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Elevated depressive affect is associated with adverse cardiovascular outcomes among African Americans with chronic kidney disease

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This study was designed to examine the impact of elevated depressive affect on health outcomes among participants with hypertensive chronic kidney disease in the African-American Study of Kidney Disease and Hypertension (AASK) Cohort Study. Elevated depressive affect was defined by Beck Depression Inventory II (BDI-II) thresholds of 11 or more, above 14, and by 5-Unit increments in the score. Cox regression analyses were used to relate cardiovascular death/hospitalization, doubling of serum creatinine/end-stage renal disease, overall hospitalization, and all-cause death to depressive affect evaluated at baseline, the most recent annual visit (time-varying), or average from baseline to the most recent visit (cumulative). Among 628 participants at baseline, 42% had BDI-II scores of 11 or more and 26% had a score above 14. During a 5-year follow-up, the cumulative incidence of cardiovascular death/hospitalization was significantly greater for participants with baseline BDI-II scores of 11 or more compared with those with scores <11. The baseline, time-varying, and cumulative elevated depressive affect were each associated with a significant higher risk of cardiovascular death/hospitalization, especially with a time-varying BDI-II score over 14 (adjusted HR 1.63) but not with the other outcomes. Thus, elevated depressive affect is associated with unfavorable cardiovascular outcomes in African Americans with hypertensive chronic kidney disease.

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Among individuals with end-stage renal disease (ESRD), depression has been shown to be highly prevalent and associated with increased rates of hospitalization, cardiovascular events, and death.[1–8] Despite uncontrolled studies suggesting possible beneficial effects of antidepressant treatment in ESRD, only a small fraction of patients with ESRD are prescribed antidepressant medications.[3,8–12]

Similarly, depression is common in individuals with earlier stages of chronic kidney disease (CKD), ranging from $\sim$15 to $>$50% in a few single-center studies.[13–17] Moreover, small studies in patients with CKD have demonstrated that depression substantially compromises quality of life.[5,11,16,18] Recently, elevated depressive affect was found to be present in at least one-third of a large multicenter cohort of African Americans with hypertensive CKD, rarely treated with antidepressants, and associated with significantly poorer quality of life and satisfaction with life.[19] In contrast to ESRD, little is known about the effects of depression on

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health outcomes in individuals with CKD. In a recent study of a male veteran cohort with CKD, a major depressive episode was found to be associated with nearly a two-fold increased risk of a combined outcome of death, dialysis initiation, or hospitalization.[20] The impact of depression on a broad range of individual health outcomes in a representative outpatient population with CKD has not been assessed.

The African-American Study of Kidney Disease and Hypertension (AASK) Cohort Study was designed to identify important risk factors for decline in kidney function and to improve the understanding of CKD in African Americans with hypertensive kidney disease.[21–22] In this longitudinal prospective analysis of the AASK cohort, we examined the relationship between elevated depressive affect and cardiovascular events, progression of CKD, hospitalization, and death.

RESULTS

Study participants and characteristics

Among the 628 AASK participants enrolled in the cohort study, 26–42% were found to have elevated depressive affect at baseline, depending on the threshold Beck Depression Inventory II (BDI-II) score >14 or $\geqslant 11$, respectively. Detailed characteristics of AASK participants by strata of baseline BDI-II scores and elevated depressive affect have been extensively characterized previously.[19] In brief, the mean age of the cohort was 60.1 years, 38% were female, the mean estimated glomerular filtration rate (eGFR) was 43.1 ml/min per m^2, and the mean protein/creatinine ratio was 0.38 g/g.

Compared with participants without elevated depressive affect, participants with elevated depressive affect were more likely to be unemployed, more likely to have an annual household income $<\$15{,}000$, and more likely to have a history of cardiovascular disease (CVD) and psychiatric problems. eGFR and the magnitude of proteinuria were not significantly different between those with and without depressive affect ($P>0.05$).

