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Original Article

ORIGINAL ARTICLE

Association between incident depression and clinical outcomes in patients with chronic kidney disease

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ABSTRACT

Background. Depression is highly prevalent and related to increased morbidity and mortality in patients on dialysis, but less is known among patients with earlier stages of CKD. This study investigated the associations between depression and clinical outcomes in patients with CKD not receiving dialysis.

Methods. We identified 157 398 adults with CKD stages 3–5 not previously diagnosed with depression from the Stockholm CREAtinine Measurements (SCREAM) project. The primary outcomes included hospitalization, CKD progression (>40% decline in eGFR, initiation of kidney replacement therapy, or death due to CKD), major adverse cardiovascular events (MACE; myocardial infarction, stroke, or cardiovascular death), and all-cause mortality. Survival analyses were used to estimate the associations between incident depression and adverse health outcomes, adjusting for socio-demographics, kidney disease severity, healthcare utilization, comorbidities, and concurrent use of medications.

Results. During a median follow-up of 5.1 (interquartile range: 2.3–8.5) years, 12 712 (8.1%) patients received an incident diagnosis of depression. A total of 634 471 hospitalizations (4 600 935 hospitalized days), 42 866 MACEs, and 66 635 deaths were recorded, and 9795 individuals met the criteria for CKD progression. In the multivariable-adjusted analyses, incident depression was associated with an elevated rate of hospitalized days [rate ratio: 1.77, 95% confidence interval (CI): 1.71–1.83], as well as an increased rate of CKD progression [hazard ratio (HR): 1.38, 95% CI: 1.28–1.48], MACE (HR: 1.22, 95% CI: 1.18–1.27), and all-cause mortality (HR: 1.41, 95% CI: 1.37–1.45). The association with CKD progression was more evident after one year of depression diagnosis (HR: 1.47, 95% CI: 1.36–1.59). Results were robust across a range of sensitivity analyses.

Conclusion. Among patients with nondialysis-dependent CKD stages 3–5, incident depression is associated with poor prognosis, including hospitalization, CKD progression, MACE, and all-cause mortality.

LAY SUMMARY

Depression is a common mental disorder that is related to poor prognosis in patients on dialysis, but whether these findings can be extended to patients with earlier stages of CKD is less certain. We used data from the Stockholm CREAtinine Measurements (SCREAM) project linked to regional and national health registers to investigate the relationship between depression and clinical outcomes in patients with CKD not receiving dialysis. We have found that depression was consistently associated with adverse clinical outcomes, including hospitalization, CKD

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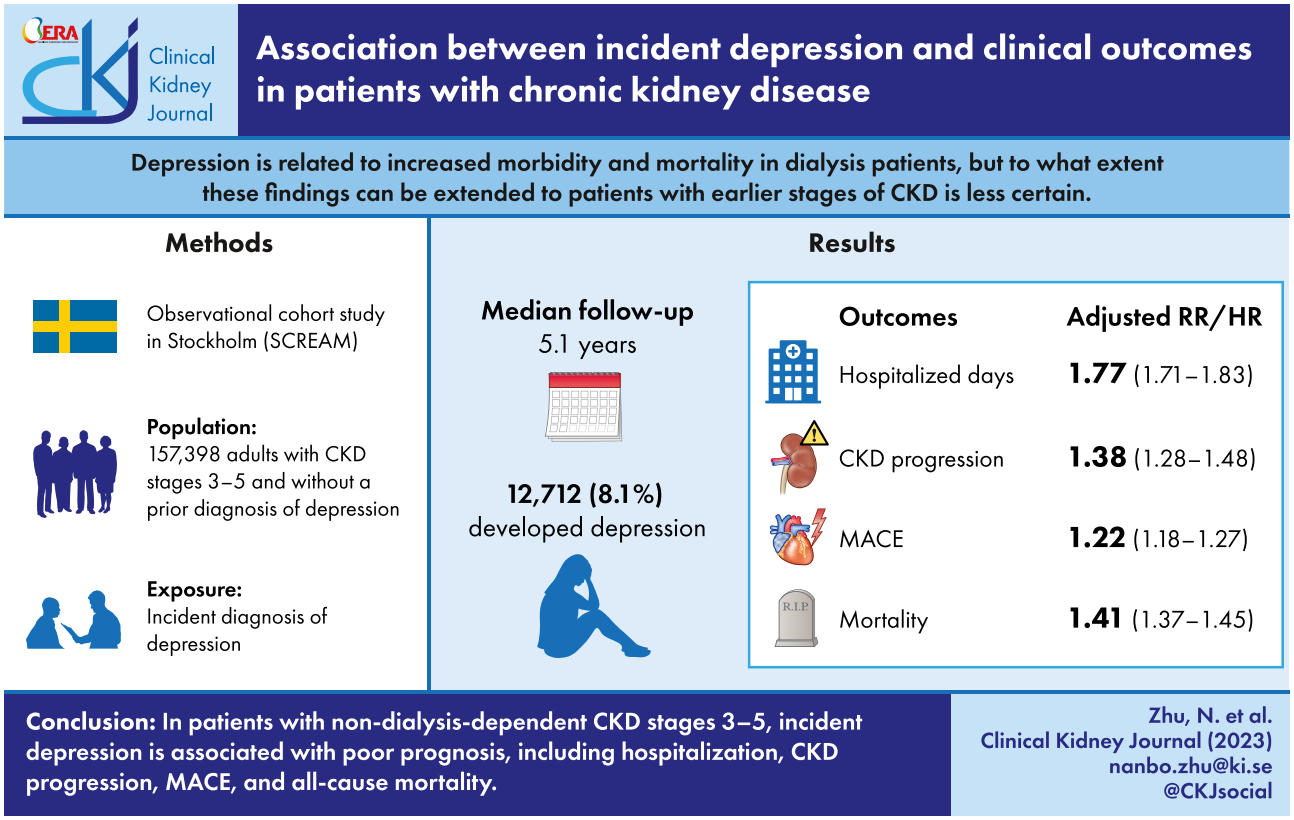
progression, major adverse cardiovascular events, and all-cause mortality. Our study highlights the need for future research on the management of depression in early-stage CKD.

