Kidney Medicine

Depressive Symptoms, Antidepressants, and Clinical Outcomes in Chronic Kidney Disease: Findings from the CRIC Study

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Rationale & Objective: The extent to which depression affects the progression of chronic kidney disease (CKD) and leads to adverse clinical outcomes remains inadequately understood. We examined the association of depressive symptoms (DS) and antidepressant medication use on clinical outcomes in 4,839 adults with nondialysis CKD.

Study Design: Observational cohort study.

Setting and Participants: Adults with mild to moderate CKD who participated in the multicenter Chronic Renal Insufficiency Cohort Study (CRIC).

Exposure: The Beck Depression Inventory (BDI) was used to quantify DS. Antidepressant use was identified from medication bottles and prescription lists. Individual effects of DS and antidepressants were examined along with categorization as follows: (1) BDI <11 and no antidepressant use, (2) BDI <11 with antidepressant use, (3) BDI ≥11 and no antidepressant use, and (4) BDI ≥11 with antidepressant use.

Outcomes: CKD progression, incident cardiovascular disease composite, all-cause hospitalizations, and mortality.

Analytic Approach: Cox regression models were fitted for outcomes of CKD progression, incident cardiovascular disease, and all-cause mortality, whereas hospitalizations used Poisson regression.

Results: At baseline, 27.3% of participants had elevated DS, and 19.7% used antidepressants. Elevated DS at baseline were associated with significantly greater risk for an incident cardiovascular disease event, hospitalization, and all-cause mortality, but not CKD progression, adjusted for antidepressants. Antidepressant use was associated with higher risk for all-cause mortality and hospitalizations, after adjusting for DS. Compared to participants without elevated DS and not using antidepressants, the remaining groups (BDI <11 with antidepressants; BDI ≥11 and no antidepressants; BDI ≥11 with antidepressants) showed higher risks of hospitalization and all-cause mortality.

Limitations: Inability to infer causality among depressive symptoms, antidepressants, and outcomes. Additionally, the absence of nonpharmacological data, and required exploration of generalizability and alternative analytical approaches.

Conclusions: Elevated DS increased adverse outcome risk in nondialysis CKD, unattenuated by antidepressants. Additionally, investigation into the utilization and counterproductivity of antidepressants in this population is warranted.

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Depressive symptoms (DS) are common in adults with nondialysis-dependent chronic kidney disease (CKD), with an estimated prevalence in the range of ∼15% to >50%.[1-6] Despite this high prevalence, limited available data suggest that only a small fraction of patients with CKD are screened for depression, and even fewer receive depression treatment.[3,7] In the Chronic Renal Insufficiency Cohort (CRIC) Study, 27.4% of adults with nondialysis-dependent CKD had elevated DS, but only 31% of them were prescribed antidepressant medication.[7] In the African American Study of Kidney Disease and Hypertension (AASK), only 12% of participants with increased depressive affect were receiving antidepressant drug therapy.[3] Even less is known about nonpharmacological approaches to depression in CKD.[5]

Depression, either diagnosed by a clinician or ascertained using a survey, appears to negatively affect a variety of health-related outcomes in adults with nondialysis-dependent CKD. For example, in male Veterans with CKD, a major depressive episode was associated with a nearly 2-fold increase risk of a combined outcome of death, dialysis initiation, or hospitalization at 1-year follow-up.6 However, results from more recent studies have inconsistent findings.[1,8-10] Impacts of depression on CKD progression remain largely unclear, particularly given the following shortcomings in studies of nondialysis-dependent CKD: short follow-up periods, limited racial/ethnicity diversity, small sized samples, single outcome focus, and paucity in accounting for concomitant use of antidepressant medication.[1,2,9-14]

The prospective multicenter CRIC Study offers an excellent opportunity for a more comprehensive examination of the role of depression across multiple health-related outcomes in patients with nondialysis-dependent

PLAIN-LANGUAGE SUMMARY

We analyzed data from 4,839 nondialysis chronic kidney disease (CKD) patients in the Chronic Renal Insufficiency Cohort Study to explore how depression and antidepressants affect CKD-related outcomes. Using the Beck Depression Inventory (BDI), we assessed depressive symptoms (DS) and identified antidepressant use through medication records. Outcomes included CKD progression, cardiovascular events, hospitalizations, and mortality. Elevated DS at baseline raised the risk of cardiovascular events, hospitalizations, and mortality, regardless of antidepressant use. Antidepressant use alone was associated with higher mortality and hospitalization risks. In comparison to those without elevated DS and no antidepressant use, all other groups faced increased hospitalization and mortality risks. Elevated DS posed a significant risk to nondialysis CKD patients, and antidepressants did not mitigate this risk.

CKD.[15-17] Medication data available in CRIC further allow testing for independent effects of antidepressant use on clinical outcomes. This is particularly salient as some antidepressants may increase the risks of adverse cardiac events, possibly making them less suitable for depression treatment in CKD.[18] Leveraging the diverse national sample of the CRIC Study, we examined the independent association of baseline measures of DS and antidepressant medication use on CKD progression, cardiovascular disease (CVD) events, hospitalizations, and mortality. Participants were additionally categorized into 4 well-recognized clinical groups, as follows: (1) BDI <11 and no antidepressant use, (2) BDI <11 with antidepressant use, (3) BDI ≥11 and no antidepressant use, and (4) BDI ≥11 with antidepressant use.

METHODS

Study Sample and Design

Prospective longitudinal analyses were performed to test the association of DS and antidepressant medication use with health outcomes in CRIC participants. Details of the design and protocol of CRIC are published elsewhere.[15,16] Briefly, a total of 5,499 participants were recruited across 7 US clinical centers.[19] Major eligibility criteria included adults aged 21-74 years with mild to moderate CKD. The institutional review boards at the scientific and data-coordinating center and each clinical center approved the CRIC Study.