Cumulative incidence and rate of cardiovascular events, ESRD, and death by the presence of baseline depressive affect

Over 5 years of follow-up, 22% of the cohort had a doubling of serum creatinine or reached ESRD (kidney disease composite), 14% had a cardiovascular hospitalization or death (CVD composite), and 16% died (Table 1). Compared with those without elevated baseline depressive affect, participants with baseline elevated depressive affect (BDI-II $\geqslant 11$) had a higher rate of the CVD composite (4.3/100 patient-years vs 2.9/100 patient-years) and kidney disease composite (5.8/100 patient-years vs 4.9/100 patient-years), but similar mortality (3.3/100 patient-years vs 3.5/100 patient-years). Similar relationships were observed when elevated depressive affect was defined by a BDI-II >14.

Cumulative incidence was plotted against time from cohort enrollment by the presence of baseline elevated depressive affect (BDI-II $\geqslant 11$) for all-cause death, the kidney disease composite outcome, and the CVD composite outcome (Figure 1). The cumulative incidence of mortality was similar in those with or without baseline elevated depressive affect (BDI-II $\geqslant 11$) (Figure 1a). Treating ESRD and death as competing risks, the cumulative incidence of the CVD composite seemed to be greater in those with baseline elevated depressive affect than in those without (Figure 1b and c).

Association between baseline, time-varying, and cumulative depressive affect and cardiovascular events, ESRD, and death

In regression analyses (Table 2) adjusted for randomized group of participants in the AASK trial (model 1) and demographic characteristics, eGFR, and proteinuria (model 2), elevated depressive affect was generally associated with an increased risk of the cardiovascular composite, irrespective of the analytic approach (that is, analysis of baseline, time-varying, or cumulative elevated depressive affect) or definition used (that is, categorical thresholds or continuous scores for elevated depressive affect). Although these findings were generally similar, there was some fluctuation in significance

Table 1 | Cumulative incidence and rates of cardiovascular events, end-stage renal disease, and death by the presence of baseline elevated depressive affect

	CV composite event		Doubling of SCr or ESRD		All-cause mortality	
BDI Groups	Total *N* (No. events, %)	Rate/100 patient-years	Total *N* (No. events, %)	Rate/100 patient-years	Total *N* (No. events, %)	Rate/100 patient-years
BDI 0–10	363 (43, 12%)	2.9	363 (74, 20%)	4.9	363 (58, 16%)	3.5
BDI 11–14	99 (19, 19%)	4.6	98 (22, 22%)	5.4	99 (16, 16%)	3.5
BDI 15–21	95 (12, 13%)	3.5	94 (25, 27%)	7.1	95 (13, 14%)	3.0
BDI >21	71 (13, 18%)	4.7	70 (14, 20%)	4.9	71 (11, 15%)	3.5
Overall	628 (87, 14%)	3.5	625 (135, 22%)	5.3	628 (98, 16%)	3.4
BDI<11	363 (43, 12%)	2.9	363 (74, 20%)	4.9	363 (58, 16%)	3.5
BDI$\geqslant$11	265 (44, 17%)	4.3	262 (61, 23%)	5.8	265 (40, 15%)	3.3
BDI$\leqslant$14	462 (62, 13%)	3.3	461 (96, 21%)	5.0	462 (74, 16%)	3.5
BDI>14	166 (25, 15%)	4.0	164 (39, 24%)	6.1	166 (24, 14%)	3.2

Abbreviations: BDI, Beck Depression Inventory; CV, cardiovascular; SCr, serum creatinine.