GRAPHICAL ABSTRACT



Keywords: cardiovascular event, chronic kidney disease, depression, disease progression, mortality

INTRODUCTION

CKD is a highly prevalent condition but encompasses a broad range of disease severity with significant heterogeneity [1], extending from slight decrease to near-total loss of kidney function. Depression is one of the most frequently reported psychiatric disorders comorbid with CKD, affecting approximately one-quarter of patients with CKD [2]. It has been suggested that lower levels of kidney function are associated with elevated depressive symptoms [3].

Previous studies in the CKD population, primarily conducted in patients with end-stage kidney disease (ESKD) on dialysis, have linked co-occurring depression to negative health outcomes such as low quality of life, hospitalization, and death [4–8]. Meta-analyses have identified depression as an independent risk factor for all-cause mortality in patients receiving maintenance dialysis [9, 10]. Mechanisms underlying these associations remain unclear, but comorbid depression has been shown to be related to noncompliance with medical treatment [11], unfavorable lifestyle changes [12], and less social support [13]. Moreover, depression is associated with adverse physiological correlates, such as impaired nutritional status, increased inflammation, and immune activation [14–16].

There is limited evidence on the relationship between depression and clinical outcomes among patients with earlier stages of CKD [17–27]. While some studies found depression to be associated with an increased risk of subsequent hospitalization and dialysis initiation in CKD patients not receiving dialysis, the association of depression with mortality is inconclusive due to small sample sizes and few death cases [17, 21–24]. Furthermore, cardiovascular disease (CVD), rather than ESKD, is the leading cause of death in patients with CKD [28], but the relationship between depression and CVD has rarely been studied in this vulnerable population. One study found that elevated depressive symptom was associated with an increased risk of cardiovascular hospitalization and death in CKD patients of African American ethnicity [22]. However, it is unknown whether such an association persists in other populations.

The aim of this study was to investigate the associations between depression and adverse clinical outcomes including hospitalization, CKD progression, major adverse cardiovascular events (MACE), and all-cause mortality among patients with

stages 3–5 CKD not receiving dialysis, using a general population sample from Stockholm, Sweden with valid laboratory measures of kidney function.

MATERIALS AND METHODS

Study population

This study was based on the Stockholm CREAtinine Measurements (SCREAM) project, a health care utilization cohort that includes all residents in the Stockholm region during 2006–2019 [29, 30]. Using the unique personal identification number assigned to all Swedish residents, laboratory tests from routine clinical care were linked to several regional and national health registers, including the Stockholm regional healthcare data warehouse (VårdAnalysdataLager, VAL), the Cause of Death Register, the Prescribed Drug Register, and the Swedish Renal Register. The VAL databases are established by Stockholm's health care services and contain information on all consultations in primary and secondary care (specialist outpatient care), as well as hospitalizations. Data for primary care are available since 2003, and for secondary care and hospitalization since 1997 [31]. The Swedish Renal Register includes patients with CKD referred to nephrologists in Sweden, which has registered initiation of kidney replacement therapy (KRT) since 1991 [32]. Because register data are de-identified, informed consent was not required. The study was approved by the Regional Ethics Review Board in Stockholm and adhered to the Declaration of Helsinki.

Eligible individuals for this study were adults (≥18 years old) with stages 3–5 CKD not receiving KRT and without a prior diagnosis of depression. eGFR was calculated using the 2009 CKD Epidemiology Collaboration creatinine equation without correction for race [33], based on isotope dilution mass spectrometry standardized serum/plasma creatinine tests. Inpatient creatinine measurements, as well as implausible values (<25 or >1500 µmol/l) were excluded. We identified 225 076 individuals who had at least one eGFR <60 ml/min/1.73 m^2 during 2007–2018. The date of the first eGFR <60 ml/min/1.73 m^2 was defined as the index date (i.e. baseline). Individuals whose all subsequent eGFR measurements were ≥60 ml/min/1.73 m^2 were excluded (n = 45 826). Other exclusion criteria were history of kidney transplant or dialysis (n = 442), history of depression (n = 20 303), and having emigrated or died on/before the index date (n = 1107). The final study cohort included 157 398 individuals with stages 3–5 CKD not previously diagnosed with depression at baseline (Fig. 1).

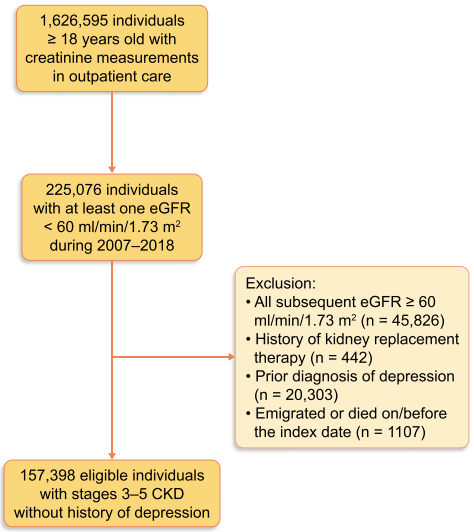


Figure 1: Flow chart of the sample selection.

