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Factors Associated With Depressive Symptoms and Use of Antidepressant Medications Among Participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC Studies

Michael J. Fischer, MD, MSPH^{1,2}, Dawei Xie, PhD³, Neil Jordan, PhD^{2,4}, Willem J. Kop, PhD^{5,6}, Marie Krousel-Wood, MD, MSPH⁷, Manjula Kurella Tamura, MD, MPH⁸, John W. Kusek, PhD⁹, Virginia Ford, CNP³, Leigh K. Rosen, MUEP³, Louise Strauss, BSN¹⁰, Valerie L. Teal, MS³, Kristine Yaffe, MD¹¹, Neil R. Powe, MD, MBA¹², James P. Lash, MD¹, and on behalf of the CRIC Study Group Investigators[†]

¹Medicine, Jesse Brown VA Medical Center and University of Illinois Medical Center, Chicago, IL

²Center for Management of Complex Chronic Care, Edward Hines Jr., VA Hospital, Hines, IL

³Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA ⁴Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL ⁵Medicine, University of Maryland, Baltimore, MD ⁶Medical Psychology and Neuropsychology, Tilburg University, The Netherlands ⁷Epidemiology and Family and Community Medicine at Tulane University and Center for Health Research at Ochsner Clinic Foundation, New Orleans, LA ⁸Medicine, Stanford University School of Medicine ⁹National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD ¹⁰University Hospitals of Cleveland Case Medical Center, Cleveland, OH ¹¹Psychiatry, Neurology and Epidemiology, University of California San Francisco and San Francisco VA Medical Center ¹²San Francisco General Hospital and University of California San Francisco, San Francisco, CA

Abstract

Background—Depressive symptoms are correlated with poor health outcomes in adults with chronic kidney disease (CKD). The prevalence, severity, and treatment of depressive symptoms and potential risk factors, including level of kidney function, in diverse populations with CKD have not been well studied.

Study Design—Cross-sectional analysis

Settings and Participants—Participants at enrollment into the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC (H-CRIC) Studies. CRIC enrolled Hispanics and non-Hispanics at seven centers from 2003-2007, and H-CRIC enrolled Hispanics at the University of Illinois from 2005-2008.

Measurement—Depressive symptoms measured by Beck Depression Inventory (BDI)

Corresponding Author: Michael J. Fischer, MD, MSPH, Center for Management of Complex Chronic Care, Hines VA Hospital and Jesse Brown VAMC, 5000 S. 5th Avenue (151H), Hines, IL. 60141, Phone: 708.202.2414 Fax: 708.202.2316 fischer@muc.edu.

[†]**N section:** A list of the CRIC Study Group investigators can be found in references 18-19 and in the acknowledgements

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Predictors—Demographic and clinical factors

Outcomes—Elevated depressive symptoms (BDI ≥ 11) and antidepressant medication use

Results—Among 3853 participants, 28.5% had evidence of elevated depressive symptoms and 18.2% were using antidepressant medications; 30.8% of persons with elevated depressive symptoms were using antidepressants. The prevalence of elevated depressive symptoms varied by level of kidney function: 25.2% among participants with eGFR ≥ 60 ml/min/1.73m², and 35.1% of those with eGFR < 30 ml/min/1.73m². Lower eGFR (OR per 10 ml/min/1.73m² decrease, 1.09; 95% CI, 1.03-1.16), Hispanic ethnicity (OR, 1.65; 95% CI, 1.12-2.45), and non-Hispanic black race (OR, 1.43; 95% CI, 1.17-1.74) were each associated with increased odds of elevated depressive symptoms after controlling for other factors. In regression analyses incorporating BDI score, while female sex was associated with a greater odds of antidepressant use, Hispanic ethnicity, non-Hispanic black race, and higher levels of urine albumin were associated with decreased odds of antidepressant use ($p < 0.05$ for each).

Limitations—Absence of clinical diagnosis of depression and use of non-pharmacologic treatments

Conclusions—Although elevated depressive symptoms were common in individuals with CKD, use of antidepressant medications is low. African Americans, Hispanics, and individuals with more advanced CKD had higher odds of elevated depressive symptoms and lower odds of antidepressant medication use.

Depression is often observed in patients with chronic kidney disease (CKD) and is substantially more prevalent in these patients than in non-medically ill adults (1-7). The reported prevalence of elevated depressive symptoms and depression has varied substantially among individuals with CKD, from 15% to 50% (1-6,8). The relationship between depression and severity of CKD as assessed by estimated glomerular filtration rate (eGFR) and albuminuria has not been clearly established. While some studies have observed an increase in the prevalence of depression among individuals with increasing severity of CKD, others have not (1-6,8). These inconsistent findings across studies may be due to the use of different diagnostic threshold and instruments for measuring depression and by the lack of inclusion of diverse racial, ethnic, aged, socioeconomic, and geographic groups.

Depression is associated with substantial morbidity and increased mortality for patients with CKD (1-2,8-11). Depressive symptoms have been shown to substantially increase the risk of adverse renal outcomes in older adults with CKD (8) and a composite outcome of cardiovascular hospitalization or death in African Americans with CKD (11). Moreover, a major depressive episode has been found to be associated with nearly a doubling of the risk of a combined outcome of death, dialysis initiation, or hospitalization among male Veterans with CKD (10). A clinical diagnosis of depression or elevated depressive symptoms also reduces quality of life in adults with CKD (2,9). Although small uncontrolled studies and clinical trials suggest that antidepressant medications and cognitive behavioral therapy are effective treatments for depression in chronic dialysis patients, little is known about treatment of depression in patients with earlier stages of CKD (1,12-16,17).

The Chronic Renal Insufficiency Cohort (CRIC) Study and its ancillary study, the Hispanic-CRIC (H-CRIC) Study, are prospective observational studies designed to examine risk factors for the progression of CKD and the development and worsening of cardiovascular disease among adults with CKD (18-20). These studies offer an opportunity to better characterize the associations between depressive symptoms, use of antidepressant medications, sociodemographic factors, comorbid health conditions, and severity of CKD. We examined whether severity of CKD, as determined by level of kidney function and

albuminuria, and race/ethnicity were associated with depressive symptoms and use of antidepressant medications among CRIC/H-CRIC participants.