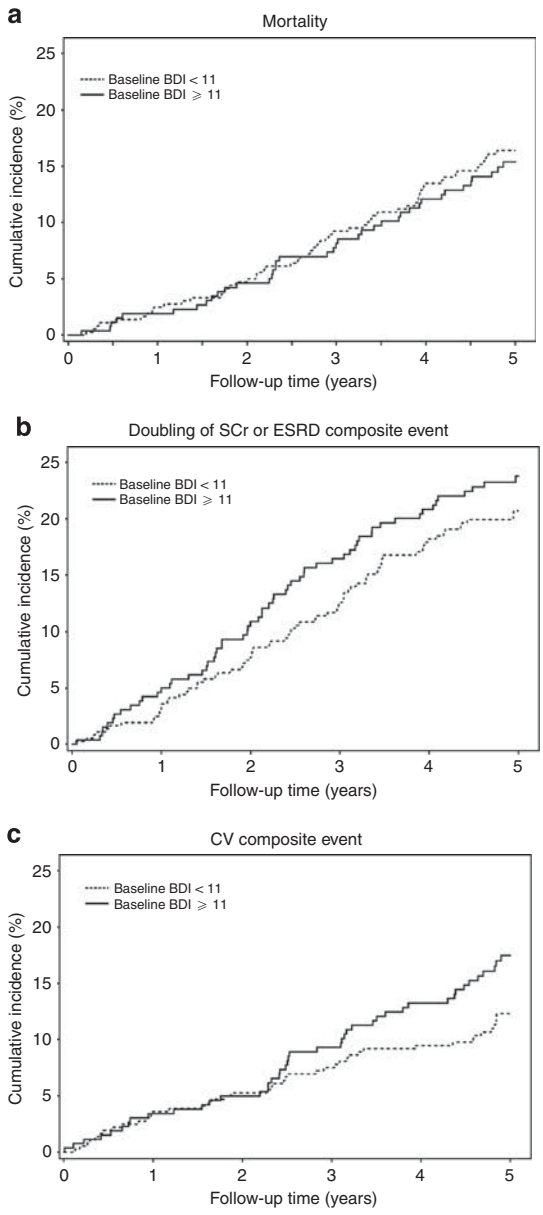

Figure 1 | Association between baseline elevated depressive affect and adverse clinical outcomes. Cumulative incidence plotted against time from cohort enrollment by the presence of baseline elevated depressive affect for (**a**) all-cause death, (**b**) for the kidney disease composite (treating death as a competing risk), and (**c**) for the CV composite (treating both death and ESRD as competing risks). BDI, Beck Depression Inventory; CV, cardiovascular; ESRD, end-stage renal disease.

as defined at the 0.05 level. The most pronounced association between elevated depressive affect and the cardiovascular composite (model 2) was observed in the analysis of time-varying elevated depressive affect as defined by a BDI > 14 (hazard ratio 1.82; 95% confidence interval: 1.19–2.80). In contrast, elevated depressive affect was not found to be significantly associated with the kidney disease composite or all-cause death in any of these regression models.

In regression analyses additionally adjusted for baseline CVD (model 3), the strength of association between elevated depressive affect and the cardiovascular composite was generally attenuated across analytic approaches and definitions for elevated depressive affect. Nonetheless, a significant association at the 0.05 level remained for time-varying elevated depressive affect (BDI > 14) and increased the risk of the cardiovascular composite (hazard ratio 1.63; 95% confidence interval: 1.05–2.51) in this adjusted model. Elevated depressive affect was not found to be significantly associated with the kidney disease composite or all-cause death in this adjusted model (model 3). The results of analyses from this model were not significantly changed in sensitivity analyses in which patients prescribed antidepressant medications at baseline were excluded.

Association between baseline depressive affect and number of hospitalizations

In regression analyses (Table 3) adjusted for randomized group in the AASK trial (model 1) and demographic characteristics, eGFR, and proteinuria (model 2), baseline elevated depressive affect characterized by either BDI-II score ⩾11 (hazard ratio 1.30; 95% confidence interval: 1.00–1.69) or 5-Unit increments in BDI-II score (hazard ratio 1.09; 95% confidence interval: 1.00–1.19) was significantly associated with an increased number of hospitalizations. However, baseline elevated depressive affect was no longer significantly associated with the number of hospitalizations after additional adjustment for baseline CVD (model 3). In sensitivity analyses in which patients prescribed antidepressant medications at baseline were excluded, the association between elevated baseline depressive affect and number of hospitalizations was no longer statistically significant in any of the regression models.