Exposure

The exposure was incident diagnosis of depression according to the International Classification of Diseases, 10th revision (ICD–10 codes: F32, F33), during a consultation in either primary care or specialist care. Patients with a recorded ICD–10 diagnosis of depression at baseline were excluded, but some individuals might have been diagnosed with depression before the establishment of the VAL databases. Therefore, individuals could receive a diagnostic code of F33 in this study, representing a new episode of recurrent depression.

Outcomes

The study outcomes of interest included all-cause hospitalization, CKD progression, MACE, and all-cause mortality. Hospitalization was considered a recurrent event, and the cumulative hospitalized days during follow-up were counted for each patient. MACE was defined as the composite of myocardial infarction (ICD–10 codes: I21, I22, I25.2), stroke (ICD–10 codes: G45, I60–I64, I67, I69), or cardiovascular death (ICD–10 codes: I00–I99). The date and the cause of death were ascertained from the Cause of Death Register. Only the first two hospital discharge diagnoses and the primary cause of death were used to define the outcomes.

CKD progression was defined as the composite of a relative eGFR decline of >40% from baseline, initiation of KRT as ascertained by linkage with the Swedish Renal Register, or death due to CKD (ICD–10 codes: N18, N19). We estimated the eGFR trajectory with all available outpatient eGFR values from the index date to the end of follow-up, using a linear mixed model [34]. To be considered a sustained decline in eGFR, the eGFR slope needed to be negative, and the decline threshold had to be reached before the last eGFR measurement. Timing of the decline in eGFR was determined based on the estimated date when the regression line crossed the 40% decline threshold.

Patients were followed up from the index date until the date of a specific outcome, death, moving away from the Stockholm region, or study end (31 December 2019), whichever occurred first. Since laboratory tests (e.g. creatinine) were only available until 2018, the end of follow-up was 31 December 2018 for kidney-related outcomes, but 31 December 2019 for the other study outcomes.

Covariates

Directed acyclic graphs were used to inform our multivariable adjustment strategy (Supplementary Fig. S1, see online supplementary material for a color version of this figure). The adjustment set included socio-demographics (age, sex, educational attainment, marital status, and household disposable income), kidney function (eGFR and albuminuria), prior healthcare utilization, nursing home care, comorbidities, and concurrent use of medications at baseline. Tobacco-related disorders and alcohol-related disorders were used as surrogates for lifestyle factors. Year of cohort entry was included in the models to account for changes in practice patterns during the study

period. To avoid collider bias, mediators such as antidepressant use were not adjusted for.

The presence of albuminuria was ascertained through extraction of all tests of dipstick albuminuria/proteinuria, urine albumin to creatinine ratio, urine protein to creatinine ratio, and albuminuria excretion rates using the conversion equations whenever applicable [35], and classified into KDIGO categories A1–A3. We have identified the most recent albuminuria test preceding the index date to evaluate albuminuria status at baseline. Nevertheless, these measurements were not universally performed in routine care, 57% of the included CKD patients had no albuminuria data. In addition, the missing rate of education, marital status, and disposable income was 4%, <1%, and <1%, respectively. We used multiple imputation by chained equations to impute five complete datasets, assuming missing at random [36].

Prior healthcare utilization was defined as the number of hospitalizations and the number of emergency department visits during the past year. Comorbid physical illnesses were defined as history of obesity, hypertension, diabetes mellitus, myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, malignancy other than nonmelanoma skin cancer, lung disease, liver disease, and thyroid disease. Hypertension and diabetes were also defined by recent dispensation of medications for these conditions, based on the Anatomical Therapeutic Chemical (ATC) codes. Comorbid neuropsychiatric disorders were ascertained for dementia, psychotic disorders, manic episode/bipolar disorder, and anxiety disorders. Medication use within 6 months prior to the index date was ascertained for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, antiplatelet drugs, statins, glucagon-like peptide-1 receptor agonists, and sodium–glucose cotransporter-2 inhibitors. ICD–10/ATC codes are presented in Supplementary Table S1.

Statistical analyses

Baseline characteristics of the study cohort were described as median with interquartile range (IQR) or frequency with percentage. We used negative binomial regression to examine the association between incident depression and hospitalized days. Results were reported as rate ratios (RRs) with 95% confidence intervals (CIs). We used Cox proportional hazard regression, with age as the underlying time scale, to estimate the hazard ratios (HRs) and 95% CIs for the associations between incident depression and risks of CKD progression, MACE, and all-cause mortality. Depression was treated as a time-varying exposure to avoid immortal time bias. That is, patients developing depression during follow-up contributed time to the unexposed period until they received a diagnosis of depression, and thereafter contributed time to the exposed period. In the multivariable analyses, models were adjusted for the aforementioned covariates identified from directed acyclic graphs. The effect estimates were estimated separately in each imputed dataset and then pooled using Rubin's rule [36]. Considering albuminuria can be tested by indications, thus violating the assumption of missing at random for multiple imputation, we explored the consistency of the associations by stratifying on albuminuria measurement and severity (missing albuminuria, albuminuria A1, and albuminuria A2/A3).