Methods

Study Sample and Design

We conducted a cross-sectional analysis of depressive symptoms among participants at enrollment into the CRIC and H-CRIC Studies. Details of the design, methods, and baseline characteristics of the CRIC study have been previously published (18-19). Major eligibility criteria for the CRIC included adults aged 21 to 74 years with mild to moderate CKD using age-based glomerular filtration rate (eGFR). Exclusion criteria included inability to consent, New York Heart Association Class III or IV heart failure, cirrhosis, HIV, polycystic kidney disease, prior dialysis or transplant, immunosuppressive therapy within 6 months, or chemotherapy for cancer within 2 years. Identical eligibility and exclusion criteria were used in the H-CRIC Study (20). A total of 170 Hispanic and 3,442 non-Hispanic participants were recruited at seven clinical centers from May 2003 through March 2007 in the CRIC Study, and 327 Hispanic participants were enrolled in the H-CRIC Study at the University of Illinois from October 2005 through June 2008. The study was approved by the Institutional Review Boards of the participating centers. All study participants provided written informed consent.

Variables and Data Sources

The Beck Depression Inventory (BDI) was administered as either a self- or interviewer-administered questionnaire to all CRIC participants at their baseline visit in English or Spanish depending on primary language preference. The BDI is a widely used and validated instrument to assess depressive symptoms in patients with CKD (21-24). Scores for each of the 21 items range from 0 to 3 with a higher score representing greater symptom intensity. The total score range is 0-63 where a score of < 10 indicates absence of depression, and higher scores reflecting more severe depression in the general non-medically ill population (25). Although a number of studies have reported that BDI scores of 14-16 have the best diagnostic accuracy for a clinical diagnosis of depression among diverse populations with end-stage kidney disease (21-23), a recent study found that a BDI score ≥ 11 was a sensitive and specific threshold for a major depressive episode in patients with CKD (24). Thus, while we evaluated strata of BDI scores, we considered a BDI threshold of ≥ 11 to define clinically meaningful depressive symptoms.

Sociodemographic characteristics (e.g., age, sex, race/ethnicity, education, annual household income, etc.) and medical conditions (e.g., hypertension, high cholesterol, chronic heart failure, peripheral arterial disease, diabetes, myocardial infarction or coronary revascularization) were self-reported at baseline. Anthropometric measures (height, weight) were obtained by trained study personnel and recorded at enrollment. Current medications were reviewed and documented at study visits (i.e., participant medication bottles or updated medication list), including medications designated as antidepressants, which were independently confirmed by three investigators. Consistent with prior literature (26), we classified antidepressants into the following categories: selective serotonin reuptake inhibitors, tricyclic (TCA) and older antidepressants (e.g., monoamine oxidase inhibitors), and newer antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, tetracyclic antidepressants, norepinephrine reuptake inhibitors). For each participant at baseline, urine creatinine and protein excretion were determined from a 24-hour urine collection, and eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) estimating equation (27), using a locally measured serum creatinine level calibrated to the Roche enzymatic method (Roche Diagnostics, Inc,

www.roche-diagnostics.us). in a subcohort of study participants, measured GFR (mGFR) was assessed using renal clearance of 125-iodine iothalamate (18-20).

Statistical Analysis

Baseline participant characteristics were described overall, among four BDI strata (0-10, 11-14, 15-21, 22), and by use of antidepressant medications, using mean $\pm$ standard deviation (SD) or median (25th-75th percentile) for continuous variables and frequencies and percents for categorical variables. Bivariate analyses involving Chi-square tests and ANOVA were used as appropriate to assess differences in participant characteristics among BDI score strata and by use of antidepressant medications.

Multivariable logistic regression analysis was used to evaluate the presence, strength, and independence of a cross-sectional relationship between elevated depressive symptoms (i.e., BDI ≥ 11) and participant characteristics at baseline. As sensitivity analyses, models were also examined with BDI > 14 as threshold for elevated depressive symptoms and fit with and without including the presence of baseline antidepressant medication use. Separate multivariable logistic regression models were used to assess the cross-sectional relationship between antidepressant medication use and participant characteristics at baseline, and a subgroup analyses were also conducted among participants with a BDI scores > 14 and 22. Baseline characteristics included in the models were chosen based on known clinical importance. For these multivariable models, we also added a quadratic term of eGFR to assess for a non-linear relationship between eGFR and outcomes. Associations are reported as odds ratio (OR) and 95% confidence intervals (CI). All p-values are two-sided and statistical significance is defined as $p < 0.05$. All statistical analyses were conducted with SAS, version 9.1 (Cary, NC, www.sas.com).

Results

Participant Characteristics and Depressive Symptoms

Out of a total of 3,939 participants recruited into the CRIC and H-CRIC studies, 3,853 had complete data that were required for this analysis. Among these participants, the median baseline BDI score was 6 (25th-75th percentile, 3-12) and 28.5% ($n=1099$) had evidence of elevated depressive symptoms (BDI ≥ 11) (Table 1). The distribution of CRIC participants by strata of baseline BDI scores was: 1-10 stratum, 71.5%; 11-14 stratum, 11.5%; 15-21 stratum, 9.4%; 22 stratum, 7.6%.

