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Elevated depressive symptoms and risk of all-cause and cardiovascular mortality among adults with and without diabetes: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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Abstract

Aims: To examine the association of elevated depressive symptoms with all-cause and cardiovascular disease (CVD) mortality and determine whether these associations differ for those with and without diabetes.

Methods: We included 22,807 black and white men and women aged 45-98 years at baseline (2003-2007) from the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. Elevated depressive symptoms were defined as a score ≥ 4 on the 4-item Centers for

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Epidemiologic Studies of Depression Scale. Participants were classified as having diabetes, prediabetes, or no prediabetes/diabetes based on glucose levels and diabetes medication use. All-cause mortality events were available through 2018 and adjudicated CVD mortality events were available through 2015.

Results: During follow-up, there were 5,383 all-cause deaths, of which 1,585 were adjudicated CVD deaths. The mean survival time was lower for participants with elevated depressive symptoms than those without elevated depressive symptoms for those with diabetes, prediabetes, and no prediabetes/diabetes. In multivariable adjusted models, elevated depressive symptoms increased the risk of all-cause mortality for those with diabetes (HR=1.15; 95% CI=1.00-1.32), prediabetes (HR=1.56; 95% CI=1.28-1.91), and neither prediabetes/diabetes (HR=1.34; 95% CI=1.19-1.50) (p for interaction=0.0342). Findings were similar for CVD mortality.

Conclusion: Elevated depressive symptoms increased the risk of all-cause and CVD mortality among individuals with and without diabetes, with a stronger magnitude of association observed among those with prediabetes. This underscores the need for assessing depressive symptoms across the glycemic spectrum, including those with prediabetes.

Keywords

Depression; Diabetes; Mortality

1.1 Introduction

Depressive symptoms are common among individuals with diabetes, affecting approximately 30% of adults with diabetes.¹ A bi-directional association has been identified for depressive symptoms and diabetes, such that depressive symptoms increase the risk of diabetes² and diabetes increases the risk of depressive symptoms³. It has been postulated that hypothalamic-pituitary-adrenal axis dysfunction⁴ and inflammation⁵ may underlie the link between diabetes and depressive symptoms. Additionally, the co-occurrence of depressive symptoms and diabetes increases the burden of both illnesses,^{6, 7} leading to worse health outcomes, poor quality of life, and increased hospitalization and health care utilization costs.⁸⁻¹²

Less is known about whether depressive symptoms contribute to adverse health outcomes across the glycemic continuum. Previous studies have shown that depressive symptoms increases the risk of mortality among individuals with diabetes¹³⁻¹⁷ and among adults without diabetes.¹⁸⁻²⁷ However, it is unclear whether depressive symptoms increases the risk of mortality among individuals with prediabetes specifically, who are at high risk of developing type 2 diabetes. Although no association between depression and prediabetes has been reported,²⁸⁻³² recent data from the Atherosclerosis Risk in Communities Study reported the prevalence of depressive symptoms was higher among adults with prediabetes than those with diabetes.³ The American Diabetes Association recommends that individuals with diabetes or prediabetes be screened for depression.³³ However, the formal clinical diagnosis of prediabetes is rare³⁴ and screening for depressive symptoms is likely uncommon among those with prediabetes given that <30% of adults with diabetes seen in primary care clinics were screened for depression.³⁵ The purpose of this study was to

examine the association of elevated depressive symptoms with the risk of all-cause and CVD mortality and to evaluate whether these associations vary for those with diabetes, prediabetes, or neither prediabetes/diabetes.

1.2 Methods

1.2.1 Study Population

This study included participants from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. Details about the study design have been published.³⁶ Briefly, the REGARDS study includes 30,239 white and African American adults aged 45 years and older at baseline (2003-2007), with 21% from the “stroke buckle” (the coastal plain of North Carolina, South Carolina and Georgia), 35% of participants sampled from the rest of the “stroke belt” (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana and Arkansas), and the remaining 44% from other parts of the U.S. At baseline, data were collected via computer-assisted telephone interviewing (CATI), self-administered questionnaires and an in-home visit. The in-home visit included height and weight, blood pressure measurements, blood and urine samples, an electrocardiogram (ECG), and a medication inventory. Participants were contacted biannually to assess hospitalizations and vital status. The REGARDS Study was approved by the Institutional Review Boards at participating institutions and all study participants provided written informed consent.

Participants who did not have follow-up contact date (N=509), were missing depressive symptoms at baseline (N=208), were missing diabetes status at baseline (N=1,089), or were missing other covariates (N=5,626) were excluded. The final sample size for analyses was 22,807 participants.