DISCUSSION

In up to 5 years of follow-up of a large cohort of African Americans with hypertensive CKD, we found that elevated depressive affect was strongly associated with an increased risk of a composite of cardiovascular hospitalization and death. Participants with time-varying elevated depressive affect (BDI-II > 14) were more than 1.5-fold more likely to experience a cardiovascular hospitalization or death compared with those without elevated depressive affect. In contrast, we did not find that elevated depressive affect was significantly associated with overall hospitalization, progression of CKD, or all-cause mortality upon adjustment for other important factors. The high degree of concordance across exposure definitions (that is, categorical thresholds or continuous scores for depressive affect) and analytic approaches (that is, baseline, time-varying, or cumulative depressive affect) greatly underscores the robustness of these findings.

Although progression to ESRD is a burdensome outcome of CKD, the morbidity and mortality associated with CKD is even more ominous. A graded independent association exists between lower levels of kidney function and a higher risk of cardiovascular events, hospitalization, and death.[23]

Table 2 | Association between elevated depressive affect and cardiovascular events, end-stage renal disease, and death

Event	BDI-II Score	Baseline			Time-varying			Cumulative		
		Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Cardiovascular disease composite	Per 5-Unit increment	**1.12 (1.00–1.26)**	**1.13 (1.01–1.27)**	1.09 (0.96–1.23)	**1.12 (1.00–1.25)**	**1.12 (1.00–1.25)**	1.09 (0.97–1.23)	**1.13 (1.00–1.28)**	**1.14 (1.01–1.29)**	1.10 (0.96–1.25)
	⩾11	**1.53 (1.00–2.33)**	1.52 (0.99–2.34)	1.36 (0.88–2.09)	1.39 (0.92–2.08)	1.38 (0.91–2.08)	1.20 (0.79–1.83)	**1.58 (1.06–2.37)**	**1.58 (1.05–2.38)**	1.34 (0.89–2.04)
	<11	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	>14	1.30 (0.82–2.08)	1.34 (0.83–2.17)	1.25 (0.77–2.02)	**1.76 (1.15–2.69)**	**1.82 (1.19–2.80)**	**1.63 (1.05–2.51)**	**1.59 (1.04–2.45)**	**1.59 (1.03–2.47)**	1.41 (0.90–2.19)
	⩽14	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Kidney disease composite	Per 5-Unit increment	1.07 (0.97–1.18)	1.03 (0.93–1.15)	1.04 (0.93–1.16)	1.04 (0.94–1.14)	0.96 (0.86–1.06)	0.96 (0.86–1.06)	1.05 (0.94–1.16)	0.98 (0.87–1.10)	0.98 (0.87–1.10)
	⩾11	1.17 (0.83–1.65)	0.92 (0.64–1.32)	0.92 (0.64–1.32)	1.08 (0.78–1.51)	0.86 (0.61–1.22)	0.85 (0.60–1.21)	1.09 (0.79–1.52)	0.88 (0.62–1.23)	0.87 (0.62–1.23)
	<11	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	>14	1.21 (0.83–1.77)	1.15 (0.77–1.70)	1.15 (0.77–1.70)	1.02 (0.70–1.49)	0.69 (0.46–1.03)	0.68 (0.45–1.02)	0.96 (0.66–1.40)	0.68 (0.45–1.01)	0.67 (0.45–1.00)
	⩽14	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
All death	Per 5-Unit increment	1.01 (0.90–1.14)	1.03 (0.91–1.16)	1.02 (0.90–1.15)	1.07 (0.96–1.20)	1.06 (0.95–1.19)	1.06 (0.94–1.18)	1.05 (0.93–1.19)	1.05 (0.93–1.19)	1.04 (0.92–1.18)
	⩾11	0.96 (0.64–1.44)	1.00 (0.66–1.52)	0.98 (0.64–1.50)	1.10 (0.74–1.64)	1.06 (0.71–1.59)	1.05 (0.70–1.58)	1.12 (0.76–1.65)	1.12 (0.75–1.67)	1.10 (0.73–1.65)
	<11	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	>14	0.94 (0.59–1.49)	1.06 (0.65–1.71)	1.04 (0.64–1.69)	1.26 (0.82–1.94)	1.25 (0.80–1.94)	1.22 (0.78–1.91)	0.93 (0.59–1.47)	1.02 (0.64–1.64)	0.99 (0.61–1.59)
	⩽14	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)