Several characteristics differed significantly among the participants by strata of BDI scores (Table 1). Trends towards younger age and higher proportion of women were noted with higher BDI score strata ($p < .001$). Among those with BDI scores 0-10, 46.3% were non-Hispanic White, 39.9% non-Hispanic Black, and 9.7% Hispanic; however, among those with BDI scores ≥ 22 , 25.9% were non-Hispanic White, 43.2% non-Hispanic Black, and 28.2% Hispanic ($p < .001$). Compared to participants with BDI scores 0-10, those with BDI scores ≥ 22 were more than twice as likely to not achieve a high school diploma (37.1% vs. 16.8%), to have an annual income $\leq \$20,000$ (55.1% vs. 24.6%), and to receive Medicaid/public aid for health insurance (24.5% vs. 9.9%). While there was a significant trend towards a higher prevalence of peripheral arterial disease and diabetes with higher BDI score strata ($p < 0.05$), less consistent trends were observed for other medical conditions. A significant trend for lower eGFR and higher proteinuria was noted with increasing BDI score strata ($p < 0.001$). Antidepressant medication use was significantly higher among persons in higher BDI score strata ($p < 0.001$).

Depressive Symptoms by Strata of eGFR and Albuminuria

A progressive and significant increase was noted in median BDI scores and the frequency of elevated depressive symptoms (BDI ≥ 11) among participants with lower eGFR and higher albuminuria, especially below an eGFR of 50 ml/min/1.73m² or above a urine ACR ≥ 30 mg/g ($p < .001$) (Table 2). Compared to those with an eGFR ≥ 60 ml/min/1.73m², the proportion of BDI scores ≥ 11 (35.1% vs. 25.2%) was significantly greater in participants with an eGFR < 30 ml/min/1.73m² ($p < .001$). Similarly, the proportion of BDI scores ≥ 11 was significantly greater in participants with urine albumin/creatinine ≥ 300 mg/g than in those with < 30 mg/g (34.4% vs. 23.5%, $p < .001$).

Characteristics Independently Associated with Elevated Depressive Symptoms

In logistic regression analysis (model 1, Table 3), older age was significantly associated with a lower odds whereas female sex was associated with a higher odds of elevated depressive symptoms ($p < .05$). Compared with persons whose educational attainment was less than a high school diploma, those with a high school or college education had a 50% lower odds of elevated depressive symptoms at baseline ($p < .001$). A history of myocardial infarction/coronary revascularization (OR, 1.37; 95% CI, 1.12-1.67) was significantly associated with a greater odds of elevated depressive symptoms. For every 10 ml/min/1.73m² decrease in eGFR, there was a 8% increased odds of elevated depressive symptoms (OR, 1.08; 95% CI, 1.02-1.15). A quadratic term for eGFR was not significant in any of the models. A separate logistic regression model (Table 3, model 2) that included antidepressant medication use resulted in similar findings overall, and compared with non-Hispanic whites, Hispanic ethnicity (OR, 1.65; 95% CI, 1.12-2.45) and non-Hispanic Black race (OR, 1.43; 95% CI, 1.17-1.74) were significantly associated with elevated depressive symptoms at baseline. A sensitivity analysis using a BDI > 14 as a threshold for elevated depressive symptoms yielded similar findings (data not shown).

Characteristics by Antidepressant Medication Use

Overall, 18.2% ($n=700$) of all participants were using antidepressant medication, which ranged from 13.1% with BDI scores 0-10 to 41.5% with BDI scores ≥ 22 (Table 4). Most (81.5%) were taking 1 antidepressant, 17.1% were taking 2 antidepressants, and 1.4% were taking more than 2 antidepressants. The distribution by antidepressant category was: 44.6% selective serotonin reuptake inhibitors, 32.2% TCAs/older antidepressants, 23.2% newer antidepressants.

Compared to those without antidepressant medications (Table 4), participants using antidepressant medications were more likely to be female, non-Hispanic white, a current smoker, or an illicit drug user, and less likely to be non-Hispanic black or Hispanic ($p < .05$). Significant differences between antidepressant medication users and non-users were less pronounced with respect to chronic medical conditions, kidney function, and urine protein. Subgroup analyses (not shown) among those with BDI > 14 and BDI ≥ 22 revealed similar findings.

Characteristics Independently Associated with Antidepressant Medication Use

In multivariable logistic regression analysis including adjustment for BDI score, female sex was associated with over a 2-fold increased odds of antidepressant medication use ($p < .001$) (Table 5). Compared with non-Hispanic Whites, both non-Hispanic Blacks (OR, 0.40; 95% CI, 0.32-0.50) and Hispanics (OR, 0.52; 95% CI, 0.31-0.86) had significantly lower odds of taking antidepressant medications. Significantly lower odds of antidepressant medication use (OR, 0.77; 95% CI, 0.61-0.97) were found with higher levels of urine albumin.

Subgroup analyses (not shown) among those with BDI > 14 and BDI ≤ 22 revealed similar findings.

Discussion

In a large ethnically and racially diverse group of adults with CKD, more than one in four reported elevated depressive symptoms, of whom less than one in three were receiving antidepressant medications. Two of our findings are of particular importance. First, lower levels of kidney function and higher levels of albuminuria were each independently associated with higher odds of elevated depressive symptoms and lower odds of treatment with antidepressant medications, respectively. For every 10 ml/min/1.73m² decrement in eGFR, the odds of elevated depressive symptoms increased 8%. Second, we observed racial and ethnic disparities in the distribution of elevated depressive symptoms and use of antidepressant medications. Compared to non-Hispanic Whites, non-Hispanic Black and Hispanic participants had approximately 1.5-fold greater odds of elevated depressive symptoms and had at least a 50% lower odds of use of antidepressant medications. Prior reports of prevalence of depression in adults with CKD were limited by study samples that were either small or ethnically/racially homogenous, and very few reported treatment of depression (1-2,3-6,8).

In contrast to prior studies, which found an increase in depressive symptoms only in persons with advanced CKD (eGFR < 15 ml/min/1.73m²) (1-2,3,5-6), we found that lower levels of kidney function (eGFR) were independently associated with elevated depressive symptoms in persons with mild to moderate CKD. The greater risk of depression in patients with advanced CKD may be a result of substantial lifestyle and psychological adjustments and many losses that they undergo in transitioning to ESKD requiring dialysis (14,28-29). However, even in earlier stages of CKD, patients may develop profound negative perceptions of illness and psychological reactions that correlate significantly with depression (2, 30). Alternatively, depression may have a direct contributory role to CKD disease progression and associated morbidity. Two recent studies demonstrated that elevated depressive symptoms or major depressive disorder were independently associated with severity of CKD at baseline and an increased risk of a more rapid decline in kidney function and ESKD during follow up (8, 10). Several potential mechanisms for this link have been posited, including behavioral factors such as treatment non-adherence and unhealthy lifestyle choices as well as physiologic factors such as alterations in platelet reactivity, dysregulation of the autonomic nervous system and hypothalamic pituitary adrenal axis, endothelial dysfunction, and changes in immune response and inflammation in the setting of depression (31-33).