Study Measures

Depressive Symptoms

Depressive symptoms were assessed with the Beck Depression Inventory (BDI).[20] The 21-item BDI instrument was administered to all CRIC participants at their baseline visit. The BDI is a valid and widely used instrument to assess DS in adults with CKD.[21-23] A score ≥11 is considered a sensitive and specific threshold for probable major depression in adults with CKD.[24] As such, we adopted a BDI threshold of ≥11 to demarcate clinically meaningful DS in CRIC participants.

Antidepressant Medication Use

Antidepressant use was ascertained at each study visit through review of medication bottles or medication lists. Independent CRIC investigators identified and classified medications as falling into the rubric of antidepressants, including selective serotonin reuptake inhibitors, tricyclic and older antidepressants (eg, monoamine oxidase inhibitors), and newer antidepressants (eg, tetracyclic antidepressants).[7]

Health Outcomes

Primary health outcomes included the following: (1) time to CKD progression, (2) time to the first CVD event, (3) number of all-cause hospitalizations, and (4) time to all-cause mortality. Estimated GFR (eGFR) was determined with the CRIC creatinine-cystatin C equation using a locally measured serum creatinine level calibrated to the Roche enzymatic method (Roche Diagnostics Inc, www.roche-diagnostic.us).[25] CKD progression was defined as 50% eGFR loss from baseline or incident end-stage kidney disease (ESKD) requiring maintenance hemodialysis or kidney transplantation. In conjunction with self-report data, we used the US Renal Data System to identify incident cases of ESKD. Incident CVD events considered myocardial infarction, congestive heart failure, stroke, or peripheral arterial disease.[26] Hospitalizations were ascertained through self-report and hospital queries, with confirmation from medical record.[27] Death was ascertained through participant proxies, retrieval of death certificates or published obituaries, and analysis of hospital medical records and data of the Social Security Death Master File and the National Death Index.

Covariates

Baseline demographic characteristics included age, sex, race/ethnicity, household income, education, and health insurance status. Research staff collected self-report information on use of tobacco products, illicit drugs, and alcohol use. At baseline, participants also reported history of the following medical conditions: hypertension, hypercholesterolemia, congestive heart failure, myocardial infarction or coronary vascularization, peripheral arterial disease, stroke, or diabetes mellitus. Angiotensin-converting enzyme (ACE)/angiotensin II receptor blockers (ARB) use was confirmed by reviewing prescription bottles or updated medication lists. Clinical markers were collected using standardized methods.[15]

Statistical Analysis

Baseline participant characteristics are described overall and by the presence of baseline elevated depressive symptoms using mean and standard deviation (SD) values and/or frequencies and percentages. Bivariate analyses involved χ^2 test and analysis of variance tests. Similar comparisons were done for participants with and without antidepressant medication use. Descriptive statistics for the analytic sample are also presented for the 4-category variable combining depressive symptoms and antidepressant use.

We calculated rates of (1) CKD progression, (2) incident CVD events, (3) all-cause hospitalizations, and (4) all-cause mortality, reported as the number of events per 100 person-years (n/100 person-years) and stratified by participants with and without elevated baseline depressive symptoms. We also calculated event rates for participants taking and not taking antidepressant medications at baseline. Finally, event rates were calculated using the following 4-group categorizations: (1) BDI <11 and no antidepressant use, (2) BDI <11 with antidepressant use, (3) BDI ≥11 and no antidepressant use, and (4) BDI ≥11 with antidepressant use.

Multiple Cox regression models were fitted for outcomes of CKD progression, incident CVD, and all-cause mortality. Poisson regression was used when modeling the total number of hospitalizations. Model 1 adjusted for age, race/ethnicity, sex, educational attainment, baseline smoking, baseline alcohol use and illicit drug use, body mass index (BMI) category, history of comorbid conditions, systolic blood pressure, hemoglobin A1c, serum hemoglobin, serum albumin, ACE/ARB use, baseline eGFR, and baseline proteinuria. Model 2 adjusted for antidepressant medication (for the effect of BDI) or BDI (for the effect of antidepressant medication) in addition to covariates identified in Model 1. For the effect of the 4-category variable combining BDI and antidepressant use, we ran Model 1. For variables in Cox regression models violating the proportional hazard assumption, we dichotomized the follow-up time using the median value to estimate 2 hazard ratios, one each for the period before and after the median follow-up time. Finally, we performed right censoring across survival analyses because some participants remained event free at the end of the follow-up and their data were censored at the time they were last known to be event free.

Supplementary analyses were considered applying marginal structural models (MSMs) to explore the relationship of prospective changes in depressive symptoms and antidepressant use on the aforementioned health outcomes, defined as time-to-event. However, we found that the use of MSMs did not achieve adequate model convergence.

RESULTS

Baseline Participant Characteristics

Among the 5,499 CRIC participants, 660 (12%) were excluded because of missing data on main variables of interest at baseline and/or follow-up. Among the 4,839 participants included in our analysis, 27.3% [95% CI, 26.0%-28.5%] were categorized as having elevated depressive symptoms (ie, BDI ≥11), and 19.7% [95% CI, 18.6%-20.8%] were estimated to be prescribed antidepressant medications at baseline (Table 1). Approximately 34% of participants with elevated depressive symptoms were taking antidepressant medication. The mean age was 59.6 years, 43.5% were female, and 29.2% reported an annual household income below $20,000. A total of 42.9% identified as non-Hispanics White.

