AASK) and Chronic Renal Insufficiency Cohort (CRIC) studies.

Table S3. Association between baseline BDI > 16 and all-cause mortality, overall and by race.

Supplementary material is linked to the online version of the paper at <http://www.kireports.org/>.

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