We also found that African Americans and Hispanics with CKD are at substantially higher risk of elevated depressive symptoms than non-Hispanic Whites. Prior studies of depression in CKD patients could not adequately address racial and ethnic differences in prevalence since they included racially homogenous populations that did not include Hispanics (1-2,3-6,8). Studies in nationally representative, community, and outpatient primary care samples have generally noted higher rates of major depression among African-Americans and Hispanics compared with non-Hispanic Whites, which appeared to be mediated by differences in perception of chronic illness, economic resources, disability, acculturation, and other lifestyle factors such as exercise (34-37). We were able to account for many but not all of these factors in our study. Also, because these disparities were revealed after taking into account the use of antidepressant medications in our analyses, the relative ineffectiveness of pharmacologic treatment for depression in these groups may also underpin these associations. Importantly, a recent study has suggested that a lack of measurement equivalence in depression across racial and ethnic groups exists with current instruments;

therefore, response bias could confound these findings (38). Further research is needed to clarify our understanding of these disparities.

Compounding the greater risk of depressive symptoms, more severe CKD (i.e., higher levels of albuminuria), African American race, and Hispanic ethnicity were associated with a concomitant lower odds of antidepressant medication use. The few studies characterizing antidepressant medication use in CKD and dialysis patients with depression have found infrequent usage; generally around 10% but up to 50% has been reported (1,6,8,14,39). These low treatment rates may be explained by misclassification of depressive symptoms as somatic symptoms of severe CKD, concerns about drug-drug interactions and toxicity in the setting of decreased kidney function, medication side effects, and patient non-adherence to treatment (14-16,28). While no prior reports describe pharmacologic treatment of depression in Hispanics with CKD and ESKD, it has been noted to be especially infrequent and inadequate in African Americans with kidney disease (1, 40). Similarly low rates of antidepressant medication use and adherence have been observed in minority populations without CKD and mediating factors may include lack of physician recognition, lower rates of referral to specialty mental health services, diminished financial resources and health insurance, and increased social stigma in these minority groups (41-44).

Alternatively, low rates of antidepressant medication use in this study may indicate that depression is being treated with non-pharmacologic treatments such as psychotherapy, which may be preferred by patients and has been demonstrated to be effective in ESKD (17, 26,45-46). Data regarding non-pharmacologic treatments for depression were not available in the CRIC/H-CRIC. However, the relationships between severity of CKD, race/ethnicity, and antidepressants were similar in subgroup analyses of participants with severe depressive symptoms (BDI ≥ 22), where these medications were used by only 42% of participants. Furthermore, recent reports indicate that pharmacologic therapy is the dominant and increasingly prevalent first line contemporary treatment for depression (26,50,52), even in less severe cases of depression (26,51,46-49).

Our study has several limitations. First, we evaluated depressive symptoms and not a clinical diagnosis of major depression so misclassification is possible. Prior concern about the validity of the BDI has been mainly focused on the misattribution of uremic symptoms to depression, a problem that is less likely in individuals with less severe CKD (22-24,28,31). Further, we used a validated instrument to assess depressive symptoms and selected an established BDI threshold for a clinical diagnosis of depression in patients with CKD (24). Although we used sensitivity analyses to examine different BDI thresholds (e.g., ≥ 11 , ≥ 14), it is not known if BDI thresholds for meaningful depressive symptoms vary by Hispanic ethnicity because prior validation studies have not included significant numbers of Hispanics. Second, our study was cross-sectional and thus the temporal and directional relationship of depressive symptoms and many of the factors we considered could not be ascertained. Third, although we had robust data regarding pharmacologic treatment of depression, these data do not permit us to determine the reasons for or the appropriateness of antidepressant medication initiation or discontinuation (e.g., potential coexisting psychiatric conditions, incorrect diagnoses and indication, or intolerable patient side effects).

In conclusion, depressive symptoms were common in a multi-racial/ethnic cohort of adults with CKD and infrequently treated with antidepressants. These findings are important for providers of CKD care because they may bring attention to a common chronic condition that negatively affects patient outcomes. Moreover, these results inform providers to be especially vigilant for symptoms of depression in certain high-risk CKD patients, including those of younger age, female sex, lower socioeconomic status, racial and ethnic minority background, and more severe CKD. The ongoing prospective CRIC/H-CRIC studies have

the potential to describe the impact of depressive symptoms and their treatment on a broad range of outcomes of great importance to patients with CKD and their health care providers.