We evaluated whether the associations varied by time after the incident depression (<1 versus ≥1 year), type of depression [single-episode depression (F32) versus recurrent depression (F33)], and source of depression diagnosis (primary care versus specialist care) as an index of severity. Subgroup analyses by pre-specified variables were also performed, including sex, age category (<75 versus ≥75 years), education (compulsory, secondary, and college/university), eGFR category (<45 versus ≥45 ml/min/1.73 m^2), and selected comorbid conditions (hypertension, diabetes, myocardial infarction, stroke, congestive heart disease, and anxiety disorders).

Several sensitivity analyses were conducted to assess the robustness of our results by using alternative definitions for the study cohort, exposure, covariates, and outcomes: (i) we defined the CKD cohort by requiring another eGFR measurement <60 ml/min/1.73 m^2 between 3 months and 2 years apart, with the date of the second eGFR <60 ml/min/1.73 m^2 considered as the index date. (ii) We defined the exposure by incident diagnosis of depression or incident prescription of antidepressants, whichever came first. Antidepressant prescriptions used for indications other than depression (e.g. anxiety disorders, insomnia, and chronic pain) were excluded based on the free-text prescribing instructions (included drugs were listed in Supplementary Table S2). (iii) We defined the exposure by requiring two diagnostic codes from primary care/outpatient care or one diagnostic code from inpatient care. (iv) We considered a patient to be exposed to depression 1 year before the diagnosis was made to account for possible delayed diagnosis of depression. It should be noted that, by design, death cannot occur during this 1-year period, and therefore was not included in this analysis. (v) We updated the information on all covariates at the time of incident depression. (vi) For CKD progression and MACE, we performed competing risk analyses accounting for death due to other causes with the Fine–Gray model [37]; (7) We examined the individual components of CKD progression and MACE separately.

All statistical analyses were performed using R software v.4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

The study population included 157 398 individuals with stages 3–5 CKD. At cohort entry, the median age was 75 years (IQR: 67–83), and 83 719 (53.2%) were women. Most (82.9%) individuals had an eGFR of 45–59 ml/min/1.73 m^2, 12.4% had an eGFR of 30–44 ml/min/1.73 m^2, and the remaining had an eGFR <30 ml/min/1.73 m^2. Comorbidities were common: 19.1% of patients had diabetes, 10.0% had a history of myocardial infarction, and 13.5% had a history of stroke. The prevalence of neuropsychiatric comorbidities was 4.7% for dementia and 4.4% for anxiety disorders (Table 1).

Over a median follow-up of 5.1 years (IQR: 2.3–8.5), 12 712 (8.1%) patients received an incident diagnosis of depression, corresponding to an incidence of 15.4 per 1000 person-years. Crude incidence of depression was similar across different levels of kidney function, which was 15.2, 17.5, and 16.7 per 1000 person-years among individuals with baseline eGFR of 45–59, 30–44, and <30 ml/min/1.73 m^2. Those who later developed depression were more likely to be female, had a lower socioeconomic profile, and had anxiety disorders at baseline (Table 1).

Incident depression and clinical outcomes

During the follow-up, a total of 634 471 hospitalizations (4 600 935 hospitalized days), 42 866 MACEs, and 66 635 deaths were

Table 1: Baseline characteristics of the study cohort.

Baseline characteristics	Overall (N = 157 398)	No depression (N = 144 686)	Incident depression (N = 12 712)
Age, years, median (IQR)	75 (67–83)	75 (67–83)	75 (68–82)
Female, *n* (%)	83 719 (53.2)	75 696 (52.3)	8023 (63.1)
Educational attainment, *n* (%)*			
Compulsory education	48 565 (32.0)	44 518 (31.9)	4047 (32.8)
Secondary education	60 946 (40.2)	55 901 (40.1)	5045 (40.9)
College/university	42 219 (27.8)	38 962 (28.0)	3257 (26.4)
Marital status, *n* (%)*			
Single	19 252 (12.2)	17 835 (12.3)	1417 (11.2)
Married	74 098 (47.1)	68 317 (47.3)	5781 (45.5)
Divorced	29 165 (18.5)	26 435 (18.3)	2730 (21.5)
Widowed	34 753 (22.1)	31 978 (22.1)	2775 (21.8)
Household disposable income, ×100 SEK, median (IQR)*	2486 (1504–4064)	2504 (1509–4113)	2307 (1444–3582)
eGFR category, ml/min/1.73 m^2, *n* (%)			
45–59	130 461 (82.9)	119 669 (82.7)	10 792 (84.9)
30–44	19 591 (12.4)	18 101 (12.5)	1490 (11.7)
15–29	5693 (3.6)	5345 (3.7)	348 (2.7)
<15	1653 (1.1)	1571 (1.1)	82 (0.6)
Albuminuria category, mg/g, *n* (%)			
<30	49 185 (73.5)	45 283 (73.4)	3902 (74.7)
30–299	13 320 (19.9)	12 370 (20.1)	950 (18.2)
≥300	4392 (6.6)	4020 (6.5)	372 (7.1)
Missing	90 501	83 013	7488
Healthcare use in the previous year, *n* (%)			
Any hospitalization	57 164 (36.3)	52 585 (36.3)	4 579 (36.0)
Any emergency department visit	20 855 (13.2)	19 236 (13.3)	1619 (12.7)
Nursing home care, *n* (%)	5198 (3.3)	5040 (3.5)	158 (1.2)
Physical comorbidities, *n* (%)			
Obesity	9165 (5.8)	8348 (5.8)	817 (6.4)
Hypertension	117 296 (74.5)	107 683 (74.4)	9613 (75.6)
Diabetes mellitus	30 087 (19.1)	27 630 (19.1)	2457 (19.3)
Myocardial infarction	15 803 (10.0)	14 636 (10.1)	1167 (9.2)
Stroke	21 226 (13.5)	19 415 (13.4)	1811 (14.2)
Congestive heart failure	25 072 (15.9)	23 245 (16.1)	1827 (14.4)
Peripheral vascular disease	10 343 (6.6)	9493 (6.6)	850 (6.7)
Malignancy excluding nonmelanoma skin cancer	32 521 (20.7)	30 271 (20.9)	2250 (17.7)
Lung disease	23 360 (14.8)	21 285 (14.7)	2075 (16.3)
Liver disease	3153 (2.0)	2909 (2.0)	244 (1.9)
Thyroid disease	16 950 (10.8)	15 337 (10.6)	1613 (12.7)
Neuropsychiatric comorbidities, n (%)			
Dementia	7448 (4.7)	7162 (5.0)	286 (2.2)
Psychotic disorders	1778 (1.1)	1635 (1.1)	143 (1.1)
Manic episode/bipolar disorder	866 (0.6)	765 (0.5)	101 (0.8)
Anxiety disorders	6988 (4.4)	5844 (4.0)	1144 (9.0)
Tobacco-related disorders, n (%)	4534 (2.9)	4140 (2.9)	394 (3.1)
Alcohol-related disorders, n (%)	6028 (3.8)	5395 (3.7)	633 (5.0)