1.2.2 Depressive Symptoms

Depressive symptoms were assessed using the 4-item Centers for Epidemiologic Studies Depression Scale (CESD-4), which is a validated shorter version of the Centers for Epidemiologic Studies Depression Scale 20-item self-report scale. The CESD-4 scale³⁷ assessed how often in the past week the participant felt depressed, lonely, sad and how often they had crying spells. The scale was administered using a 4-point ordinal scale from 0 to 3 with the following responses: 0 points— “Rarely or none of the time (less than 1 day)”; 1 point—“Some or a little of the time (1-2 days)”; 2 points—“Occasionally or a moderate amount of the time (3-4 days)”; or 3 points—“Most or all of the time (5-7 days)”. A summary score was calculated with a range from 0 to 12. Participants with a CESD-4 score ≥ 4 were classified as having elevated depressive symptoms and participants with a CESD-4 score < 4 were classified as not having elevated depressive symptoms.³⁸

1.2.3 Diabetes Status

Diabetes was defined as a fasting serum glucose ≥ 126 mg/dL (≥ 7 mmol/L), or a random serum glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) for participants who did not fast a minimum of 8 hours, or use of diabetes medications. Prediabetes was defined as a fasting serum glucose between 100 and 125 mg/dL (5.6 and < 7 mmol/L), or a random serum glucose between 140 and 199 mg/dL (7.8 and < 11.1 mmol/L) for participants who did not fast a minimum of 8

hours, and no use of diabetes medications. No prediabetes/diabetes was defined as a fasting serum glucose <100 mg/dL (<5.6 mmol/L), or a random serum glucose <140 mg/dL (<7.8 mmol/L) for participants who did not fast a minimum of 8 hours, and no use of diabetes medications.³⁹ The majority of REGARDS participants (86%) fasted prior to their in-home visit.

1.2.4 All-cause and Cardiovascular Disease (CVD) Mortality

Participants or their proxies were contacted every 6 months by telephone to assess health changes and vital status. Participant death and date of death were confirmed through the National Death Index, the Social Security Death Index and web-based restricted-access search engines.^{36, 40} All-cause mortality was assessed through 03/30/2018. CVD mortality included all physician-adjudicated cardiovascular deaths from definite, probable, or possible myocardial infarction, stroke, sudden death, heart failure and other cardiac or cardiovascular cause through 12/31/2015.

1.2.5 Covariates

Age, sex (male or female), race (black or white), education (<high school, high school graduate, some college, college graduate and above), marital status (married, single, divorced, widowed, other), health insurance (yes or no), smoking status (never, former, current) were self-reported. Alcohol use was categorized as none, moderate (≤ 1 drink per week for women and ≤ 2 drinks per week for men), or heavy (> 1 drink per week for women and > 2 drinks per week for men). Physical activity was derived from the question "How many times per week do you engage in intense physical activity, enough to work up a sweat?" and categorized as none, 1 to 3 times/week, or 4 times/week.⁴¹

History of coronary heart disease was defined as myocardial infarction on electrocardiogram, self-reported physician diagnosis of myocardial infarction, or prior coronary revascularization procedures. History of stroke was defined as self-reported physician diagnosis. Medication use (prescription and non-prescription) was obtained via pill bottle review and self-report during the home visit. During the in-home visit, two blood pressure measurements were taken with a standard aneroid sphygmomanometer in the seated position after 5 minutes rest, with the mean blood pressure used in this analysis. Height and weight were measured using standardized procedures with the participants not wearing shoes and used to calculate body mass index (BMI).

Blood and urine samples were collected following standardized protocols and sent to a central laboratory (University of Vermont) for analysis. Total cholesterol and HDL cholesterol were measured at the central laboratory and LDL was calculated using the Friedewald formula.⁴² Serum glucose was measured using colorimetric reflectance spectrophotometry. C-reactive protein (CRP) was measured using a high-sensitivity particle enhanced immunonephelometric assay (N High Sensitivity CRP, Dade-Behring Incorporated, Deerfield, IL). Urine albumin was measured using the BNII ProSpec nephelometer (Dade-Behring, Deerfield, IL) and urine creatinine by the Jaffe method using the Modular-P chemistry analyzer (Roche/Hitachi, Basel, Switzerland). Estimated

glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.⁴³

1.3 Statistical Analysis

Descriptive statistics were used to compare demographic, lifestyle, and health-related factors for individuals with and without elevated depressive symptoms. Follow-up time was calculated from the date of the baseline in-home visit to the date of the last follow-up contact or date of death. Kaplan Meier survival curves were used to compare survival times by depressive symptoms and diabetes status. Cox proportional hazards regression was used to evaluate the association of depressive symptoms with all-cause or CVD mortality. Model 1 was unadjusted. Model 2 was adjusted for sociodemographic variables (age, sex, race, geographic region, marital status, education, insurance). Model 3 was adjusted for variables in model 2 plus lifestyle factors (BMI, smoking status, physical activity, and alcohol use). Model 4 was adjusted for variables in model 3 plus health-related factors (systolic blood pressure, antihypertensive medication use, high density lipoprotein, low density lipoprotein, total cholesterol, statin use, eGFR<60 mL/min/1.73 m², albumin-to-creatinine ratio 30 mg/g, CRP, history of coronary heart disease, history of stroke). Effect modification was evaluated using an interaction term between elevated depressive symptoms and diabetes status with an a priori α level of <0.10. Additionally, secondary analyses investigated effect modification using a three-way interaction term for race, elevated depressive symptoms, and diabetes status as well as an alternative definition of depressive symptoms using the CESD-4 score or use of antidepressant medications. The proportional hazards assumption was tested using interaction terms with time. All analyses were conducted using SAS Enterprise Guide 7.1 or SAS 9.4 (Cary, NC).

1.4 Results

Participant characteristics are presented in Table 1. Compared with participants without elevated depressive symptoms, participants with elevated depressive symptoms were more likely to be younger, black race (51.1% vs. 38.5%), female sex (69.3% vs. 52.5%), and have <high school education (22.5% vs. 10.5%). Participants with elevated depressive symptoms were also more likely to be current smokers, have a history of coronary heart disease, history of stroke, and use antihypertensive medications (60.4% vs. 51.8%). The prevalence of elevated depressive symptoms among those with diabetes, prediabetes, and neither prediabetes/diabetes was 14.3%, 10.1% and 9.2% ($p<0.0001$), respectively.

During follow-up, there were 5,383 all-cause deaths, with 1,585 of those being adjudicated CVD deaths. The mean follow-up time after entry into the study was 9.4 years (SD=3.9) for all-cause mortality and 8.4 years (SD=3.2) for CVD mortality. Individuals with elevated depressive symptoms had lower survival times than those without elevated depressive symptoms for those with diabetes, prediabetes or neither prediabetes/diabetes for both all-cause mortality and CVD mortality. Additionally, individuals with diabetes had the lowest mean survival times for those with and without elevated depressive symptoms for all-cause-mortality (Figure 1) and CVD mortality (Figure 2).

Hazards ratios (HRs) and 95% confidence intervals (CI) for the association of elevated depressive symptoms with all-cause mortality are presented in Table 2 by diabetes status. The interaction term for depressive symptoms and diabetes was statistically significant (p -value=0.0342) for all-cause mortality, so results are presented by diabetes status. Among individuals with neither prediabetes/diabetes, elevated depressive symptoms increased the risk of all-cause mortality in the unadjusted model (HR=1.49; 95% CI=1.33-1.67) and was attenuated after adjustment for sociodemographic, lifestyle, and health-related factors (HR=1.34; 95% CI=1.19-1.50). For those with prediabetes, elevated depressive symptoms were also associated with an increased risk of all-cause mortality in the unadjusted model (HR=1.50; 95% CI=1.22-1.83) and after multivariable adjustment (HR=1.56; 95% CI=1.28-1.91). However, among individuals with diabetes, the association of elevated depressive symptoms with all-cause mortality was weaker in magnitude in the unadjusted model (HR=1.14; 95% CI=1.00-1.31) and after adjustment for sociodemographic, lifestyle, and health-related factors (HR=1.15; 95% CI=1.00-1.32).

The association of elevated depressive symptoms with CVD mortality is presented in Table 3. Although the interaction of depressive symptoms with diabetes status was not statistically significant (p =0.4238) for CVD mortality, results are presented by diabetes status. Among individuals with neither prediabetes/diabetes, elevated depressive symptoms increased the risk of CVD mortality in the unadjusted model (HR=1.55; 95% CI=1.24-1.93) and was attenuated after multivariable adjustment (HR=1.32; 95% CI=1.05-1.64). Among those with prediabetes, elevated depressive symptoms were also associated with an increased risk of CVD mortality in the unadjusted model (HR=1.55; 95% CI=1.07-2.23) and after multivariable adjustment (HR=1.55; 95% CI=1.07-2.24). Among individuals with diabetes, elevated depressive symptoms increased the risk of CVD mortality (HR=1.28; 95% CI=1.02-1.60) and this association was attenuated after adjustment for sociodemographic, lifestyle, and health-related factors (HR=1.17; 95% CI=0.93-1.47).