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Cappola, MD, ScM; Debbie Cohen, MD; Magdalena Cuevas; Mark J. Duckworth; *Daniel L. Dries, MD; Virginia Ford, MSN, CRNP; Colin M. Gorman; *Juan Grunwald, MD; Holly M. Hannah; Peter A. Kanetsky, PhD, MPH; Krishna Kellem; Lucy Kibe, MS; *Mary B. Leonard, MD, MSCE; *Maureen Maguire, PhD; Stephanie McDowell; John Murphy, MD; *Muredach Reilly, MB; *Sylvia E. Rosas, MD; Wanda M. Seamon; Angie Sheridan, MPH; Karen Teff, MD. The Johns Hopkins University: Lawrence J. Appel, MD, MPH (PI); Cheryl Anderson, PhD, MPH; Jeanne Charleston, RN; Nyaa Etheredge; Bernard Jaar, MD, MPH; Kelly Mantegna; Carla Martin; Edgar "Pete" Miller, MD; Patience Ngoh; Julia Scialla, MD; Steve Sozio, MD, MHS; Sharon Turban, MD, MHS; Hemalatha Venkatesh. University of Maryland: Jeffrey Fink, MD, MS (Co-PI); Wanda Fink, RN, BSN; Afshin Parsa, MD, MPH; Beth Scism; Stephen Seliger, MD, MS; Matthew Weir, MD. University Hospitals of Cleveland Case Medical Center: Mahboob Rahman, MD (PI); Valori Corrigan RN; Renee Dancie, CMA; Genya Kisin MA; Radhika Kanthety; Louise Strauss, RN; Jackson T. Wright Jr, MD, PhD. MetroHealth Medical Center: Jeffrey Schelling, MD (Co-PI); Patricia Kao, MD (Co-PI); Ed Horowitz, MD (Co-PI); Jacqui Bjaloncik; Theresa Fallon; John R. Sedor, MD; Mary Ann Shella, RN, BSN; Jacqueline Theurer; J. Daryl Thornton, MD, MPH. Cleveland Clinical Foundation: Martin J. Schreiber, MD (Co-PI); Martha Coleman, RN; Richard Fatica, MD; Sandra Halliburton, PhD; Carol Horner, BSN, RN; Teresa Markle, BS; Mohammed A. Rafey, MD, MS; Annette Russo; Stephanie Slattery, RN; Rita Spirko, RN, MSN; Kay Stelmach, RN; Velma Stephens, LPN; Lara Danziger-Isakov, MD, MPH. 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Lash, MD (PI); Jose Arruda, MD; Carolyn Brecklin, MD; Eunice Carmona, BA; Janet Cohan, MSN; Michael Fischer, MD, MSPH; Anne Frydrych, MS, RD; Amada Lopez; *Claudia Lora, MD; Monica Martinez; Adriana Matos; Alejandro Mercado; Brenda Moreno; Patricia Meslar, MSN; Ana Ricardo, MD, MPH; Thomas Stamos, MD; *Eve Van Cauter, PhD. Tulane University Health Science Center: Jiang He, MD, PhD (PI); Brent Alper, MD; Vecihi Batuman, MD; Lydia A. Bazzano, MD, PhD; Bernadette Borja; Adriana Burrige, MPH; Jing Chen, MD, MSc; Catherine Cooke; Patrice Delafontaine, MD; Karen B. DeSalvo, MD, MPH, MSc; Vivian A. Fonseca, MD; Lee Hamm, MD; Michelle R. Hurly, RN, BSN; Julie Legarde; Eva Lustigova, MPH; *Paul Muntner, PhD; Maria Patrocollo-Emerson, MPH; Lindsey Powers; Shea Shelton; Claire Starcke; Paul Whelton, MD, MSc. Kaiser Permanente of Northern California: Alan S. Go, MD (PI); Lynn M. Ackerson, PhD; Pete Dorin, MPA; Daniel Fernandez; Nancy G. Jensvold, MPH; Joan C. Lo, MD; Juan D. 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Table 1

Characteristics by Depressive Symptoms in Cohort Participants at Enrollment¹

Characteristic	Overall (N=3853)	BDI Score				p-value
		0-10 (n=2754)	11-14 (n=443)	15-21 (n=362)	22+ (n=294)	
Age, yr	58.17 ±11.00	58.71 ±11.11	58.00 ±11.16	56.22 ±10.38	55.83 ±9.95	<0.001
Sex						<0.001
Male	2117 (54.9%)	1586 (57.6%)	219 (49.4%)	182 (50.3%)	130 (44.2%)	
Female	1736 (45.1%)	1168 (42.4%)	224 (50.6%)	180 (49.7%)	164 (55.8%)	
Racial/Ethnic Group						<0.001
Non-Hispanic White	1614 (41.9%)	1276 (46.3%)	135 (30.5%)	127 (35.1%)	76 (25.9%)	
Non-Hispanic Black	1600 (41.5%)	1098 (39.9%)	228 (51.5%)	147 (40.6%)	127 (43.2%)	
Hispanic	490 (12.7%)	267 (9.7%)	67 (15.1%)	73 (20.2%)	83 (28.2%)	
Other	149 (3.9%)	113 (4.1%)	13 (2.9%)	15 (4.1%)	8 (2.7%)	
Annual household income						<0.001
\$20,000 or under	1208 (31.4%)	678 (24.6%)	186 (42.0%)	182 (50.3%)	162 (55.1%)	
\$20,001 - \$50,000	939 (24.4%)	688 (25.0%)	116 (26.2%)	82 (22.7%)	53 (18.0%)	
\$50,000 - \$100,000	722 (18.7%)	602 (21.9%)	60 (13.5%)	37 (10.2%)	23 (7.8%)	
More than \$100,000	389 (10.1%)	355 (12.9%)	13 (2.9%)	13 (3.6%)	8 (2.7%)	
Don't wish to answer	595 (15.4%)	431 (15.6%)	68 (15.3%)	48 (13.3%)	48 (16.3%)	
Educational attainment						<0.001
Less than HS Diploma	806 (20.9%)	463 (16.8%)	125 (28.2%)	109 (30.1%)	109 (37.1%)	
HS Graduate / Some post-HS	1842 (47.8%)	1305 (47.4%)	226 (51%)	168 (46.4%)	143 (48.6%)	
College Graduate	1205 (31.3%)	986 (35.8%)	92 (20.8%)	85 (23.5%)	42 (14.3%)	
Health Insurance						<0.001
Missing	444 (11.5%)	280 (10.2%)	57 (12.9%)	57 (15.7%)	50 (17.0%)	
None	263 (6.8%)	152 (5.5%)	45 (10.2%)	39 (10.8%)	27 (9.2%)	
Medicaid / public aid	496 (12.9%)	274 (9.9%)	74 (16.7%)	76 (21%)	72 (24.5%)	
Any Medicare	1177 (30.5%)	864 (31.4%)	139 (31.4%)	91 (25.1%)	83 (28.2%)	
VA/military/Champus	192 (5.0%)	133 (4.8%)	23 (5.2%)	20 (5.5%)	16 (5.4%)	