Abbreviations: AASK, African-American Study of Kidney Disease and Hypertension; BDI, Beck Depression Inventory; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Model 1 adjusted for AASK trial randomized group.
Model 2 adjusted for AASK trial randomized groups, age, gender, eGFR, and proteinuria.
Model 3 adjusted for AASK trial randomized groups, age, gender, eGFR, proteinuria, and baseline cardiovascular disease.
[a]*P*-values <0.05 for bold HR/95% CI values.

Table 3 | Association between baseline elevated depressive affect and number of hospitalizations

Baseline BDI-II score	Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Number of hospitalizations			
Per 5-Unit increment	1.08 (1.00–1.17)	**1.09 (1.00–1.19)**	1.07 (0.99–1.16)
⩾11	**1.31 (1.01–1.70)**	**1.30 (1.00–1.69)**	1.22 (0.95–1.58)
<11	1.0 (ref)	1.0 (ref)	1.0 (ref)
>14	1.22 (0.89–1.66)	1.25 (0.92–1.72)	1.22 (0.90–1.65)
⩽14	1.0 (ref)	1.0 (ref)	1.0 (ref)

Abbreviations: AASK, African-American Study of Kidney Disease and Hypertension; BDI, Beck Depression Inventory; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]*P*-values <0.05 for bold HR/95% CI values.
Model 1 adjusted for AASK trial randomized group.
Model 2 adjusted for AASK trial randomized groups, age, gender, eGFR, and proteinuria.
Model 3 adjusted for AASK trial randomized groups, age, gender, eGFR, proteinuria, and baseline cardiovascular disease.

Furthermore, the risk of cardiovascular events and death is generally multifold higher than that of ESRD in patients with CKD.[24–26] In contrast, a recent analysis of AASK participants in the trial and cohort phases of this study found that the rate of ESRD greatly exceeded that of total death and cardiovascular death.[27] However, rates of ESRD and a composite of cardiovascular hospitalization and death were more similar.[27] Although the relationship between depression and CVD has not been well-studied in CKD and ESRD populations, substantial epidemiological evidence for this association exists from cross-sectional and observational studies in non-CKD populations. Depression has been found to increase the risk of *de novo* coronary artery disease and the risk of cardiovascular morbidity and mortality in those with pre-existing coronary artery disease.[28–30] On the basis of animal models and human studies, various potential mechanisms for this link have been posited, including behavioral factors such as treatment adherence and lifestyle choices (such as, smoking, poor nutrition, inactivity) as well as physiological factors such as changes in platelet reactivity and activation, dysregulation of the autonomic nervous system and hypothalamic pituitary adrenal axis, endothelial dysfunction, and alterations in immune response and inflammation.[28–31] Future studies will hopefully afford a more complete understanding of the relationship between depression and ischemic heart disease.

This report is one of very few to characterize the relationship between depressive affect and cardiovascular outcomes in patients with CKD. One previous study examined the relationship between depression and CVD in patients with ESRD.[6] In a prospective multicenter study of incident hemodialysis patients, Boulware *et al.*[6] found that persistent and current depressive symptoms but not baseline depressive symptoms were significantly associated with a >1.5-fold increase in CVD events and a >3-fold increase in CVD deaths. Subgroup analyses from this study revealed that depressive symptoms were more strongly related to CVD events in Caucasians than in African Americans. Therefore,

our findings may be specific to African Americans and actually underestimate effects in other racial and ethnic populations.