Table 1 presents sample characteristics stratified separately by BDI scores (<11 vs ≥11) and antidepressant use. Compared to participants without elevated depressive symptoms, those with elevated symptoms (ie, BDI ≥11) were younger, more often female and non-Hispanic African American or Hispanic/Latino, reported lower income and education, reported more unhealthy behavioral practices (eg, smoking), had a greater number of medical comorbidities, lower eGFR values, and higher mean protein/creatinine ratios ($P < 0.05$). Participants prescribed antidepressant medications (vs not) were more likely to be female, non-Hispanic White, self-identified as smokers or illicit drug users, showed higher likelihood of CVD and diabetes mellitus, higher values of BMI and eGFR, but lower protein/creatinine ratios and a lower likelihood of being hypertensive ($P < 0.05$).

Association of Baseline Elevated DS and Antidepressant Medication Use with Clinical Outcomes

Over an 8.3-year follow-up period, 29.5% of our CRIC sample experienced CKD progression, 27.7% had an incident CVD event, and 28.2% died (Table 2). Compared to those without elevated symptoms of depression (BDI <11), participants with elevated depressive symptoms had higher rates of CKD progression (6.9/100 patient-years vs 4.8/100 patient-years), incident CVD (5.5/100 patient-years vs 3.7/100 patient-years), and death (4.3/100 patient-years vs 3.1/100 patient-years). Higher rates of all-cause hospitalization were also observed for participants with elevated depressive symptoms (85.4/100 person-years vs 54.7/100 person-years).

Participants without antidepressant use had higher rates of CKD progression (5.5/100 person-years vs 4.4/100 person-years) compared to their counterparts using antidepressants. However, participants without antidepressant use had lower rates of mortality (3.3/100 person years vs 3.8/100 person-years) and hospitalizations (57.2/100 person-years vs 82.7/100 person-years) compared to those using antidepressants. No significant difference was found for incident CVD events in persons prescribed antidepressant medications versus those not prescribed antidepressants.

In multivariable adjusted models (Table 2), over a median follow up time of 8.3 years, compared to those

Table 1. Baseline Demographic Characteristics by BDI Scores and Antidepressant Medication Use

		Depressive Symptoms			Antidepressant Use		
Variable	**Total n = 4,839**	**BDI <11 n = 3,520**	**BDI ≥11 n = 1,319**	***P***	**No n = 3,885**	**Yes n = 954**	***P* value**
BDI score	8.0 (7.8)	4.2 (3.1)	18.3 (7.4)	<0.01	7.0 (6.9)	12.3 (9.6)	<0.01
Antidepressant Medication	954 (19.7%)	503 (14.3%)	451 (34.2%)	<0.01	–	–	–
Age	59.6 (10.6)	60.2 (10.7)	58.1 (10.0)	<0.01	59.6 (10.8)	59.5 (9.6)	0.75
Female	2,106 (43.5%)	1,460 (41.5%)	646 (49%)	<0.01	1,581 (40.7%)	525 (55%)	<0.01
Race/ethnicity							
Hispanic/Latino	506 (10.5%)	284 (8.1%)	222 (16.8%)		426 (11%)	80 (8.4%)	<0.01
Non-Hispanic African American	2,082 (43.0%)	1,463 (41.6%)	619 (46.9%)		1,764 (45.4%)	318 (33.3%)	
Non-Hispanic White	2,078 (42.9%)	1,643 (46.7%)	435 (33%)	<0.01	1,552 (39.9%)	526 (55.1%)	
Other	173 (3.6%)	130 (3.7%)	43 (3.3%)		143 (3.7%)	30 (3.1%)	
Income (in US dollars)							
≤20,000 or under	1,415 (29.2%)	815 (23.2%)	600 (45.5%)	<0.01	1,114 (28.7%)	301 (31.6%)	0.11
20,001-50,000	1,206 (24.9%)	889 (25.3%)	317 (24%)		953 (24.5%)	253 (26.5%)	
50,001-100,000	930 (19.2%)	782 (22.2%)	148 (11.2%)		765 (19.7%)	165 (17.3%)	
>100,000	557 (11.5%)	499 (14.2%)	58 (4.4%)		452 (11.6%)	105 (11%)	
Do not wish to answer	731 (15.1%)	535 (15.2%)	196 (14.9%)		601 (15.5%)	130 (13.6%)	
Education							
Less than HS	893 (18.5%)	520 (14.8%)	373 (28.3%)	<0.01	722 (18.6%)	171 (17.9%)	0.75
HS graduate/some post-HS	2,321 (48.0%)	1,664 (47.3%)	657 (49.8%)		1,853 (47.7%)	468 (49.1%)	
College graduate	1,625 (33.6%)	1,336 (38%)	289 (21.9%)		1,310 (33.7%)	315 (33%)	
Health insurance							
Insured	3,434 (77.9%)	2,509 (77.4%)	925 (79.5%)	0.14	2,733 (77%)	701 (82%)	<0.01
No insurance/unknown[a]	972 (22.1%)	733 (22.6%)	239 (20.5%)		818 (23%)	154 (18%)	
Current smoker	598 (12.4%)	370 (10.5%)	228 (17.3%)	<0.01	445 (11.5%)	153 (16%)	<0.01
Any illicit drug use	1,822 (37.7%)	1,269 (36.1%)	553 (41.9%)	<0.01	1,390 (35.8%)	432 (45.3%)	<0.01
Alcohol use	3,052 (63.1%)	2,294 (65.2%)	758 (57.5%)	<0.01	2,460 (63.3%)	592 (62.1%)	0.47
Body mass index (kg/m^2)	32.4 (7.7)	31.8 (7.2)	33.8 (8.7)	<0.01	32.1 (7.5)	33.2 (8.4)	<0.01
Systolic BP (mm Hg)	127.9 (21.2)	126.9 (20.7)	130.3 (22.2)	<0.01	128.4 (21.3)	125.8 (20.6)	<0.01
Hypertension[b]	4,175 (86.3%)	2,989 (84.9%)	1,186 (89.9%)	<0.01	3,377 (86.9%)	798 (83.6%)	<0.01
eGFR (mL/min per 1.73 m^2)	47.6 (16.4)	48.6 (16.4)	44.9 (16.2)	<0.01	47.2 (16.3)	49.2 (16.8)	<0.01
Urine protein/creatinine (g/g)	0.2 (0.1-0.7)	0.1 (0.1-0.6)	0.2 (0.1-1.1)	<0.01	0.2 (0.1-0.8)	0.1 (0.1-0.4)	<0.01
Serum albumin (g/dL)	4.0 (0.4)	4.0 (0.4)	3.9 (0.5)	<0.01	4.0 (0.4)	4.0 (0.4)	0.09
Hemoglobin (g/dL)	12.7 (1.8)	12.8 (1.8)	12.3 (1.7)	<0.01	12.7 (1.8)	12.6 (1.6)	0.05
Hemoglobin A1c (%)	6.7 (1.6)	6.6 (1.5)	6.9 (1.7)	<0.01	6.6 (1.5)	6.8 (1.7)	<0.01
Diabetes[c]	2,472 (51.1%)	1,680 (47.7%)	792 (60%)	<0.01	1,954 (50.3%)	518 (54.3%)	0.03