<i>Characteristic</i>	<i>Overall (N=3853)</i>	<i>BDI Score</i>				<i>p-value</i>
		<i>0-10 (n=2754)</i>	<i>11-14 (n=443)</i>	<i>15-21 (n=362)</i>	<i>22+ (n=294)</i>	
Private/commercial	573 (14.9%)	473 (17.2%)	41 (9.3%)	42 (11.6%)	17 (5.8%)	
Unknown/incomplete info	708 (18.4%)	578 (21.0%)	64 (14.4%)	37 (10.2%)	29 (9.9%)	
Tobacco use						
Current smoker	499 (13.0%)	308 (11.2%)	66 (14.9%)	66 (18.2%)	59 (20.1%)	<0.001
>100 cigarettes during lifetime	2111 (54.8%)	1492 (54.2%)	243 (54.9%)	210 (58.0%)	166 (56.5%)	0.5
Any Illicit Drug Use	1309 (34.0%)	897 (32.6%)	149 (33.6%)	146 (40.3%)	117 (39.8%)	0.004
Medical history						
Hypertension	3318 (86.1%)	2332 (84.7%)	404 (91.2%)	325 (89.8%)	257 (87.4%)	<0.001
High cholesterol	3169 (82.2%)	2240 (81.3%)	387 (87.4%)	292 (80.7%)	250 (85.0%)	0.009
Chronic heart failure	372 (9.7%)	239 (8.7%)	54 (12.2%)	40 (11.0%)	39 (13.3%)	0.01
MI or coronary revascularization	842 (21.9%)	573 (20.8%)	119 (26.9%)	88 (24.3%)	62 (21.1%)	0.02
Peripheral arterial disease	256 (6.6%)	162 (5.9%)	32 (7.2%)	36 (9.9%)	26 (8.8%)	0.01
Diabetes	1867 (48.5%)	1254 (45.5%)	231 (52.1%)	210 (58.0%)	172 (58.5%)	<0.001
Weight, kg	91.51 ± 23.36	90.59 ± 22.06	94.11 ± 24.41	94.99 ± 26.99	91.95 ± 27.74	<0.001
BMI, kg/m ²	32.08 ± 7.80	31.50 ± 7.17	33.54 ± 8.49	33.77 ± 9.78	33.28 ± 8.84	<0.001
BMI category						
<25 kg/m ²	613 (15.9%)	456 (16.6%)	55 (12.4%)	56 (15.5%)	46 (15.6%)	<0.001
25-30 kg/m ²	1104 (28.7%)	834 (30.3%)	118 (26.6%)	83 (22.9%)	69 (23.5%)	
>=30 kg/m ²	2136 (55.4%)	1464 (53.2%)	270 (60.9%)	223 (61.6%)	179 (60.9%)	
Kidney function measures						
adjusted SCr mg/dL	1.75 ± 0.58	1.71 ± 0.55	1.86 ± 0.67	1.78 ± 0.59	1.83 ± 0.62	<0.001
eGFR, ml/min/1.73m ²	44.2 ± 15.0	45.1 ± 14.8	41.4 ± 15.1	43.2 ± 14.4	42.1 ± 16.1	<0.001
participants with mGFR ^a	1395 (36.2%)	1095 (39.8%)	128 (28.9%)	102 (28.2%)	70 (23.8%)	<0.001
mGFR, ml/min/1.73m ²	47.2 ± 19.9	49.1 ± 20.1	42.9 ± 18.8	42.3 ± 16.4	47.4 ± 21.2	<0.001
Urine studies						
urine creatinine, g/d	1.34 ± 0.59	1.37 ± 0.59	1.27 ± 0.62	1.29 ± 0.61	1.17 ± 0.53	<0.001
urine protein, g/d	0.18 (0.07 - 0.91)	0.16 (0.07 - 0.77)	0.30 (0.09 - 1.48)	0.27 (0.09 - 1.11)	0.28 (0.08 - 1.23)	<0.001

Characteristic	Overall (N=3853)	BDI Score			p-value
		0-10 (n=2754)	11-14 (n=443)	15-21 (n=362)	
urine ACR ² , mg/g	51.28 (8.61 - 463.84)	41.76 (7.58 - 377.34)	102.99 (12.51 - 756.68)	103.26 (14.73 - 715.94)	<0.001
Antidepressant Medication Use	700 (18.2%)	362 (13.1%)	100 (22.6%)	116 (32%)	<0.001

ACR, albumin-creatinine ratio; BDI, Beck Depression Inventory; BMI, body mass index; eGFR, estimated glomerular filtration rate; HS, high school; MI, myocardial infarction; mGFR, measured glomerular filtration rate ; SCr, serum creatinine; VA, Veterans Administration

¹ continuous variables are represented by mean ± standard deviation except for urine protein and urine ACR which are median (25th-75th percentile); categorical variables are given as frequency (percentage)

² 3.6% missing values

^a determined using iothalamate conversion factors for units: serum creatinine in mg/dL to mmol/L, x88.4; GFR in mL/min/1.73 m2 to mL/s/1.73 m2, x0.01667

Table 2

BDI Scores by eGFR and Albuminuria in Cohort Participants at Enrollment

eGFR strata		eGFR (mL/min/1.73 m²)					P-value^c
Depressive Symptom Status	Overall (N=3853)	< 30 (n=719)	30 - <40 (n=897)	40 - <50 (n=965)	50 - <60 (n=700)	≥60 (n=572)	
BDI Score^b	6 (3 - 12)	7 (4 - 13)	7 (3 - 12)	6 (2 - 11)	5 (2 - 10)	5 (2 - 11)	<0.001
BDI Score Category							<0.001
0-10	2754 (71.5%)	467 (65.0%)	623 (69.5%)	694 (71.9%)	542 (77.4%)	428 (74.8%)	
11-14	443 (11.5%)	109 (15.2%)	115 (12.8%)	112 (11.6%)	52 (7.4%)	55 (9.6%)	
15-21	362 (9.4%)	72 (10.0%)	86 (9.6%)	88 (9.1%)	71 (10.1%)	45 (7.9%)	
≥22	294 (7.6%)	71 (9.9%)	73 (8.1%)	71 (7.4%)	35 (5.0%)	44 (7.7%)	