It is important to underscore that African Americans with CKD constitute a vulnerable population subject to substantial health disparities and are an overrepresented group in the CKD and ESRD community, comprising approximately one-third of the ESRD population in the United States.[24,32–35] A disproportionate burden of CVD, death, and progression to ESRD exists among African Americans with CKD.[24,36] As we have previously shown, elevated depressive affect afflicts more than one-third of African Americans with CKD, is rarely treated with pharmacological therapy, and is associated with substantially worse quality of life.[19] Therefore, it is especially important to identify potentially novel modifiable risk factors for these negative clinical sequelae in this vulnerable population. By finding a strong association between elevated depressive affect and cardiovascular hospitalization and death among African Americans, our present findings further this critical objective. Moreover, building upon previous uncontrolled studies finding possible efficacy of antidepressant treatment in ESRD,[9,10] this study supports the rationale for interventional trials to examine the potential of antidepressant treatment in ameliorating cardiovascular events in African Americans with CKD and depression. Owing to the paucity of clinical trials, it remains unclear whether treating depression reduces cardiovascular complications.[37] Select previous trials in patients with acute coronary syndrome failed to find a reduction in subsequent cardiovascular events and death by depression treatment; however, clinical trials have not been performed in other high-risk groups.[38,39]

Several previous studies have examined the relationship between depression, hospitalization, and mortality, and have generally found that depressive symptoms or a clinical diagnosis of depression is independently associated with an increased risk of death and hospitalization.[1–8,13] However, the vast majority of these analyses have been conducted exclusively in patients either with severe CKD (that is, pre-ESRD) or with ESRD requiring chronic dialysis.[1–8,13] A notable exception is a recent study of a predominately Caucasian male veteran cohort with moderate-to-severe CKD by Hedayati *et al.*,[20] who found that a baseline major depressive episode increased the risk of a composite end point of death, dialysis initiation, or hospitalization by >1.8-fold during 1 year of follow-up. While recognizing that this study was powered on a broad composite outcome measure, the reported associations between depression and each individual outcome revealed that although major depressive disorder significantly increased the risk of incident ESRD, it was not significantly associated with overall mortality and its significant association with hospitalization appeared largely because of hospitalizations for dialysis initiation.[20] Hence, these results differ most substantively from ours with regard to the relationship between depression and CKD progression to ESRD. In addition to the lower mean baseline eGFR in this veteran cohort compared with the AASK cohort (that is, 31 ml/min per m^2 vs 43 ml/min per m^2) differences in demographic characteristics (such as race, gender) and the definition of the renal outcome measure may explain the discordant observations between our findings and those of Hedayati *et al.* In addition, although validated BDI score cutoffs for a physician diagnosis of depression were applied to the AASK cohort[40–43] and incremental changes in BDI score, it is important to acknowledge that the clinical implications of self-reported depressive symptoms (for example, BDI-II) may differ from those of a physician diagnosis of major depression.[2,3,7,13] Owing to the importance in identifying novel risk factors for CKD progression, more refined analyses of the influence of depression upon changes in eGFR over time are warranted.

Our study has limitations. First, it is important to stress that we evaluated the impact of elevated depressive affect and not a psychiatric diagnosis of major depression in this study; hence, misclassification is possible. However, we used both validated BDI thresholds for a clinical diagnosis of depression in patients with CKD and ESRD[40–43] and incremental changes in BDI score in all of our analyses. Furthermore, previous concerns about the reliability of the BDI were mainly focused on the misclassification of uremic symptoms as somatic symptoms of depression, which is much less likely in the AASK cohort with earlier stages of CKD.[11–12,40–42] Second, although this study was a prospective observational analysis, we cannot conclude causality or be certain of the direction of the relationship between depressive affect and the observed outcomes as subclinical disease may possibly precede event ascertainment. Nonetheless, it should be noted that longitudinal studies with baseline and repeated measures are appropriate tools with which to robustly assess epidemiological relationships.[44] Third, $\sim$9% of the AASK cohort did not complete the BDI-II questionnaire at enrollment and were excluded from the analysis. However, it is unlikely that their inclusion would significantly alter our findings because important characteristics among excluded and included participants were similar. In addition, $\sim$15% of the AASK cohort did not complete the BDI-II questionnaire at every single year during the entire follow-up period. Consistent with strategies elsewhere, we adopted a last observation carry-forward approach for participants with missing BDI-II data in such cases.

