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Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients With Diabetes With Comorbid Depression

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OBJECTIVE

It is not known if patients with diabetes with depression have an increased risk of chronic kidney disease (CKD). We examined the association between depression and incident CKD, mortality, and incident cardiovascular events in U.S. veterans with diabetes.

RESEARCH DESIGN AND METHODS

Among a nationally representative prospective cohort of >3 million U.S. veterans with baseline estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2, we identified 933,211 patients with diabetes. Diabetes was ascertained by an ICD-9-CM code for diabetes, an HbA_{1c} >6.4%, or receiving antidiabetes medication during the inclusion period. Depression was defined by an ICD-9-CM code for depression or by antidepressant use during the inclusion period. Incident CKD was defined as two eGFR levels <60 mL/min/1.73 m^2 separated by ≥90 days and a >25% decline in baseline eGFR. The associations between depression and outcomes were assessed using Cox proportional regression.

RESULTS

Depression was present in 340,806 patients at enrollment. Depressed patients were younger (61 ± 11 vs. 65 ± 11 years), had higher eGFR (84 ± 15 vs. 81 ± 14 mL/min/1.73 m^2), but had more comorbidities. Incident CKD developed in 180,343 patients. Depression was associated with 20% higher risk of incident CKD (adjusted hazard ratio [aHR] and 95% CI: 1.20 [1.19–1.21]). Similarly, depression was associated with increased all-cause mortality (aHR and 95% CI: 1.25 [1.24–1.26]).

CONCLUSIONS

The presence of depression in patients with diabetes is associated with higher risk of developing CKD compared with nondepressed patients. Intervention studies should determine if effective treatment of depression in patients with diabetes would prevent major renal and cardiovascular complications.

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Diabetes affected 29.1 million people or 9.3% of the population in the U.S. alone in 2012 (1), and its prevalence has also reached epidemic levels globally (2,3). Diabetic kidney disease is the leading cause of renal failure in the U.S. (4), and it accounts for ~50% of end-stage renal disease cases in the developed world (5). Diabetes is also strongly associated with atherosclerotic cardiovascular disease (CVD) (6), which is the primary cause of death in patients with diabetes (7). The estimated total economic cost of diabetes and diabetes-related complications has increased by 41% from $174 billion in 2007 to $245 billion in 2012 in the U.S. (8).

Similar to other chronic medical conditions, diabetes often coexists with mental health problems, primarily depression, distress, and anxiety (3,9–11). There is compelling evidence for a bidirectional relationship between diabetes and depression (12,13). Depressed adults are more likely to develop type 2 diabetes (14,15). In contrast, depression is twice as common in patients with previously diagnosed type 2 diabetes compared with subjects without diabetes, occurring in ~20% of patients with prevalent diabetes (16). The prevalence of depression is significantly higher in women with diabetes than in men with diabetes, although this difference may vary depending on assessment methods and health care settings (16).

Comorbid depression in patients with diabetes is important because of its association with negative psychosocial outcomes and negative health behaviors, such as decreased self-efficacy (17) and suboptimal adherence to diabetes treatment plans and lifestyle changes concerning diet, exercise, and smoking (18–20). Research indicates that depression contributes to suboptimal metabolic control (21), mediated in part by diabetes-specific emotional distress (10,22). Furthermore, the presence of depression in diabetes has been linked to advanced diabetes-related complications (23), greater functional impairment (24), more frequent intensive care unit admissions (25), and increased cardiac and all-cause mortality (26–28). In turn, it is suggested that frequent hyperglycemia, the presence of diabetes complications, and comorbid conditions are associated with increased risk of depression (29).

The primary aim of our study was to examine if the presence of medically diagnosed and/or treated depression in patients with previously diagnosed diabetes predicts incident chronic kidney disease (CKD) in a large national database. We also wanted to assess the association of medically diagnosed and/or treated depression with incident macrovascular complications and mortality in this patient population.