(Continued)

Table 1 (Cont'd). Baseline Demographic Characteristics by BDI Scores and Antidepressant Medication Use

Variable	Total n = 4,839	Depressive Symptoms		P	Antidepressant Use		P value
		BDI <11 n = 3,520	BDI ≥11 n = 1,319		No n = 3,885	Yes n = 954	
Hyperholesterolemia[d]	3,869 (80.0%)	2,792 (79.3%)	1,077 (81.7%)	0.07	3,092 (79.6%)	777 (81.4%)	0.20
Hx of prior CVD[e]	1,619 (33.5%)	1,087 (30.9%)	532 (40.3%)	<0.01	1,250 (32.2%)	369 (38.7%)	<0.01
Comorbidity Hx composite[f]	4,619 (95.5%)	3,343 (95%)	1,276 (96.7%)	<0.01	3,726 (95.9%)	893 (93.6%)	<0.1
ACE inhibitors or ARBs	3,330 (68.8%)	2 447 (69.5%)	883 (66.9%)	0.09	2,715 (69.9%)	615 (64.5%)	<0.01

Abbreviations: BDI, Beck Depression Inventory; BP, blood pressure; CVD, cardiovascular disease; HS, high school; Hx, history.
[a]Total with missing responses for health insurance status: N = 433.
[b]Hypertension is defined as a systolic blood pressure >140, diastolic >90, or self-reported use of prescribed hypertension medication.
[c]Fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or use of insulin or antidiabetic medication.
[d]High cholesterol is ascertained if the participant has the following: (1) elevated total cholesterol, low-density lipoprotein, or triglycerides; (2) has depressed high-density lipoprotein; or (3) self-reported use of lipid-lowering medications.
[e]History of congestive heart failure, myocardial infarction or prior revascularization, peripheral arterial disease, and stroke.
[f]History of hypertension, hypercholesterolemia, congestive heart failure, myocardial infarction or coronary revascularization, peripheral arterial disease, stroke, and diabetes.

without elevated symptoms of depression (BDI <11), participants with elevated symptoms of depression had greater risk of an incident CVD event (hazard ratio [HR] = 1.21; 95% CI, 1.06-1.36), hospitalizations (risk ratio [RR] = 1.28; 95% CI, 1.24-1.32), and all-cause mortality (HR = 1.20; 95% CI, 1.06-1.36) but similar risk of CKD progression (HR = 1.02; 95% CI, 0.87-1.20 for the period of 0-4 years and HR = 0.91; 95% CI, 0.75-1.10 for the period of 4+ years) after adjusting for other factors. Because of violations of the proportional hazard assumptions for the outcomes of CKD progression (BDI and BDI + antidepressant analyses) and incident CVD (antidepressant and BDI + antidepressant analyses), the follow-up time periods were split for analyses. Across regression models, associations of elevated depressive symptoms and health outcomes were largely unaltered after accounting for antidepressant use.

Compared to participants not using antidepressants, antidepressant use was associated with higher risk of hospitalizations (HR = 1.38; 95% CI, 1.34-1.43) and all-cause mortality (HR = 1.31; 95% CI, 1.13-1.50), but displayed similar risk of CKD progression and incident CVD events after accounting for other factors; associations were largely unaltered by further adjustment for BDI score.

Association of 4-Group Categorization (BDI Score ≥ 11 X Antidepressant Medication Use) at Baseline with Clinical Outcomes

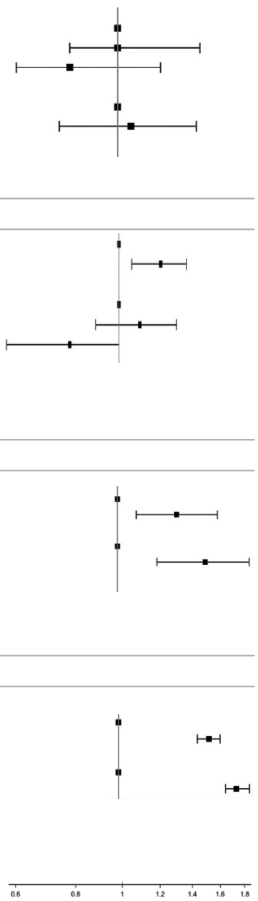
Table 3 presents sample characteristics stratified by the 4-category variable combining elevated depressive symptoms and antidepressant medication use.