Albuminuria^a strata		Urine ACR (mg/g)			p-value^c
Depressive Symptom Status	Overall (N=3712)	< 30 (n=1598)	30 - <300 (n=977)	≥300 (n=1137)	
BDI Score^b	6 (3 - 11)	5 (2 - 10)	7 (3 - 11)	7 (3 - 13)	<0.001
BDI Score Category					<0.001
0-10	2672 (72.0%)	1221 (76.4%)	705 (72.2%)	746 (65.6%)	
11-14	419 (11.3%)	157 (9.8%)	113 (11.6%)	149 (13.1%)	
15-21	350 (9.4%)	122 (7.6%)	100 (10.2%)	128 (11.3%)	
≥22	271 (7.3%)	98 (6.1%)	59 (6.0%)	114 (10.0%)	

ACR, albumin-creatinine ratio; BDI = Beck depression inventory; eGFR = estimated glomerular filtration rate

^a only includes participants with available urine ACR (3.6% missing from total cohort)

^b median (25th-75th percentile)

^c p-value for trend across categories

Table 3

Characteristics Associated with Depressive Symptoms

<i>Characteristic</i>	<i>Model 1 *</i>		<i>Model 2 **</i>	
	<i>aOR (95% CI)</i>	<i>p-value</i>	<i>aOR (95% CI)</i>	<i>p-value</i>
Age (per 1 yr)	0.98 (0.97- 0.98)	<0.001	0.98 (0.97- 0.98)	<0.001
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	1.39 (1.18- 1.63)	<0.001	1.22 (1.03- 1.44)	0.02
Racial/Ethnic Group				
Non-Hispanic White	1.00 (reference)		1.00 (reference)	
Non-Hispanic Black	1.18 (0.98- 1.43)	0.08	1.43 (1.17- 1.74)	<0.001
Hispanic	1.44 (0.98- 2.12)	0.06	1.65 (1.12- 2.45)	0.01
Other	1.20 (0.78- 1.86)	0.4	1.38 (0.89- 2.16)	0.2
Educational attainment				
Less than HS Diploma	1.00 (reference)		1.00 (reference)	
Some College or Vocational Training	0.70 (0.57- 0.86)	<0.001	0.73 (0.59- 0.90)	0.003
College Graduate	0.50 (0.39- 0.65)	<0.001	0.52 (0.40- 0.68)	<0.001
Hypertension	1.19 (0.92- 1.54)	0.2	1.23 (0.95- 1.61)	0.1
High cholesterol	1.06 (0.85- 1.32)	0.6	1.03 (0.82- 1.29)	0.8
Chronic heart failure	1.10 (0.85- 1.43)	0.5	1.09 (0.84- 1.43)	0.5
MI or coronary revascularization	1.37 (1.12- 1.67)	0.002	1.35 (1.10- 1.66)	0.004
Peripheral arterial disease	1.29 (0.96- 1.73)	0.09	1.22 (0.91- 1.65)	0.2
Diabetes	1.17 (0.99- 1.39)	0.06	1.14 (0.96- 1.35)	0.1
Obesity ¹	1.16 (0.99- 1.37)	0.07	1.15 (0.97- 1.35)	0.1
eGFR (per 10 ml/min/1.73m ² decrease)	1.08 (1.02- 1.15)	0.01	1.09 (1.03- 1.16)	0.006
ln(urine albumin + 1) ²	1.02 (0.87- 1.20)	0.8	1.07 (0.90- 1.26)	0.4
Antidepressant medication use	-	-	3.44 (2.84- 4.17)	<0.001

Depressive symptoms defined as BDI (Beck Depression Inventory) score ≥ 11

BMI, body mass index; CI, confidence interval; eGFR = estimated glomerular filtration rate; HS, high school; MI, myocardial infarction; aOR, adjusted odds ratio;

* all covariates in adjusted model as listed above

** adjusted for covariates in model 1 + antidepressant medication use

¹ BMI ≥ 30 kg/m²

² natural log of 24 hr urine albumin

Table 4Characteristics of Cohort Participants by Antidepressant Medication Use at Enrollment ¹

<i>Characteristic</i>	<i>Antidepressant Use</i>		<i>p-value</i>
	<i>No (n=3153)</i>	<i>Yes (n=700)</i>	
Age, yr	58.2 ± 11.3	58.1 ± 9.8	0.8
Sex			<0.001
Male	1829 (58.0%)	288 (41.1%)	
Female	1324 (42.0%)	412 (58.9%)	
Racial/Ethnic Group			<0.001
Non-Hispanic White	1232 (39.1%)	382 (54.6%)	
Non-Hispanic Black	1371 (43.5%)	229 (32.7%)	
Hispanic	423 (13.4%)	67 (9.6%)	
Other	127 (4.0%)	22 (3.1%)	
Annual household income			0.2
\$20,000 or under	966 (30.6%)	242 (34.6%)	
\$20,001 - \$50,000	764 (24.2%)	175 (25.0%)	
\$50,000 - \$100,000	609 (19.3%)	113 (16.1%)	
More than \$100,000	321 (10.2%)	68 (9.7%)	
Don't wish to answer	493 (15.6%)	102 (14.6%)	
Educational attainment			0.9
Less than HS Diploma	662 (21.0%)	144 (20.6%)	
HS Graduate / Some post-HS	1509 (47.9%)	333 (47.6%)	
College Graduate	982 (31.1%)	223 (31.9%)	
Health Insurance			0.02
Missing	348 (11.0%)	96 (13.7%)	
None	227 (7.2%)	36 (5.1%)	
Medicaid / public aid	388 (12.3%)	108 (15.4%)	
Any Medicare	962 (30.5%)	215 (30.7%)	
VA/military/Champus	160 (5.1%)	32 (4.6%)	
Private/commercial	471 (14.9%)	102 (14.6%)	
Unknown/incomplete info	597 (18.9%)	111 (15.9%)	
Tobacco use			
Current smoker	375 (11.9%)	124 (17.7%)	<0.001
>100 cigarettes during lifetime	1708 (54.2%)	403 (57.6%)	0.1
Any Illicit Drug Use	1016 (32.2%)	293 (41.9%)	<0.001
Medical history			
Hypertension	2735 (86.7%)	583 (83.3%)	0.02
High cholesterol	2591 (82.2%)	578 (82.6%)	0.8
Chronic heart failure	302 (9.6%)	70 (10.0%)	0.7