RESEARCH DESIGN AND METHODS

Study Setting and Cohort Definition

The institutional review committees at the Memphis and Long Beach Veterans Affairs Medical Centers approved the study. Data were obtained from the Racial and Cardiovascular Risk Anomalies in CKD (RCAV) study, which examines risk factors in patients with incident CKD in U.S. veterans and has previously been described in detail (30,31). Diabetes and depression were identified from the Veterans Affairs (VA) Inpatient and Outpatient Medical SAS Datasets using ICD-9-CM diagnostic and procedure codes (32). The algorithm for cohort definition is shown in Supplementary Fig. 1. Patients were included in the RCAV cohort if they had a baseline estimated glomerular filtration rate (eGFR) $\geq$60 mL/min/1.73 m^2 at the first encounter in the inclusion period (1 October 2004 to 30 September 2006); other comorbidities were listed at the time of that encounter. The final cohort for this study included 933,211 patients with diabetes from the original RCAV cohort.

Exposure and Covariates

Diabetes was ascertained using ICD-9-CM codes for diabetes (250.x), receiving any type of oral antidiabetes or insulin treatment, or having at least one measured hemoglobin A1c >6.4% (46 mmol/mmol) during the inclusion period. Depression was defined using ICD-9-CM codes for depression (296.x) or receiving any type of antidepressant medication during the inclusion period. Posttraumatic stress disorder (PTSD) was defined using ICD-9-CM code 309.81. We also performed sensitivity analyses when depression was defined only as an ICD-9-CM code for depression during the inclusion period. All medication use (antidepressants, statins, and antihypertensives) has been defined by specific codes used by the VA pharmacy database. This database uses unique and specific codes that categorize all medications by their pharmacologic category and mechanism of action.

Sociodemographic characteristics, comorbid conditions and laboratory characteristics were obtained, as previously described (30–34). Information about age, sex, and race were obtained through the VA Corporate Data Warehouse and from Medicare through the VA-Medicare data merge project (35). Information about comorbidities, incident clinical events, and conditions was collected from the VA Inpatient and Outpatient Medical SAS Datasets using ICD-9-CM diagnostic and procedure codes and Current Procedural Terminology codes as published previously (30,32). Prevalent comorbidities were defined as those diagnosed during 1 October 2004 to 30 September 2006.

Outcomes

We defined four different outcomes: *1*) incident CKD, *2*) all-cause mortality, *3*) incident coronary heart disease (CHD), and *4*) incident ischemic stroke. Incident CKD was defined as having two eGFR levels <60 mL/min/1.73 m^2 separated by $\geq$90 days after the enrollment period and a >25% decline from baseline eGFR (36). eGFR was calculated from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration equation (37). Data on all-cause mortality were obtained from the VA Vital Status Files, which contain dates of death or last medical/administrative encounter from all sources in the VA system with sensitivity and specificity of 98.3 and 99.8%, respectively, as compared with the National Death Index (38). Incident CHD was defined as the composite outcome of a first occurrence of an ICD-9-CM or Current Procedural Terminology code for acute myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention after 1 October 2006 in patients without such diagnoses prior to this date. Incident stroke was defined as the first occurrence of ICD-9-CM codes for ischemic stroke after 1 October 2006 in patients without such diagnoses prior to this date.

Statistical Analysis

Data were summarized using proportions, means $\pm$ SD, or median (interquartile range) as appropriate. Continuous variables were compared using the Student *t* test and Mann-Whitney *U* test for

normally distributed and skewed variables, respectively. Predictors of depression were assessed using logistic regression analyses. The associations between depression and outcomes were assessed using the Kaplan-Meier curves and Cox proportional hazard models. The start of the follow-up period for mortality and incident CKD was the date of the first eGFR $\geq$60 mL/min/1.73 m^2 between 1 October 2004 to 30 September 2006. Patients were followed until different end points developed, censoring at the date of last health care or administrative visit, or on 26 July 2013 (end of the study period). Incident CHD and stroke events were identified after 1 October 2006 in patients without such diagnoses prior to this date; therefore, to ensure that only incident events are recorded and avoid immortal time bias, the start of the follow-up period for these end points was 1 October 2006.

All associations were examined in both unadjusted and adjusted models. Models were adjusted for the following confounders based on a priori considerations: model 1: age, sex, and race/ethnicity; model 2: model 1 variables and baseline eGFR; model 3: model 2 variables and comorbidities at baseline (hypertension, CVD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, lung disease, dementia, rheumatic disease, malignancy, HIV/AIDS, and PTSD) and the use of statins and antihypertensive medications; and model 4: model 3 variables and BMI and serum albumin level. The final multivariable model 4 analyses were repeated in different a priori selected subgroups. We repeated all analyses in a cohort of patients in whom the depression diagnosis was based on the above-mentioned ICD-9 codes only. Finally, we analyzed the association between baseline depression and mortality, incident stroke, and CHD separately in patients who maintained eGFR $\geq$60 mL/min/1.73 m^2 versus in patients who developed incident CKD during the follow-up period. Statistical analyses were performed using Stata MP version 12 (Stata Corporation, College Station, TX).