In secondary analyses, the three-way interaction of race, elevated depressive symptoms, and diabetes status was not statistically significant for all-cause mortality (p =0.6359) or CVD mortality (p =0.2804). Additionally, using an alternative definition of depressive symptoms (elevated depressive symptoms on the CESD-4 score ≥ 4 or use of antidepressant medications), depressive symptoms were associated with an increased risk of all-cause mortality for those with neither prediabetes/diabetes (HR=1.37; 95% CI=1.25, 1.50), prediabetes (HR=1.42; 95% CI=1.21, 1.67) and diabetes (HR=1.23; 95% CI=1.10, 1.38) after multivariable adjustment. However, the interaction of depressive symptoms and diabetes status was not statistically significant (p =0.2271). Findings were similar for CVD mortality.

1.5 Discussion

In this population-based cohort study of middle-aged and older adults in the US, elevated depressive symptoms were associated with an increased risk of all-cause and CVD mortality among individuals with diabetes, prediabetes, and neither prediabetes/diabetes. Of particular interest, our finding that the magnitude of the association with all-cause mortality was greater among adults with prediabetes than those with diabetes aligns with the American

Diabetes Association recommendation for depression screening among those at high risk for diabetes to improve health outcomes.³³

Previous studies reported elevated depressive symptoms increased the risk of mortality among adults without diabetes^{18-27, 44} which is consistent with our findings. However, few studies have investigated the association of depression with mortality among adults with prediabetes separately, and prior studies have reported no association between depression and prediabetes.^{28, 45} In the Atherosclerosis Risk in Communities Study, the prevalence of depressive symptoms was higher among adults with prediabetes than those with diabetes,³ which differs from our findings of a higher prevalence among those with diabetes than those with prediabetes. Moreover, findings from a meta-analysis showed that depression was associated with a small increase in insulin resistance (as a measure of high-risk for diabetes), but this association was not statistically significant after adjustment for confounders⁴⁶ Because prediabetes is considered a high-risk state for developing type 2 diabetes,⁴⁷ it is plausible that depression may increase the risk of mortality in this group.³¹ Our study found that elevated depressive symptoms were associated with a 56% increase in the risk of all-cause mortality among individuals with prediabetes that persisted after multivariable adjustment, and highlights the potential relevance of depression screening in this high-risk group to provide appropriate mental health care.

The factors underlying the association between depressive symptoms and mortality remain unclear. Our study showed that individuals with elevated depressive symptoms were more likely to have adverse lifestyle factors, such as smoking and sedentary lifestyle, consistent with some prior literature. The extent to which depressive symptoms might influence mortality through these lifestyle factors and other mechanisms requires additional investigation. Moreover, interventions designed to ameliorate depressive symptoms and improve health outcomes among those with prediabetes are needed. Findings from a cluster randomized trial showed peer support was effective for reducing hospitalizations among adults with comorbid diabetes and depression;⁴⁸ however, the efficacy of peer support or other similar interventions among those with comorbid prediabetes and depression warrants further study.

The strengths of this study are its biracial population, large sample size, extensive range of sociodemographic, lifestyle, and clinical data collected, and its long-term follow-up. This study also has some potential limitations. Our study did not have a formal clinical diagnosis for depression; however, the CESD-4 is a validated scale to identify persons with elevated depressive symptoms. While our sensitivity analysis explored the use of antidepressant medication to define depressive symptoms, we were not able to assess the reason for antidepressant use and a prior study reported that 48% of those using antidepressants reported other indications for use (e.g., anxiety, neuropathic pain)⁴⁹. Additionally, our study had a single assessment of glucose, so we were unable to assess glycemic changes after the baseline examination. Our analysis also excluded participants missing covariate data, with the variable with the most missing being a lab-based measure (i.e., albumin-to-creatinine ratio). Lastly, we were only able to evaluate adjudicated cause-specific mortality for CVD mortality.

In summary, elevated depressive symptoms increased the risk of mortality among those with diabetes, prediabetes, and neither prediabetes/diabetes, with the magnitude of the association being greater among those with prediabetes than those with diabetes. This suggests that elevated depressive symptoms may be an important target for clinical interventions, even prior to an individual developing diabetes.

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Highlights

- Individuals with elevated depressive symptoms had lower survival than those without elevated depressive symptoms for those with diabetes, prediabetes or neither prediabetes/diabetes.
- Elevated depressive symptoms were associated with an increased risk of all-cause mortality, and the magnitude of this association was greater among adults with prediabetes.
- Elevated depressive symptoms were also associated with an increased risk of CVD mortality although no significant interaction between depressive symptoms and diabetes status was identified.