When participants were classified into 4 categories based on presence or absence of elevated depressive symptoms and antidepressant medication use at baseline (Table 4), the highest outcome rates were observed for those with elevated depressive symptoms not prescribed antidepressant medications, including CKD progression (7.6/100 person-years), incident CVD events (6.0/100 person-years), and all-cause mortality (4.4/100 person-years). The highest hospitalization rates were seen for those with elevated depressive symptoms using antidepressants (95.9/100 person-years). The lowest outcome rates were consistently observed in participants without elevated depressive symptoms, with small differences in event rates by presence or absence of concomitant antidepressant medication use.

Combinations of elevated depressive symptoms and antidepressant use on health outcomes were also examined (Table 4). Regarding the risk for all-cause mortality, those with baseline BDI <11 and not using antidepressants had the lowest risk compared to remaining combinations at baseline, ie, BDI <11 + antidepressants (HR = 1.37; 95% CI, 1.14-1.64), BDI ≥11 + no antidepressants (HR = 1.23; 95% CI, 1.07-1.42), and BDI ≥11 + antidepressants (HR = 1.51; 95% CI, 1.25-1.83). Similar findings were evident for hospitalizations, where low symptoms of

Table 2. Event Rates and Rate/Hazard Ratios for CKD-Related Health Outcomes Based on Elevated Depressive Symptoms and Antidepressant Medication Use

Outcome	No. of Events	Event Rate (/100 person-y)	Model 1[a]	Model 2[b]	RR/HR Forest Plot
50% decrease eGFR/ incident dialysis/Tx	1,428				
BDI score					
BDI <11	999	4.8	1.00 (Ref)	1.00 (Ref)	
BDI ≥11	429	6.9	$Y_{0\text{-}4}$: 1.03 (0.88-1.20) Y_{4+}: 0.91 (0.76-1.10)	$Y_{0\text{-}4}$: 1.02 (0.87-1.20) Y_{4+}: 0.91 (0.75-1.10)	
Antidepressant use					
No antidepressant	1,200	5.5	1.00 (Ref)	1.00 (Ref)	
Antidepressant	228	4.4	1.02 (0.88-1.18)	1.03 (0.88-1.19)	
Incident CVD event	1,342				
BDI score					
BDI <11	918	3.7	1.00 (Ref)	1.00 (Ref)	
BDI ≥11	424	5.5	**1.19 (1.06-1.36)**	**1.21 (1.06-1.36)**	
Antidepressant use					
No antidepressant	1,102	4.2	1.00 (Ref)	1.00 (Ref)	
Antidepressant	240	3.9	$Y_{0\text{-}5}$: 1.11 (0.94-1.33) Y_{5+}: 0.82 (0.64-1.05)	$Y_{0\text{-}5}$: 1.06 (0.89-1.27) Y_{5+}: 0.77 (0.60-1.00)	
All-cause mortality	1,365				
BDI score					
BDI <11	937	3.1	1.00 (Ref)	1.00 (Ref)	
BDI ≥11	428	4.3	**1.26 (1.11-1.42)**	**1.20 (1.06-1.36)**	
Antidepressant use					
No antidepressant	1,086	3.3	1.00 (Ref)	1.00 (Ref)	
Antidepressant	279	3.8	**1.36 (1.19-1.56)**	**1.31 (1.13-1.50)**	
Hospitalization					
BDI score					
BDI <11	15,424	54.7	1.00 (Ref)	1.00 (Ref)	
BDI ≥11	7,942	85.4	**1.36 (1.32-1.40)**	**1.28 (1.24-1.32)**	
Antidepressant use					
No antidepressant	17,504	57.2	1.00 (Ref)	1.00 (Ref)	
Antidepressant	5,862	82.7	**1.47 (1.42-1.52)**	**1.38 (1.34-1.43)**	



Note: Statistically significant values, denoted by bold font, indicate results with a *P*-value of ≤0.05, suggesting a significant difference or effect.
Abbreviations: AD, Antidepressant drugs; BDI, Beck Depression Inventory; HR, hazard ratio; RR, risk ratio; Tx, treatment.If there were no differences in HR estimates across 2 periods, then that variable did not violate the proportional hazards assumption in the model.
[a]Model 1: adjusted for age, race/ethnicity, sex, educational attainment, baseline smoking, baseline alcohol use and illicit drug use, body mass index category, history of comorbid conditions (hypertension, high cholesterol, congestive heart failure, myocardial infarction, or coronary vascularization, peripheral arterial disease, stroke, and diabetes), systolic blood pressure, hemoglobin A1c, serum hemoglobin, serum albumin, ACE/ARB use, baseline eGFR, and baseline proteinuria.
[b]Model 2: adjusted for Model 1 + antidepressant use or BDI score, as appropriate.

depression combined with no antidepressant use resulted in the lowest hazard ratios compared to all other combinations, i.e., BDI <11 + antidepressants (RR = 1.45; 95% CI, 1.39-1.51), BDI ≥11 + no antidepressants (RR = 1.32; 95% CI, 1.27-1.37), and BDI ≥11 + antidepressants (RR = 1.72; 95% CI, 1.65-1.80). No significant differences in hazard ratios were seen for CKD progression and incident CVD events across the 4-category subgroups.

DISCUSSION

In a large racially/ethnically diverse multicenter cohort of US adults with nondialysis-dependent CKD, elevated baseline levels of depressive symptoms were strongly associated with higher risk of incident CVD events, hospitalizations, and all-cause mortality, which remained largely unchanged after accounting for antidepressant medication use. Antidepressant use also conferred greater risk for all-cause mortality and hospitalizations, despite adjustment for depressive symptoms. Moreover, compared to adults with CKD without elevated depressive symptoms and not taking antidepressants, all other permuted categories displayed higher risks for hospitalizations and death. Collectively, these findings underscore the substantial negative impact of elevated depressive symptoms on a broad range of health outcomes for adults with CKD and stress the need to further examine the impact of antidepressants in this population.