RESULTS

Baseline Characteristics

Baseline characteristics of the cohort are shown in Table 1 and Supplementary Table 1. More than 340,000 (37%) patients had depression at baseline. Patients with depression were younger (61 $\pm$ 11 vs. 65 $\pm$ 11 years), were more likely to be divorced (28 vs. 21%), had higher baseline eGFR (84 $\pm$ 15 vs. 81 $\pm$ 14 mL/min/1.73 m^2), and had more comorbidities at baseline. The median follow-up varied for the various outcomes, and it was 2,659, 2,916, 2,451, and 2,453 days for incident CKD, mortality, CHD, and stroke, respectively.

Table 1—Baseline characteristics of study population grouped according to the presence or absence of depression at baseline

	Total population (933,211)	Depression (*n* = 340,806)	No depression (*n* = 592,405)
Age, years	64 $\pm$ 11	61 $\pm$ 11	65 $\pm$ 11
Sex (male), *n* (%)	901,958 (97)	324,321 (95)	577,637 (97)
Baseline eGFR (mL/min/1.73 m^2)	82 $\pm$ 15	84 $\pm$ 15	81 $\pm$ 14
BMI (kg/m^2)	31 $\pm$ 5	31 $\pm$ 6	31 $\pm$ 5
Serum albumin (g/L)	40.2 $\pm$ 4.5	39.8 $\pm$ 4.8	40.4 $\pm$ 4.3
Income (USD)	23,389 (12,354–34,263)	22,240 (11,953–31,480)	24,043 (12,630–38,760)
Race, *n* (%)			
White	665,100 (77)	253,793 (78)	411,307 (76)
African American	153,515 (18)	56,095 (17)	97,420 (18)
Hispanic	25,541 (3)	9,567 (3)	15,974 (3)
Other race	19,828 (2)	6,925 (2)	12,903 (2)
Marital status, *n* (%)			
Married	541,271 (60)	182,537 (56)	358,734 (62)
Single	67,947 (8)	26,833 (8)	41,114 (7)
Divorced	211,508 (23)	92,302 (28)	119,206 (21)
Widow	79,771 (9)	25,235 (8)	54,536 (9)
Service connection, *n* (%)	400,757 (43)	182,630 (54)	218,127 (37)
Comorbidities, *n* (%)			
CVD	167,682 (18)	69,261 (20)	98,421 (17)
CHF	77,986 (8)	35,931 (10)	42,055 (7)
Hypertension	749,696 (80)	276,708 (81)	472,988 (80)
Cerebrovascular disease	83,282 (9)	38,093 (11)	45,189 (8)
Peripheral arterial disease	87,693 (9)	38,240 (11)	49,453 (8)
Chronic lung disease	185,012 (20)	89,470 (26)	95,542 (16)
Dementia	10,363 (1)	6,670 (2)	3,693 (0.6)
Rheumatologic disease	13,086 (1)	5,938 (2)	7,148 (1)
Peptic ulcer	18,643 (2)	8,781 (3)	9,862 (2)
Mild/severe liver disease	15,399 (2)	8,510 (2)	6,889 (1)
Hemiplegia	5,053 (0.5)	2,939 (0.9)	2,114 (0.4)
All malignancies	108,029 (12)	40,366 (12)	67,663 (11)
AIDS/HIV	3,486 (0.3)	1,837 (0.5)	1,649 (0.3)
PTSD	96,918 (10)	83,365 (24)	13,553 (2)
Statin use	191,691 (21)	70,520 (21)	121,171 (20)
Antihypertensive medication use	517,298 (55)	193,203 (57)	324,095 (55)

CHF, congestive heart failure; USD, U.S. dollars.