Abbreviations: IQR, interquartile range; SEK, Swedish Krona.
*Missing data for each of the following: educational attainment *n* = 5668; marital status *n* = 130; household disposable income *n* = 130.

recorded. We identified 9795 individuals meeting the criteria of CKD progression. The rate of hospitalized days, CKD progression, and MACE, as well as the mortality rate was higher after a depression diagnosis was made (Table 2). After adjusting for potential confounders, depression remained associated with an elevated rate of hospitalized days (RR: 1.77, 95% CI: 1.71–1.83), as well as an increased hazard of CKD progression (HR: 1.38, 95% CI: 1.28–1.48), MACE (HR: 1.22, 95% CI: 1.18–1.27), and all-cause mortality (HR: 1.41, 95% CI: 1.37–1.45).

The associations for hospitalized days, MACE, and all-cause mortality were more evident within the first year after depression diagnosis, yet remained significant beyond 1 year (Table 3). On the contrary, the association between depression and CKD progression was only significant after 1 year of follow-up (HR: 1.47, 95% CI: 1.36–1.59). The associations between incident depression and clinical outcomes were stronger for single-episode depression than recurrent depression (Supplementary Table S3), and were stronger for depression diagnosis from specialist care than primary care (Supplementary Table S4). The associations were consistently observed in individuals with or without albuminuria measurements, and appeared to be stronger in those with albuminuria A1, compared with albuminuria A2/A3 (Supplementary Table S5).

In the subgroup analyses, the associations of incident depression with hospitalized days, MACE, and all-cause mortality were stronger in patients of male sex, with eGFR

Table 2: Association between incident depression and clinical outcomes.

	No depression period		Depression period				
	No. of events	Incidence rate (per 1000 person-years)	No. of events	Incidence rate (per 1000 person-years)	Crude RR/HR* (95% CI)	Adjusted RR/HR* (95% CI)	$P_{interaction}$
Hospitalized days							
Overall	4 177 673	5073.9	423 262	8445.8	1.46 (1.41–1.51)	1.77 (1.71–1.83)	
Men	1 998 097	5345.7	164 498	9889.7	1.64 (1.55–1.74)	1.92 (1.82–2.03)	<0.001
Women	2 179 576	4847.9	258 764	7728.5	1.38 (1.31–1.44)	1.68 (1.61–1.75)	
CKD progression							
Overall	9011	12.5	784	19.1	1.44 (1.34–1.55)	1.38 (1.28–1.48)	
Men	4747	14.6	309	23.1	1.49 (1.33–1.67)	1.35 (1.20–1.52)	0.602
Women	4264	10.7	475	17.1	1.52 (1.38–1.67)	1.39 (1.27–1.53)	
MACE							
Overall	40 193	54.0	2673	66.3	1.12 (1.08–1.17)	1.22 (1.18–1.27)	
Men	19 941	60.0	1045	83.3	1.33 (1.25–1.41)	1.31 (1.23–1.39)	0.024
Women	20 252	49.1	1628	58.6	1.10 (1.05–1.16)	1.17 (1.11–1.23)	
All-cause mortality							
Overall	61 221	74.4	5414	108.0	1.30 (1.27–1.34)	1.41 (1.37–1.45)	
Men	29 222	78.2	2196	132.0	1.55 (1.49–1.62)	1.52 (1.45–1.59)	<0.001
Women	31 999	71.2	3218	96.1	1.24 (1.20–1.29)	1.35 (1.30–1.40)	

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; RR, rate ratio.
*RR was reported for hospitalized days, and HR was reported for the other outcomes.
Model adjusted for age, year of cohort entry, sex, education, marital status, disposable income, eGFR, albuminuria, prior healthcare utilization, nursing home care, tobacco-related disorders, alcohol-related disorders, physical comorbidities (obesity, hypertension, diabetes mellitus, myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, malignancy excluding nonmelanoma skin cancer, lung disease, liver disease, thyroid disease), neuropsychiatric comorbidities (dementia, psychotic disorders, manic episode/bipolar disorder, anxiety disorders), and concurrent use of medications (ACEi/ARBs, β-blockers, calcium channel blockers, diuretics, antiplatelet drugs, statins, GLP–1 receptor agonists, SGLT2 inhibitors) at baseline.