In conclusion, elevated depressive affect greatly increased the risk of cardiovascular hospitalization and death in African Americans with hypertensive CKD. Additional studies are required in diverse patient populations with CKD to understand more fully the clinical sequelae of depression and to address the utility of screening for depression. Although antidepressant treatment seems to reduce depressive symptoms in patients with ESRD, it remains unknown whether such treatment also improves medical outcomes such as the incidence of cardiovascular events. Considering

the high prevalence of depression and cardiovascular morbidity and mortality in African Americans with CKD, clinical trials should be considered to evaluate the role of antidepressant treatment strategies in this vulnerable population.

MATERIALS AND METHODS

Study design and sample

We conducted a prospective longitudinal analysis of depressive affect and health-related outcomes in participants of the AASK Cohort Study from 1 April 2002 to 30 June 2007. The AASK Cohort Study was a multicenter prospective study of individuals with hypertensive CKD whose hypertension was managed with a recommended blood pressure goal ($<130/80$ mm Hg) and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Participants were seen at least twice per year and more often if required to achieve blood pressure control. The AASK Cohort Study enrolled only subjects who had previously participated in the AASK clinical trial. Details of both of these studies have been published previously.[21–22] All subjects who were alive at the completion of the clinical trial and had not begun dialysis therapy or received a kidney transplant were eligible to enroll in the cohort study. Out of 764 eligible subjects from the clinical trial who had not begun dialysis therapy or received a kidney transplant, 691 were enrolled in 2002 and followed through 2007, and 628 completed a BDI-II questionnaire at enrollment. Major eligibility criteria for the clinical trial included self-identified African American race, ages 18–70 years, an iothalamate-measured GFR between 20 and 65 ml/min per 1.73 m^2, and no apparent cause of CKD other than hypertension.[22] The study was approved by the Institutional Review Boards of the participating centers. All study participants provided written informed consent.

Variables and data sources

The BDI-II was administered as a self-completed questionnaire to all AASK participants at their baseline visit and annually thereafter. The BDI-II is an adaptation of the BDI, which is a widely used validated instrument to assess depressive affect.[41–43,45] Scores for each of the 21 items range from 0 to 3, with a higher score representing a higher level of depressive affect. The total score range is 0–63 in which a score of <10 indicates the absence of depression, and higher scores reflect more severe depression in the general non-medically ill population.[45] Several studies have shown that BDI scores >14 are accurate at diagnosing depression among patients with ESRD,[41–43] whereas one recent study found that a BDI score $\geqslant 11$ was an accurate threshold for a clinical diagnosis of depression in patients with CKD.[40] Therefore, we evaluated the effects of elevated depressive affect categorically by BDI-II thresholds of $\geqslant 11$ or >14, and continuously by 5-Unit increments in BDI-II score.

Baseline demographic variables (such as age, gender, education, marital status, insurance, annual household income, employment status, current exercise, smoking/alcohol/drug use) were self-reported. Baseline comorbid health conditions (such as cancer, stroke, CVD, peripheral vascular disease, asthma or chronic obstructive pulmonary disease, psychiatric problem) were self-reported and identified by review of medical records. CVD included any of the following: coronary artery disease, heart failure or diastolic dysfunction, left ventricular hypertrophy, heart rhythm, or conduction problem. Prescription records of AASK participants were reviewed at baseline, and medications designated as antidepressants were independently confirmed by three clinicians. Blood pressure was measured in a standardized manner by trained, certified observers using the Tycos Classic Handheld Aneroid device (Skaneateles, NY) as discussed previously.[21–22] For each subject, urine protein/creatinine ratio was measured at baseline as well as eGFR (ml/min per 1.73 m^2), which was calculated using an average of serum creatinine values with the AASK Study equation obtained within the first 3 months after participant enrollment.