Predictors of the Presence of Depression

In a multivariable logistic regression model (Supplementary Table 2), several baseline characteristics, such as female sex, African American race, lower income, being unmarried, and the presence of comorbidities were all significantly associated with baseline depression. In a sensitivity analysis, we tested the same model with depression (as the dependent variable) being defined by ICD-9 codes only (n = 84,912), and the model yielded qualitatively similar results (not shown).

Incident CKD

During the follow-up period, 180,343 patients developed incident CKD (19%; event rate: 32.7; [95% CI 32.6–32.9]/1,000 patient-years). Patients with depression had a significantly higher risk of developing CKD (21%; event rate: 36.3 [95% CI 36.1–36.6]/1,000 patient-years) compared with nondepressed patients (18%; event rate: 30.7 [95% CI 30.5–30.9]/1,000 patient-years) (Fig. 1*A*). Figure 2 shows the results of multivariable adjusted Cox proportional hazard models assessing the association of depression with outcomes. The presence of depression was associated with an unadjusted hazard ratio of 1.19 (95% CI 1.18–1.21) for developing incident CKD. This association was robust following sequential adjustments for an expanding set of covariates. In the final model (Model 4), the hazard ratio for incident CKD was 1.18 (95% CI 1.17–1.20) in patients with versus without depression. Similar associations were found in all subgroups (Supplementary Fig. 2).

Mortality

During the follow-up period, 253,763 patients died (27%; mortality rate: 39.8 [95% CI 39.6–39.9]/1,000 patient-years). Patients with (29%; mortality rate: 42.6 [95% CI 42.4–42.9]/1,000 patient-years) versus without depression (26%; mortality rate: 38.1 [95% CI 37.9–38.3]/1,000 patient-years) had significantly higher mortality (Fig. 1*B*). In the final multivariable adjusted Cox model (Model 4), the hazard ratio for mortality was 1.30 (95% CI: 1.28–1.31) in patients with versus without depression (Fig. 2). Depression was associated with higher mortality in most subgroups, except among patients with very low (<25 g/L) serum albumin (Supplementary Fig. 3).

Incident Cardiovascular Events

During the follow-up period, 40,016 patients had an incident CHD event (4.5%, event rate 8.1 [95% CI 8.0–8.2]/1,000 patient-years). In addition, 25,729 patients had an incident stroke event (3%, stroke rate: 5.2 [95% CI 5.1–5.3]/1,000 patient-years). Depression was associated with an increased risk for both CHD events (10.3 [95% CI 10.2–10.5]/1,000 patient-years vs. 6.9 [95% CI 6.8–7.0]/1,000 patient-years) and stroke (6.4 [95% CI 6.3–6.6]/1,000 patient-years vs. 4.5;