Table 3: Association between incident depression and clinical outcomes within or beyond 1 year.

	No depression period	<1 year after incident depression			≥1 year after incident depression		
	Incidence rate (per 1000 person-years)	Incidence rate (per 1000 person-years)	Crude RR/HR* (95% CI)	Adjusted RR/HR* (95% CI)	Incidence rate (per 1000 person-years)	Crude RR/HR* (95% CI)	Adjusted RR/HR* (95% CI)
Hospitalized days	5073.9	12 806.0	1.45 (1.40–1.51)	1.77 (1.71–1.83)	7168.8	0.89 (0.86–0.93)	1.16 (1.12–1.20)
CKD progression	12.5	14.2	1.10 (0.93–1.29)	1.08 (0.91–1.27)	20.7	1.55 (1.43–1.68)	1.47 (1.36–1.59)
MACE	54.0	83.1	1.49 (1.39–1.60)	1.50 (1.39–1.61)	61.1	1.02 (0.97–1.06)	1.13 (1.08–1.19)
All-cause mortality	74.4	129.8	1.69 (1.61–1.78)	1.69 (1.60–1.78)	101.6	1.20 (1.16–1.24)	1.32 (1.28–1.37)

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; RR, rate ratio.
*RR was reported for hospitalized days, and HR was reported for the other outcomes.
Model adjusted for age, year of cohort entry, sex, education, marital status, disposable income, eGFR, albuminuria, prior healthcare utilization, nursing home care, tobacco-related disorders, alcohol-related disorders, physical comorbidities (obesity, hypertension, diabetes mellitus, myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, malignancy excluding nonmelanoma skin cancer, lung disease, liver disease, thyroid disease), neuropsychiatric comorbidities (dementia, psychotic disorders, manic episode/bipolar disorder, anxiety disorders), and concurrent use of medications (ACEi/ARBs, β-blockers, calcium channel blockers, diuretics, antiplatelet drugs, statins, GLP–1 receptor agonists, SGLT2 inhibitors) at baseline.

≥45 ml/min/1.73 m^2, and with hypertension ($P_{interaction} < 0.05$). Some of these associations were also stronger in the absence of CVD (myocardial infarction, stroke, and congestive heart failure) or anxiety disorders. The association between incident depression and CKD progression was generally similar across subgroups (Supplementary Figs S2–S5, see online supplementary material for color versions of these figures).

Sensitivity analyses

Among the study population, 93 152 individuals had another eGFR measurement <60 ml/min/1.73 m^2 between 3 months and 2 years apart, and the results after applying this chronicity criterion to identify the CKD cohort were consistent with the primary analyses (Table 4). When using alternative definitions of depression or updating covariates, depression was also robustly associated with adverse clinical outcomes.

In the competing risk analyses, incident depression was associated with CKD progression (subdistribution HR: 1.36, 95% CI: 1.26–1.46), but not with MACE (subdistribution HR: 1.01, 95% CI: 0.97–1.06) (Supplementary Table S6). We found a significant association between incident depression and each component of CKD progression (Supplementary Table S7). When investigating the individual components of MACE, incident depression was associated with an increased hazard of stroke (HR: 1.18, 95% CI: 1.11–1.25) and cardiovascular death (HR: 1.53, 95%

Table 4: Sensitivity analyses of the association between incident depression and clinical outcomes.