Prior literature characterizing the relationship between depression and health outcomes has been inconsistent,

Table 3. Baseline Demographic Characteristics Based on the 4-Category Variable Combining Elevated Depressive Symptoms and Antidepressant Medication Use

Variable	Total n = 4,839	BDI <11, No Antidepressants n = 3,017	BDI <11, Antidepressants n = 503	BDI ≥11, No Antidepressants n = 868	BDI ≥11, Antidepressants n = 451	*P*
Beck's Depression Inventory	8.0 (7.8)	4.0 (3.1)	5.2 (3.0)	17.3 (6.8)	20.2 (8.1)	<0.01
Antidepressant medication	954 (19.7%)	–	503 (100%)	–	451 (100%)	<0.01
Age	59.6 (10.6)	60.1 (10.9)	60.8 (10.0)	58.1 (10.6)	58.1 (9.0)	<0.01
Female	2,106 (43.5%)	1,183 (39.2%)	277 (55.1%)	398 (45.9%)	248 (55%)	<0.01
Race/ethnicity						
Hispanic/Latino	506 (10.5%)	263 (8.7%)	21 (4.2%)	163 (18.8%)	59 (13.1%)	<0.01
Non-Hispanic African American	2,082 (43.0%)	1,319 (43.7%)	144 (28.6%)	445 (51.3%)	174 (38.6%)	
Non-Hispanic White	2,078 (42.9%)	1,318 (43.7%)	325 (64.6%)	234 (27%)	201 (44.6%)	
Other	173 (3.6%)	117 (3.9%)	13 (2.6%)	26 (3%)	17 (3.8%)	
Income (in US dollars)						
≤20,000 or under	1,415 (29.2%)	699 (23.2%)	116 (23.1%)	415 (47.8%)	185 (41%)	<0.01
20,001-50,000	1,206 (24.9%)	744 (24.7%)	145 (28.8%)	209 (24.1%)	108 (23.9%)	
50,001-100,000	930 (19.2%)	680 (22.5%)	102 (20.3%)	85 (9.8%)	63 (14%)	
>100,000	557 (11.5%)	419 (13.9%)	80 (15.9%)	33 (3.8%)	25 (5.5%)	
Do not wish to answer	731 (15.1%)	475 (15.7%)	60 (11.9%)	126 (14.5%)	70 (15.5%)	
Education						
Less than HS	893 (18.5%)	453 (15%)	67 (13.3%)	269 (31%)	104 (23.1%)	<0.01
HS graduate/some post-HS	2,321 (48.0%)	1,431 (47.4%)	233 (46.3%)	422 (48.6%)	235 (52.1%)	
College graduate	1,625 (33.6%)	1,133 (37.6%)	203 (40.4%)	177 (20.4%)	112 (24.8%)	
Health insurance						
Insured	3,434 (77.9%)	2,140 (76.8%)	369 (81.1%)	593 (77.6%)	332 (83%)	0.01
No insurance/unknown[a]	972 (22.1%)	647 (23.2%)	86 (18.9%)	171 (22.4%)	68 (17%)	
Current smoker	598 (12.4%)	297 (9.8%)	73 (14.5%)	148 (17.1%)	80 (17.7%)	<0.01
Any illicit drug use	1,822 (37.7%)	1,045 (34.6%)	224 (44.5%)	345 (39.7%)	208 (46.1%)	<0.01
Alcohol use	3,052 (63.1%)	1966 (65.2%)	328 (65.2%)	494 (56.9%)	264 (58.5%)	<0.01
Body mass index (kg/m^2)	32.4 (7.7)	31.7 (7.0)	32.4 (7.9)	33.6 (8.6)	34.1 (8.9)	<0.01
Systolic BP (mm Hg)	127.9 (21.2)	127.3 (20.8)	124.8 (19.8)	132.1 (22.4)	126.9 (21.3)	<0.01
Hypertension[b]	4,175 (86.3%)	2,587 (85.7%)	402 (79.9%)	790 (91%)	396 (87.8%)	<0.01
eGFR (mL/min per 1.73 m^2)	47.6 (16.4)	48.3 (16.3)	50.5 (16.9)	43.4 (15.8)	47.7 (16.6)	<0.01
Urine protein/creatinine (g/g)	0.2 (0.1-0.7)	0.1 (0.1-0.6)	0.1 (0.1-0.3)	0.3 (0.1-1.2)	0.2 (0.1-0.6)	<0.01
Serum albumin (g/dL)	4.0 (0.4)	4.0 (0.4)	4.0 (0.4)	3.9 (0.5)	3.9 (0.4)	<0.01
Hemoglobin (g/dL)	12.7 (1.8)	12.8 (1.8)	12.8 (1.7)	12.3 (1.8)	12.4 (1.6)	<0.01
Hemoglobin A1c (%)	6.7 (1.6)	6.5 (1.5)	6.7 (1.6)	6.9 (1.7)	7.0 (1.8)	<0.01
Diabetes[c]	2,472 (51.1%)	1,427 (47.3%)	253 (50.3%)	527 (60.7%)	265 (58.8%)	<0.01
Hypercholesterolemia[d]	3,869 (80.0%)	2,385 (79.1%)	407 (80.9%)	707 (81.5%)	370 (82%)	0.24

(Continued)

Table 3 (Cont'd). Baseline Demographic Characteristics Based on the 4-Category Variable Combining Elevated Depressive Symptoms and Antidepressant Medication Use