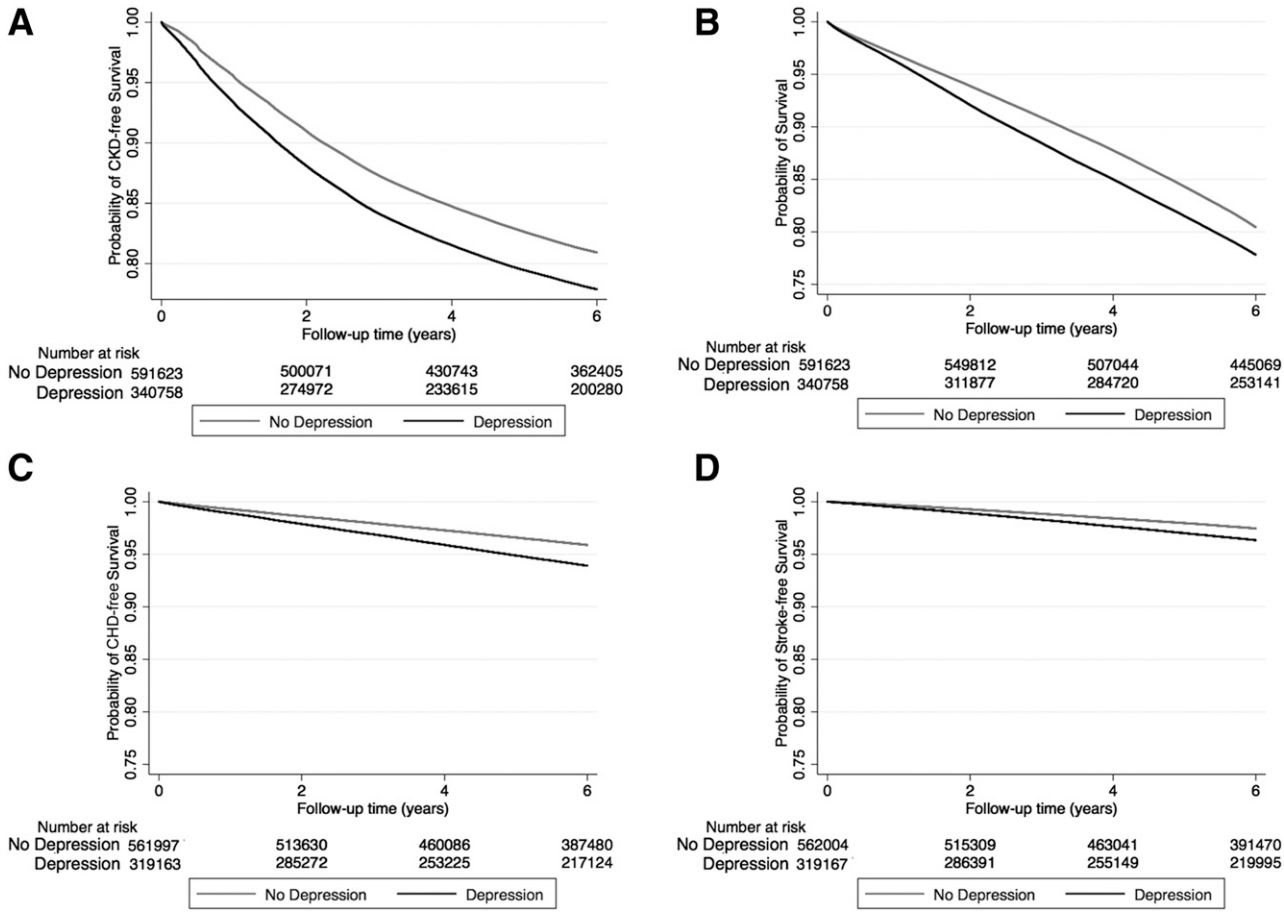

Figure 1—Kaplan-Meier curves showing the association between the presence of depression at baseline and incident CKD (*A*), all-cause mortality (*B*), incident CHD (*C*), and incident stroke (*D*) in the study cohort.

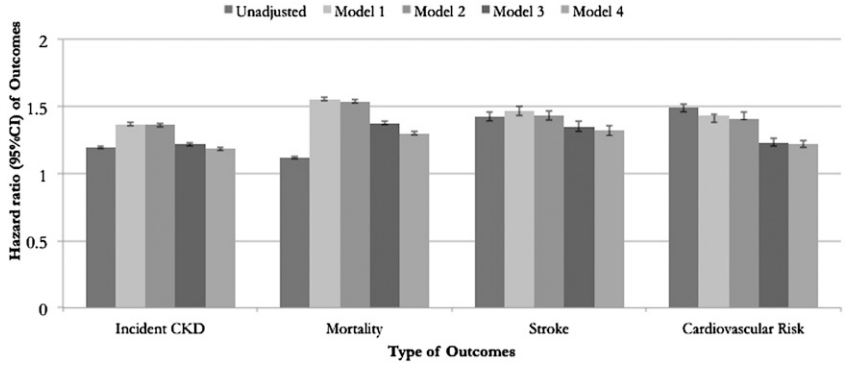

Figure 2—Associations of the presence of depression at baseline with various outcomes in the cohort of veterans with diabetes. Patients without depression at baseline served as reference. Model 1: age, sex, and race/ethnicity; model 2: model 1 variables, marital status, and baseline eGFR; model 3: model 2 variables and comorbidities at baseline (hypertension, CVD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, lung disease, dementia, rheumatic disease, malignancy, HIV/AIDS, and PTSD) and the use of statins or antihypertensive medications; and model 4: model 3 variables and BMI and serum albumin level.

95%CI [4.4–4.6]/1,000 patient-years) (Fig. 1*C* and *D*, respectively). The relative hazard for both CHD events (1.22 [95% CI 1.19–1.24]) and stroke (1.32 [95% CI 1.28–1.36]) remained significantly higher in the final multivariable adjusted Cox models (model 4) (Fig. 2). The association of depression with incident CHD and stroke, respectively, remained qualitatively similar in all subgroups (not shown).