	No depression period		Depression period			
	No. of events	Incidence rate (per 1000 person-years)	No. of events	Incidence rate (per 1000 person-years)	Crude RR/HR* (95% CI)	Adjusted RR/HR* (95% CI)
Requiring two eGFR <60 ml/min/1.73 m^2 (3 months to 2 years apart) to define the study cohort (*N* = 93 152)						
Hospitalized days	2 506 525	5658.2	229 432	9504.2	1.63 (1.55–1.71)	1.72 (1.65–1.80)
CKD progression	6936	18.3	482	25.1	1.33 (1.21–1.45)	1.29 (1.18–1.42)
MACE	22 651	58.1	1436	75.9	1.17 (1.11–1.24)	1.27 (1.21–1.34)
All-cause mortality	38 479	86.9	3166	131.2	1.35 (1.30–1.40)	1.48 (1.42–1.53)
Using incident depression diagnosis or incident antidepressant prescription to define the exposure (*N* = 137 219)						
Hospitalized days	3 295 785	4745.9	635 194	7903.9	1.36 (1.32–1.40)	1.63 (1.59–1.67)
CKD progression	7505	12.3	1349	20.4	1.52 (1.43–1.61)	1.43 (1.35–1.52)
MACE	32 272	51.0	4921	77.1	1.28 (1.24–1.31)	1.32 (1.28–1.36)
All-cause mortality	45 372	65.3	11 647	144.9	1.82 (1.79–1.86)	1.84 (1.80–1.88)
Requiring two diagnostic codes from primary care/outpatient care or one diagnostic code from inpatient care to define the exposure (*N* = 157 398)						
Hospitalized days	4 285 240	5110.3	315 695	9038.2	1.59 (1.53–1.66)	1.94 (1.86–2.01)
CKD progression	9225	12.6	570	20.2	1.52 (1.40–1.65)	1.44 (1.32–1.57)
MACE	41 022	54.2	1844	66.4	1.13 (1.08–1.18)	1.25 (1.19–1.31)
All-cause mortality	62 756	74.8	3879	111.1	1.34 (1.30–1.39)	1.45 (1.41–1.50)
Moving forward the date of incident depression by one year (*N* = 157 398)						
Hospitalized days	4 052 240	4988.3	548 695	8974.5	1.13 (1.09–1.17)	1.47 (1.42–1.52)
CKD progression	8865	12.5	930	18.1	1.38 (1.29–1.47)	1.33 (1.24–1.42)
MACE	39 357	53.6	3509	70.2	1.21 (1.17–1.26)	1.30 (1.25–1.34)
Updating all the covariates at the time of incident depression (*N* = 157 398)						
Hospitalized days	4 177 673	5073.9	423 262	8445.8	1.46 (1.41–1.51)	1.47 (1.40–1.55)
CKD progression	9011	12.5	784	19.1	1.44 (1.34–1.55)	1.49 (1.32–1.68)
MACE	40 193	54.0	2673	66.3	1.12 (1.08–1.17)	1.21 (1.14–1.29)
All-cause mortality	61 221	74.4	5414	108.0	1.30 (1.27–1.34)	1.25 (1.20–1.31)

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; RR, rate ratio.

*RR was reported for hospitalized days, and HR was reported for the other outcomes.

Model adjusted for age, year of cohort entry, sex, education, marital status, disposable income, eGFR, albuminuria, prior healthcare utilization, nursing home care, tobacco-related disorders, alcohol-related disorders, physical comorbidities (obesity, hypertension, diabetes mellitus, myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, malignancy excluding nonmelanoma skin cancer, lung disease, liver disease, thyroid disease), neuropsychiatric comorbidities (dementia, psychotic disorders, manic episode/bipolar disorder, anxiety disorders), and concurrent use of medications (ACEi/ARBs, β-blockers, calcium channel blockers, diuretics, antiplatelet drugs, statins, GLP–1 receptor agonists, SGLT2 inhibitors) at baseline.

CI: 1.46–1.60), but not with myocardial infarction (HR: 1.02, 95% CI: 0.95–1.11) (Supplementary Table S8).

DISCUSSION

In this large population-based cohort of patients with stages 3–5 CKD not receiving dialysis, incident depression was associated with increased morbidity (including hospitalization, CKD progression, and MACE) and mortality, independent of a range of covariates including socio-demographics, kidney disease severity, and comorbidities. The rates of hospitalization, MACE, and all-cause mortality were higher within the first year following depression diagnosis, whereas the association with CKD progression was more evident beyond 1 year of follow-up.

A few previous studies have demonstrated a positive association between depression and CKD progression [17, 23–25], whereas others have not [22, 27]. There is notable heterogeneity in the definition of CKD progression across studies, where dialysis initiation was the most often used kidney endpoint, with a HR estimate ranging from 1.1 to 3.5. In addition, Tsai *et al.* found that participants with higher depressive symptoms experienced more rapid kidney function decline [23], which yet was not supported by another study in older patients with advanced CKD [27]. Our study yielded significant estimates for three single kidney outcomes that manifest different degrees of disease progression, with a 38% increased rate for >40% decline in eGFR, 32% for initiation of KRT, and 84% for death due to CKD. Furthermore, this association only became significant after 1 year of depression diagnosis, suggesting that depression has a long-lasting influence on CKD progression. There are several possible explanations for our observed association. First, depression may directly influence kidney function through inflammatory and immune–metabolic pathways [14, 15]. It has been shown that elevated levels of inflammatory biomarkers are related to faster eGFR decline and CKD progression [38]. Second, depression is associated with cardiovascular and cerebrovascular disease, which are further risk factors for CKD progression [39]. Third, depression is linked to unfavorable changes in social, lifestyle, and medical behaviors, which can accelerate decline in kidney function [40, 41]. A Mendelian randomization study supports a causal link between depressive symptoms and kidney health [42]. Alternatively, depression could serve as a risk marker for poor health condition that is undetected.

Our finding of associations between depression and a higher rate of all-cause hospitalization and all-cause mortality is in line with most, but not all, existing literature [17, 18, 20–27].

Prior studies generally had small sample sizes with low statistical power to detect a significant association between depression and mortality. One notable exception was a study of almost 0.6 million US veterans with stages 1–5 CKD by Balogun *et al*., who found depression to be associated with a 25% increased mortality rate [20], in comparison with a 41% increase in the present study. In addition, the associations were stronger for those with more severe or complicated depression who were treated in specialist care. With the already high mortality risk, if this association proves to be causal, excess deaths due to depression would be considerable in patients with CKD. Moreover, we observed that the associations of depression with hospitalization and mortality were more evident in men and in patients with eGFR $\geq$45 ml/min/1.73 m^2. This sex difference has been previously reported [27], besides biological pathways, it may also be attributed to psychosocial aspects. For example, men are less likely to report mild depressive symptoms and have fewer help-seeking behaviors [43]. The stronger association among patients with less severe CKD is in line with one previous study [20], and it is possibly because the effect of chronic illness burden in those with poorer health overshadows the effect of depression. Another explanation might be our exclusion of patients with pre-existing depression, which was more common in those with advanced CKD. This finding has clinical and public health relevance, since it could potentially represent a unique opportunity for treating depression at early stages of CKD.