Variable	Total n = 4,839	BDI <11, No Antidepressants n = 3,017	BDI <11, Antidepressants n = 503	BDI ≥11, No Antidepressants n = 868	BDI ≥11, Antidepressants n = 451	*P*
Hx of prior CVD[e]	1,619 (33.5%)	907 (30.1%)	180 (35.8%)	343 (39.5%)	189 (41.9%)	<0.01
Comorbidity Hx composite[f]	4,619 (95.5%)	2,881 (95.5%)	462 (91.8%)	845 (97.4%)	431 (95.6%)	<0.1
ACE inhibitors or ARBs	3,330 (68.8%)	2,120 (70.3%)	327 (65%)	595 (68.5%)	288 (63.9%)	<0.01

Abbreviations: BDI, Beck Depression Inventory; BP, blood pressure; CVD, cardiovascular disease; HS, high school; Hx, history.
[a]Total with missing responses for health insurance status: N = 433.
[b]Hypertension is defined as a systolic blood pressure >140, diastolic >90, or self-reported use of prescribed hypertension medication.
[c]Fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or use of insulin or antidiabetic medications.
[d]High cholesterol is ascertained if the participant has the following: (1) has elevated total cholesterol, low-density lipoprotein, or triglycerides; (2) has depressed high-density lipoprotein; or (3) self-reported use of lipid-lowering medications.
[e]History of congestive heart failure, myocardial infarction or prior revascularization, peripheral arterial disease, and stroke.
[f]History of hypertension, hypercholesterolemia, congestive heart failure, myocardial infarction or coronary revascularization, peripheral arterial disease, stroke, and diabetes.

with multiple shortcomings.[1,2,9-14] Leveraging a large diverse cohort with detailed medication history and long follow-up time, our results agree with a systematic review of 22 cohort studies that found symptoms of depression to be associated with higher risk for all-cause mortality.[9] Hedayati et al[2] (2004) reported similar effects for all-cause mortality in CKD patients hospitalized for congestive heart failure. Detrimental effects of depression are also reported for outcomes of acute kidney injury, CVD hospitalizations, and deaths.[1,11]

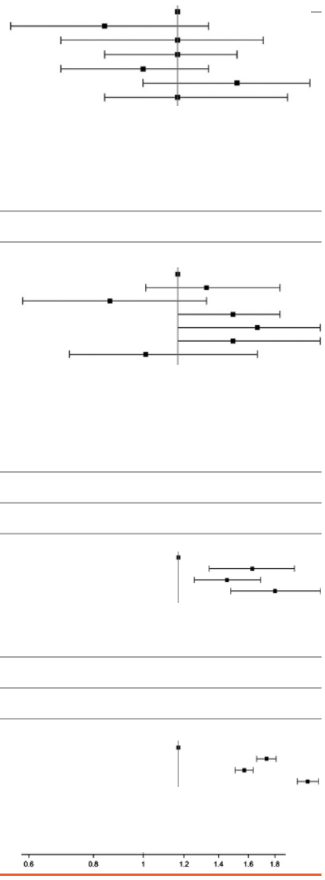
Consistent with our results, others have reported nonsignificant associations between depression and eGFR declines and incident ESKD.[1,11,14] Questions remain about the impact of psychosocial antecedents on CKD progression and whether they exert greatest influence earlier in the disease process or during latter periods when severe comorbidity becomes evident.[28] Evidence does not yet allow for definitive conclusions given inconsistent findings across disease outcomes, particularly given heterogeneity throughout the literature when operationalizing CKD progression.[6,11,12] Inconsistencies are also likely due to differences in sample characteristics and methodological differences, where some studies only assess depression at a single point in time, usually baseline, and instances where antidepressant use remains unaccounted.

In contrast to most prior studies, we accounted for the potential impact of antidepressant medication on outcomes. In our cohort, the effects of depressive symptoms on health outcomes in adults with nondialysis-dependent CKD were largely unattenuated after accounting for antidepressant medication use. This observation is consistent with limited prior studies. Tuot et al[8] found that antidepressant medication use did not attenuate the association between baseline elevated depressive symptoms and increased risk for all-cause mortality in adults with mild to moderate CKD. In a study of adults with ESKD on hemodialysis, each standard deviation increase in the Center for Epidemiologic Studies Depression Scale measuring depression was associated with a 21% increased risk for mortality, even after adjusting for antidepressant use at baseline.[29] Thus, it appears that antidepressants make a negligible difference.

There are several possible explanations for absence of risk reduction when accounting for antidepressant use. First, elevated depressive symptoms may have conferred disease risk as a consequence of chronicity where a critical threshold of exposure has been reached to affect disease outcomes.[30] Substantiating this hypothesis, a Dutch study found that chronic antidepressant use was more prevalent in adults with severe kidney disease when compared to matched controls.[31] Second, it is important to recognize that a prescription does not always translate into adherence as indicated by a medical provider. Individuals with elevated BDI scores on antidepressants may lack medication adherence.[32,33] Third, antidepressants occasionally lack efficacy in ameliorating depression in patients with

Table 4. Event Rates and Rate/Hazard Ratios for CKD-Related Health Outcomes Based on the Four-Category Variable Combining Elevated Depressive Symptoms and Antidepressant Use