Sensitivity Analyses

The association between baseline depression and mortality, incident stroke, and CHD was significant both in patients who maintained eGFR $\geq$60 mL/min/1.73 m^2 and in patients who developed incident CKD during the follow-up period. However, the hazard ratios associated with depression were lower in the incident CKD group for all outcomes, respectively (Supplementary Table 3). The association of depression with incident CKD, CHD, and stroke, respectively, remained qualitatively similar in sensitivity analyses in which the depression diagnosis was based on the above-mentioned ICD-9 codes only (not shown).

CONCLUSIONS

In a large cohort of U.S. veterans with diabetes and eGFR $\geq$60 mL/min/1.73 m^2, we demonstrated that the presence of depression is associated with higher risk of incident CKD. We also showed that comorbid depression is associated with higher all-cause mortality, incident cardiac events, and incident stroke in this cohort. Importantly, these associations remained significant after extensive adjustment for potential sociodemographic and clinical covariates and were also consistently seen in subgroup analyses.

The presence of depression in individuals with diabetes is associated with increased risk of incident retinopathy, another microangiopathic complication of diabetes (39). In a previous report, clinically significant depression symptoms were associated with microalbuminuria but not with decline in eGFR in a cohort of subjects with diabetes (40). In a smaller cohort, Chiang et al. (41) reported that depression symptoms at baseline could independently predict the risk of dialysis initiation in patients with CKD. Together, our current findings and these previous results strongly suggest that comorbid depression represents an augmented renal risk for patients with diabetes.

Similarly to previous publications (26–28,42–44), we found that comorbid depression was associated with a higher risk of all-cause mortality. Previous studies (26,44) and a recent meta-analyses (27) reported higher hazard ratios for mortality compared with our results. These differences could potentially be explained by the different definitions of depression and also the significantly different patient populations. Our cohort consisted of mainly middle-aged or elderly males with a high comorbidity burden and cardiovascular risk. These characteristics may render the relative contribution of depression to the overall mortality risk smaller. Compatible with this assumption is our finding that depression was not associated with mortality in the subgroup of patients with very low serum albumin. It is likely that those patients have a substantially higher baseline mortality risk, presumably due to advanced illness or very high comorbidity burden. The relative contribution of depression to the risk of mortality among those patients, therefore, became negligible. On the contrary, the hazard ratio for mortality in depressed versus nondepressed participants was considerably higher in younger individuals ($<$50 years) compared with older participants. It is likely that baseline mortality risk is lower in those individuals and the relative contribution of depression becomes more prominent. In addition, our sample consisted mainly of males and previous studies suggested that the contribution of depression to chronic disease outcomes might be stronger in women due to differential coping mechanisms (45).

Baseline depression was associated with a 32% increase in the hazard of incident stroke during the follow-up period. This finding is also consistent with results published in several recent reports (23,28,46). Interestingly, pre-existing depression has been a consistent risk factor for ischemic stroke in the general population according to a recent meta-analysis (47). The hazard ratio of ischemic stroke for depressed versus nondepressed patients in all of those studies was quite similar to our findings.

It is important to note, however, that the assessment of depression was quite variable across all of those studies, and it was different from the method used to define depression in our cohort. Most previous studies used self-report of depressive symptoms to define "depression," with the majority of the studies using either the Center for Epidemiological Studies Depression or the Patient Health Questionnaire-9 instruments. In contrast, we relied on administrative records of the medical diagnosis of depression or the use of antidepressant medications. Given these differences, it is remarkable that the prevalence of depression in our cohort was similar to what was reported by many of the cited studies. More advanced age and higher comorbidity burden in our cohort may explain the relatively high prevalence of depression. Future research will need to consider the potential impact of assessing specific depression profiles and constructs

and also the severity of depression on the association between depression and health outcomes in patients with diabetes (10).