A limited number of studies among dialysis patients have reported mixed results for the association between depression and cardiovascular events [4, 9, 44, 45]. Our study showed that depression was associated with a 22% higher rate of MACE, even in patients with stages 3–5 CKD. This is of particular importance as the risk of developing CVD surpasses the risk of reaching ESKD in patients with CKD [28]. Additionally, our analysis of the individual components of MACE suggested that depression was associated with an increased rate of stroke and cardiovascular death. Depression may contribute to the risk of stroke through several plausible mechanisms: first, depression could lead to biological alterations, such as dysregulation of sympathetic nervous system and activation of pro-inflammatory cytokines [46], which could influence subsequent stroke risk. Second, depression is associated with unhealthy behaviors, such as poor diet, physical inactivity, and nonadherence to medication treatment [11, 12], which in turn are established risk factors for stroke. Third, the "vascular depression" hypothesis proposes that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes [47]. The magnitude of the depression–stroke association observed in this study (adjusted HR: 1.18, 95% CI: 1.11–1.25) is lower than that from a meta-analysis of studies in the general population (pooled HR: 1.45, 95% CI: 1.29–1.63) [48]. However, considering the high prevalence of depression in CKD patients who are particularly susceptible to stroke [49], excess burden related to depression should not be neglected.

The complex interplay between mental health and kidney disease is likely driven by the combined effect of biological, behavioral, and psychosocial factors [50]. Although the underlying mechanisms remain to be clarified, it is clinically important to recognize and manage depression in patients with early stages of CKD. However, current evidence base for treatment of depression in the CKD population is limited [51]. Recent clinical trials found that sertraline versus placebo did not significantly improve depressive symptoms in patients with CKD [52], or patients undergoing hemodialysis [53]. Whether antidepressant treatment will influence the clinical outcomes in this population is largely unknown. On the other hand, multimorbidity and polypharmacy commonly present in patients with CKD may predispose them to the potential risk of drug–disease and drug–drug interactions. Observational studies have documented several adverse health outcomes associated with long-term use of selective serotonin reuptake inhibitors in patients with CKD, such as hip fracture, gastrointestinal bleeding, and sudden cardiac death due to QT prolongation [54–56]. Further studies on the risks and benefits of antidepressant treatment in patients with early to end-stage CKD are needed.

A strength of this study is the large and information-rich sample of patients with CKD covering the complete universal tax-funded healthcare of the region. The main limitation in the interpretation of our study is its observational nature, which means that residual/unmeasured confounding and reverse causality cannot be completely ruled out, and thus we are unable to prove causality. Some important lifestyle factors (e.g. smoking, alcohol drinking, and obesity), which could serve as either confounders or mediators, cannot be fully accounted for in the present study, although we used proxy measures derived from clinical consultations. Second, there were unavoidable measurement errors in identification of CKD patients from health registers, as well as ascertainment of depression and timing of its onset by clinical diagnosis. A Danish register study found that laboratory-based algorithms produced CKD cohorts with similar prognosis [57]. Previous research showed that defining depression using administrative data had moderate sensitivity and high specificity, with greater validity for moderate/severe depression [58, 59]. Nevertheless, we performed sensitivity analyses attempting to quantify the extent of these systematic errors and observed similar significant associations. Third, in a predominantly elderly and frail population, non-GFR determinants such as low muscle mass may affect the validity of our creatinine-based eGFR estimations. Albuminuria was available in less than half of the study cohort and could be tested by indications, but we obtained consistent results among those with/without albuminuria testing. Fourth, despite our consideration of the type, severity, and duration of depression, the full course of illness cannot be captured by our study. Longitudinal studies with repeated measures can more robustly assess the relationships. Fifth, the Cox proportional hazards models were used in our primary analyses. In case of nonproportionality, the HR could be interpreted as a weighted average of the time-varying HRs throughout the follow-up [60]. Finally, CKD patients included in our analysis overrepresented older adults, and may not be representative of younger populations. Our data reflect routine care in the Stockholm region, Sweden, and generalization to other settings should be made with caution.

To conclude, this study shows that incident depression is associated with poor prognosis among patients with nondialysis-dependent CKD, including hospitalization, CKD progression, MACE, and all-cause mortality. Excess morbidity and mortality related to depression highlights the need for appropriate management of depression in these patients. Future studies are warranted to elucidate the underlying mechanisms, and to investigate the risks and benefits of antidepressant treatment in CKD patients.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

N.Z., Z.C., and J.J.C. designed the study. N.Z. and S.V. analyzed the data. N.Z. wrote the manuscript. S.V., H.X., J.J.C., and Z.C. were involved in the critical revision of the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data will be available for collaborative research under reasonable request and fulfillment of GDPR regulations. For inquiries, please send your proposal to the Steering Committee of the SCREAM project (E-mail: juan.jesus.carrero@ki.se).

CONFLICT OF INTEREST STATEMENT

J.J.C. has been a consultant, speaker, or grant recipient for Abbott, Nestle, Bayer, Amgen, Astra–Zeneca, MSD, Fresenius, Fresenius Kabi and ViforPharma, for topics unrelated to this work. All remaining authors declare no conflicts of interest.

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