The primary outcomes included doubling of serum creatinine or development of end-stage kidney disease (kidney disease composite), cardiovascular hospitalization or cardiovascular mortality (CVD composite), all-cause death, and number of hospitalizations. Local clinical center personnel provided documentation on each hospitalization and death as it occurred and noted for each if any of the following occurred: myocardial infarction, new or exacerbated ischemic heart disease, new or exacerbated congestive heart failure, new or exacerbated peripheral vascular disease, and stroke or cerebrovascular event. The clinical center personnel also noted a primary and secondary cause of death. The Cardiovascular Outcome Committee reviewed and confirmed whether events met the study protocol definition of a cardiovascular hospitalization or death.

Statistical analyses

Patient characteristics at baseline entry into the cohort were described overall and by the presence of elevated depressive affect using mean ± s.d. for quantitative variables and frequencies and percentages for categorical variables. Bivariate analyses involving χ^2 tests and ANOVA (analysis of variance) were used as appropriate to assess differences in patient characteristics.

Event rates for the kidney disease composite outcome, CVD composite outcome, and all-cause death, expressed as the number of events per 100 patient-years, were calculated as the ratio of the number of patients reaching the event divided by the total patient-years of follow-up before an event or until censoring. In computations of event rates and in Cox regression analyses, follow-up time for the cardiovascular composite was censored at occurrence of ESRD or non-cardiovascular death, and follow-up time for the kidney disease composite was censored at all-cause death. All-cause death was ascertained until the administrative end date of the study. A Kaplan–Meier curve was constructed to display the cumulative probability of all-cause death. Cumulative incidence curves were estimated for the cardiovascular composite event while treating ESRD and death as competing risks, and for the kidney disease composite event, while treating death as a competing risk as described by Gray.[46] In this competing risk framework, only loss to follow-up and the administrative end date of the study were treated as censoring events.

Cox proportional hazards regression models were used to assess the association between each of these three outcomes and depressive affect assessed at enrollment (that is, baseline) among all participants who had baseline BDI-II data. Owing to exclusion of participants with missing covariates, the final sample sizes varied slightly among these baseline regression models from 618 to 628. Time-dependent Cox regression was used to relate the hazard ratio for the same outcomes to the most recent assessment preceding each follow-up time point (that is, time-varying) and the cumulative average of assessments preceding each follow-up time point (that is, cumulative) among participants with at least one BDI-II value during follow-up. Owing to exclusion of participants with missing covariates, the final sample sizes varied slightly among these

regression models from 668 to 680. The sample sizes for the time-dependent analyses exceeded that for the analyses of baseline BDI-II as the former included participants with missing baseline BDI-II scores as long as they had at least one follow-up BDI-II measure. The assumption of proportional hazards in the Cox regression models was checked using Schoenfeld residuals for all included covariates. Significant violations of the proportional hazards assumption were found for baseline eGFR with the kidney composite outcome, and for baseline urine protein-to-creatinine ratio with all-cause death. Therefore, a linear interaction term between baseline eGFR and follow-up time and a linear interaction term between baseline log urine protein-to-creatinine ratio and follow-up time were added to the corresponding models.

The association between baseline depressive affect and number of hospitalizations was assessed using overdispersed negative binomial regression models.[47] As for Cox regressions of the cardiovascular composite, follow-up time was censored at death and ESRD for this analysis.

For all aforementioned analyses, sensitivity analyses were performed in which patients prescribed antidepressant medications at baseline were excluded. All statistical analyses were conducted using SAS, version 9.1 (Cary, NC).

DISCLOSURE

All the authors declared no competing interests.

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