We defined depression in this study based on administrative records of the medical diagnosis of depression or the use of antidepressant medications. Consequently, the majority of the patients with depression at baseline were prescribed antidepressant treatment. We did not have data about the proportion of patients who received psychotherapy or about the effect of the antidepressant treatment. In other words, we do not know the severity of depressive symptoms our patients experienced at the time of enrollment in our cohort or the amount of time those symptoms were present in the depressed group. It has been repeatedly documented that clinical care provided to patients with mood disorders varies significantly, with patients too often receiving suboptimal doses of antidepressant medications for insufficient periods of time (48). Therefore, it is quite possible that many of the patients who had been prescribed antidepressants were still depressed. Well-designed, treatment-to-target interventional studies will be needed to determine if effectively treating depression in patients with diabetes will reduce micro- and macrovascular complications.

The underlying mechanisms linking depression to higher risk of diabetic complications are likely to be multifactorial. Comorbid depression was shown to impair the ability to perform self-care (18), and it is also reportedly associated with obesity and lack of physical exercise (49). Other potential mechanisms may include a higher level of low-grade systemic inflammation, activation of the hypothalamic–pituitary–adrenal axis (increased cortisol secretion) and activation of the sympathetic nervous system, which have all been frequently reported in association with depression (11,50,51). These factors may lead to a higher incidence and more rapid progression of diabetic vascular complications. Importantly, the same factors may also contribute to the development and progression of diabetic kidney disease; therefore, it seems plausible that patients with diabetes with depression would be at a higher risk for diabetic nephropathy. Although our results are compatible with this proposed model, our data set did not allow for assessing potential mediators of the observed association between depression and outcomes.

Regardless of the underlying mechanisms, the association between depression and medical outcomes in patients with diabetes is clinically important because it points to the possibility of improving outcomes through managing depression, in addition to focusing on treatment of diabetes. In fact, recent randomized trials and a recent systematic review demonstrated that collaborative care models that aimed at treating depression and diabetes improved both mental health and disease control, as well (52–55).

Our study is notable for its large sample size and event numbers and for being representative of veterans with diabetes who received care in the VA system across the entire U.S. To our knowledge, this is the largest study to assess the associations between a diagnosis of comorbid depression and incident CKD in patients with diabetes. This study also has several limitations that need to be acknowledged. Because this is an observational study, we can only report associations, and we cannot claim that depression was indeed the cause of the worse clinical outcomes. Furthermore, although we adjusted our multivariable models for an extensive set of potential confounders, we cannot rule out residual confounding. Our study is also limited by the use of diagnostic codes and utilization of antidepressants to define depression and also to define cardiovascular outcomes (CHD and stroke). The sensitivity and specificity of these codes in ascertaining these conditions is not known, and it is likely lower than prospective adjudication of clinical diagnoses. However, the significant correlates of baseline depression in our study were similar to those found in previous studies. In addition, some antidepressants may have been prescribed for diagnoses other than depression. Because we used medication use to define depression, we cannot determine if the adverse outcomes were a result of underlying depression or a complication of the medications used to treat depression (or a combination of the two). Our results were, however, similar when we only used ICD-9 codes to define depression in sensitivity analyses. We did not have access to metrics quantifying the success rate of depression therapy, hence we cannot determine if successful management of depression over time might alleviate some of the observed adverse effects. Our study population consisted of mostly male U.S. veterans, with relatively high prevalence of depression that might be related to, in part, the past history of military engagement, so these findings may not be generalizable to populations with different characteristics. We did not have detailed data about each individual diabetes complication in the data set; therefore, we could not assess the graded association between the number of diabetic complications and depression. Furthermore, we did not have detailed data about baseline glycemic level and lifestyle risk factors; therefore, we could not adjust for these important covariables either. We did not have information about cause of death for our cohort. Additionally, we did not have data about albuminuria; consequently, we can only comment on associations between depression and CKD defined by eGFR, but not on associations with incident CKD defined by albuminuria and eGFR.

In summary, we report for the first time that comorbid depression at baseline predicted a higher incidence of CKD in a large cohort of U.S. veterans with diabetes and eGFR $\geq$60 mL/min/1.73 m^2. We have also demonstrated that pre-existing depression was associated with higher all-cause mortality, increased risk of incident CHD, and stroke. We propose that appropriate intervention studies are needed to test the hypothesis that effective treatment of comorbid depression would reduce micro- and macrovascular complications of diabetes and improve clinical outcomes.

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Duality of Interest. K.K.-Z. and C.P.K. are employees of the U.S. Department of Veterans Affairs. No other potential conflicts of interest relevant to this article were reported.

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