Outcome	No. of Events	Event Rate (/100 person-y)	Model 1[a]	RR/HR Forest Plot
50% decrease eGFR/ incident dialysis/Tx	1,428			
BDI × antidepressant use				
BDI <11, no antidepressant	896	5.0	1.00 (Ref)	
BDI <11, antidepressant	103	3.5	$Y_{0\text{-}4}$: 0.83 (0.60-1.14) Y_{4+}: 0.97 (0.74-1.27)	
BDI ≥11, no antidepressant	304	7.6	$Y_{0\text{-}4}$: 0.96 (0.80-1.15) Y_{4+}: 0.87 (0.70-1.08)	
BDI ≥11, antidepressant	125	5.6	$Y_{0\text{-}4}$: 1.16 (0.90-1.50) Y_{4+}: 1.01 (0.75-1.35)	
Incident CVD event	1,342			
BDI × antidepressant use				
BDI <11, no antidepressant	806	3.8	1.00 (Ref)	
BDI <11, antidepressant	112	3.3	$Y_{0\text{-}5}$: 1.12 (0.88-1.42) Y_{5+}: 0.79 (0.56-1.13)	
BDI ≥11, no antidepressant	296	6.0	$Y_{0\text{-}5}$: 1.22 (1.03-1.44) Y_{5+}: 1.25 (0.99-1.58)	
BDI ≥11, antidepressant	128	4.7	$Y_{0\text{-}5}$: 1.24 (0.98-1.56) Y_{5+}: 0.93 (0.66-1.30)	
All-cause mortality	1,365			
BDI × antidepressant use				
BDI <11, no antidepressant	793	3.0	1.00 (Ref)	
BDI <11, antidepressant	144	3.6	**1.37 (1.14-1.64)**	
BDI ≥11, no antidepressant	293	4.4	**1.23 (1.07-1.42)**	
BDI ≥11, antidepressant	135	4.1	**1.51 (1.25-1.83)**	
Hospitalization				
BDI × antidepressant use				
BDI <11, no antidepressant	12,596	51.8	1.00 (Ref)	
BDI <11, antidepressant	2,828	72.6	**1.45 (1.39-1.51)**	
BDI ≥11, no antidepressant	4,908	79.8	**1.32 (1.27-1.37)**	
BDI ≥11, antidepressant	3,034	95.9	**1.72 (1.65-1.80)**	



Note: Statistically significant values, denoted by bold font, indicate results with a p-value of ≤0.05, suggesting a significant difference or effect.
Abbreviations: AD, Antidepressant drugs; BDI, Beck Depression Inventory; HR, hazard ratio; RR, risk ratio; Tx, treatment.
Model 1: adjusted for age, race/ethnicity, sex, educational attainment, baseline smoking, baseline alcohol use and illicit drug use, body mass index category, history of comorbid conditions (hypertension, high cholesterol, congestive heart failure, myocardial infarction or coronary vascularization, peripheral arterial disease, stroke, and diabetes), systolic blood pressure, hemoglobin A1c, serum hemoglobin, serum albumin, ACE/ARB use, baseline eGFR, and baseline proteinuria.
If there were no differences in HR estimates across 2 periods, then that variable did not violate the proportional hazards assumption in the model.

CKD. In a double-blind randomized trial of 201 patients with nondialysis-dependent CKD, those randomized to receive sertraline did not differ in improvements in depressive symptoms at 12 weeks compared to the placebo control arm, where both conditions experienced decreases in depressive symptoms.[34] Work is needed to better understand the pharmacokinetics and efficacy of antidepressants in CKD.

We also found that antidepressant use in the absence of elevated depressive symptoms conferred risk for detrimental health outcomes. This finding was unexpected because we anticipated that the amelioration of depression symptoms by pharmacologic therapy would also lessen negative associated outcomes. This may be pointing to the notion of a critical period where early or chronic exposure to depressive affectivity confers a potentially irreversible negative impact on the biological system and overall healthy longevity.[35-37] It is possible that long-term exposure to depressive symptoms, eg, early in life, triggers a cascade of abnormal biological responses that remain even after introducing effective pharmacological treatment years later.[38] Additionally, this finding may reflect direct negative effects of antidepressants. Antidepressants may induce QT prolongation, which has dangerous cardiac consequences, particularly in populations with high CVD burden, frequent electrolyte abnormalities, and risk for polypharmacy induced interactions.[18] Considerably more examination of the use of antidepressants in nondialysis CKD is needed.

Although this study had several strengths, including a large diverse national participant sample, psychometrically valid measures of depressive symptoms and biological

outcomes, and detailed medication review to identify antidepressant use, it does have limitations. First, we are unable to make inferences regarding causality among depressive symptoms, antidepressant medication use, and adverse outcomes. Moreover, despite robust adjustment for other important factors, we cannot exclude the possibility for residual confounding. Second, we did use a formal clinical diagnosis of depression. However, we did use a BDI cutoff for elevated depressive symptoms that has been specifically validated in patients with CKD.[24] Another limitation is the lack of adjustment for changes in antidepressant use during the follow-up period. We attempted to address this concern by employing marginal structural models; however, we encountered difficulties with model convergence. This issue could likely be attributed to the lack of confounding variables available to account for the association between antidepressant use and depressive symptoms. Third, CRIC does not capture information on nonpharmacological approaches to depression treatment among, so we are unable to account for its potential role. Although we were able to identify the presence of antidepressants, we cannot confirm their indication and extent of treatment compliance. In rare circumstances, antidepressants may have been prescribed for reasons other than depression (eg, diabetic neuropathy), which could confound our interpretation of their association with outcomes.[10,39] Generalizability may be limited to US adults from predominantly urban settings. Additionally, given the complexity of the relationships among depression, antidepressant use, and clinical outcomes, future research could also explore alternative analytical approaches, such as mediation analysis or machine learning techniques, to more accurately capture the potential causal pathways and identify subgroups of patients who may benefit most from different treatment strategies.

In conclusion, our results underscore the substantial negative impact of depression on adults with CKD. Given the lack of apparent benefit of antidepressants in adults with depression and nondialysis CKD, these results inform the need not only to further investigate the role of antidepressants in this population but also to further evaluate alternative treatment options, especially nonpharmacologic treatments.

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