<i>Characteristic</i>	<i>Antidepressant Use</i>		<i>p-value</i>
	<i>No (n=3153)</i>	<i>Yes (n=700)</i>	
MI or coronary revascularization	675 (21.4%)	167 (23.9%)	0.2
Peripheral arterial disease	200 (6.3%)	56 (8.0%)	0.1
Diabetes	1515 (48.0%)	352 (50.3%)	0.3
Weight, kg	91.26 +/- 22.77	92.64 +/- 25.81	0.2
BMI, kg/m ²	31.86 +/- 7.50	33.10 +/- 8.94	<0.001
BMI category			0.2
<25 kg/m ²	506 (16%)	107 (15.3%)	
25-<30 kg/m ²	919 (29.1%)	185 (26.4%)	
>=30 kg/m ²	1728 (54.8%)	408 (58.3%)	
Kidney function measures			
adjusted SCr, mg/dL	1.77±0.59	1.62 ±0.53	<0.001
eGFR, ml/min/1.73m ²	43.9 ±14.9	45.8 ±15.3	0.002
eGFR category			0.03
<30 ml/min/1.73m ²	606 (19.2%)	113 (16.1%)	
30 - <40 ml/min/1.73m ²	744 (23.6%)	153 (21.9%)	
40 - <50 ml/min/1.73m ²	789 (25.0%)	176 (25.1%)	
50 - <60 ml/min/1.73m ²	571 (18.1%)	129 (18.4%)	
>= 60 ml/min/1.73m ²	443 (14.1%)	129 (18.4%)	
participants with mGFR	1182 (37.5%)	213 (30.4%)	<0.001
mGFR, ml/min/1.73m ²	47.5 ±19.8	50.5±20.5	0.04
Urine studies			
urine creatinine, g/d	1.35± 0.59	1.27±0.59	0.002
urine protein, g/d	0.20 (0.08 - 0.99)	0.13 (0.07 - 0.54)	<0.001
UACR ² , mg/g	58.33 (9.11 - 04.04)	34.17 (7.56 - 281.14)	<0.001
UACR category			<0.001
<30 mg/g	1267 (41.7%)	331 (48.9%)	
30-<300 mg/g	797 (26.3%)	180 (26.6%)	
>=300 mg/g	971 (32.0%)	166 (24.5%)	
BDI Score	6 (2 - 10)	10 (5 - 18)	<0.001
BDI Category			<0.001
0-10	2392 (75.9%)	362 (51.7%)	
11-14	343 (10.9%)	100 (14.3%)	
15-21	246 (7.8%)	116 (16.6%)	
>=22	172 (5.5%)	122 (17.4%)	

UACR, urine albumin-creatinine ratio; BDI, Beck Depression Inventory; BMI, body mass index; eGFR, estimated glomerular filtration rate; HS, high school; MI, myocardial infarction; mGFR, measured glomerular filtration rate ; SCr, serum creatinine; VA, Veterans Administration

¹ continuous variables are represented by mean ± standard deviation except for urine protein and urine ACR which are median (25th-75th percentile); categorical variables are given as frequency (percentage)

²3.6% missing values conversion factors for units: serum creatinine in mg/dL to mmol/L, x88.4; GFR in mL/min/1.73 m² to mL/s/1.73 m², x0.01667

Table 5

Characteristics Associated with Antidepressant Medication Use

<i>Characteristic</i>	<i>aOR(95% CI)</i>	<i>p-value</i>
Age (per 1 yr)	1.00 (0.99- 1.01)	0.9
Sex		
Male	1.00 (reference)	
Female	2.04 (1.67- 2.49)	<0.001
Racial/Ethnic Group		
Non-Hispanic White	1.00 (reference)	
Non-Hispanic Black	0.40 (0.32- 0.50)	<0.001
Hispanic	0.52 (0.31- 0.86)	0.01
Other	0.58 (0.35- 0.97)	0.04
Educational attainment		
Less than HS Diploma	1.00 (reference)	
HS Graduate / Some post-HS	0.85 (0.65- 1.12)	0.3
College Graduate	0.86 (0.63- 1.18)	0.3
Hypertension	0.91 (0.69- 1.19)	0.5
High cholesterol	1.13 (0.88- 1.47)	0.3
Chronic heart failure	1.04 (0.75- 1.45)	0.8
MI or coronary revascularization	1.06 (0.84- 1.35)	0.6
Peripheral arterial disease	1.27 (0.89- 1.81)	0.2
Diabetes	1.14 (0.93- 1.39)	0.2
Obesity ¹	1.06 (0.88- 1.29)	0.5
eGFR (per 10 ml/min/1.73m ² decrease)	0.94 (0.87- 1.01)	0.07
ln(urine albumin + 1) ²	0.77 (0.61- 0.97)	0.03
BDI Score (per 1 point increase)	1.09 (1.08- 1.10)	<0.001

BDI, Beck Depression Inventory; BMI, body mass index; CI, confidence interval; eGFR = estimated glomerular filtration rate; HS, high school; MI, myocardial infarction; aOR, adjusted odds ratio;

¹BMI $\geq$ 30 kg/m²

²24 hr urine albumin