Figure 1:
Kaplan-Meier survival curves for all-cause mortality by diabetes status and elevated depressive symptoms, the REGARDS Study

Figure 2:
Kaplan-Meier survival curves for cardiovascular mortality by diabetes status and elevated depressive symptoms, the REGARDS Study

Table 1.

Baseline characteristics of participants with and without elevated depressive symptoms *, the REGARDS Study (2003-2007)

Characteristic	No Elevated Depressive Symptoms (N=20,436)	Elevated Depressive Symptoms (N=2,371)
<i>Sociodemographics</i>		
Age (years), mean±SD	65.1±9.3	63.2±9.8
Women, n (%)	10,722 (52.5)	1,643 (69.3)
Black race, n (%)	7,872 (38.5)	1,211 (51.1)
Lives outside stroke belt/buckle region, n (%)	9,233 (45.2)	927 (39.1)
Education < high school, n (%)	2,139 (10.5)	533 (22.5)
Married, n (%)	12,816 (62.7)	958 (40.4)
Has health insurance, n (%)	19,281 (94.4)	2,107 (88.9)
<i>Lifestyle factors</i>		
Body mass index (kg/m ²), mean, SD	29.1±6.0	30.5±6.9
Physical activity, n (%)		
4 or more times per week	6,359 (31.1)	523 (22.1)
1 to 3 times per week	7,621 (37.3)	750 (31.6)
None	6,456 (32.6)	1,098 (46.3)
Alcohol use, n (%)		
Never	12,518 (61.3)	1,608 (67.8)
Moderate	3,528 (17.3)	356 (15.0)
Heavy	4,390 (21.5)	407 (17.2)
Smoking status, n (%)		
Never	9,428 (46.1)	1,002 (42.3)
Former	8,371 (41.0)	799 (33.7)
Current	2,637 (12.9)	570 (24.0)
<i>Health-related factors</i>		
Systolic blood pressure (mmHg), mean, SD	127.1±16.4	128.3±18.0
Diastolic blood pressure (mmHg), mean, SD	76.3±9.5	76.8±10.4
Antihypertensive medication use, n (%)	10,584 (51.8)	1,433 (60.4)
History of heart disease, n (%)	3,442 (16.8)	506 (21.3)
History of stroke, n (%)	1,103 (5.4)	228 (9.6)
eGFR<60 mL/min/1.73 m ² , n (%)	2,239 (11.0)	273 (11.5)
Albumin-to-creatinine ratio ≥ 30 mg/g, n (%)	2919 (14.3)	422 (17.8)
C-reactive protein > 3mg/L, n (%)	7935 (38.8)	1174 (49.5)
Statin use, n (%)	6,495 (31.8)	769 (32.4)
LDL cholesterol (mg/dL), mean, SD	113.6±34.3	115.0±36.7
HDL cholesterol (mg/dL), mean, SD	52.0±16.1	52.8±16.1

Characteristic	No Elevated Depressive Symptoms (N=20,436)	Elevated Depressive Symptoms (N=2,371)
Total cholesterol (mg/dL), mean, SD	190.7±38.9	194.0±40.8
Diabetes status, n (%)		
No prediabetes or diabetes	11,508 (62.0)	1,191 (54.3)
Prediabetes	3,252 (17.5)	372 (17.0)
Diabetes	3,796 (20.5)	632 (28.8)

* Elevated depressive symptoms defined as 4-item Center for Epidemiologic Studies Depression Scale (CESD-4) score ≥ 4 .

Table 2:

Hazard ratios (HR) and 95% CI for the association of elevated depressive symptoms with all-cause mortality for participants with and without diabetes, the REGARDS Study

	No Prediabetes or Diabetes (N=14,229)	Prediabetes (N=3,986)	Diabetes (N=4,592)
	HR (95% CI)		
Model 1	1.49 (1.33-1.67)	1.50 (1.22-1.83)	1.11 (1.00-1.31)
Model 2	1.52 (1.35-1.71)	1.74 (1.42-2.13)	1.27 (1.10-1.46)
Model 3	1.42 (1.26-1.60)	1.55 (1.27-1.90)	1.23 (1.07-1.42)
Model 4	1.34 (1.19-1.50)	1.56 (1.28-1.91)	1.15 (1.00-1.32)

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race, geographic region, marital status, education and health insurance

Model 3: Model 2 variables plus BMI, smoking status, physical activity and alcohol use

Model 4: Model 3 variables plus systolic blood pressure, antihypertensive medication use, total cholesterol, HDL cholesterol, LDL cholesterol, statin use, estimated glomerular filtration rate, albumin-to-creatinine ratio, C-reactive protein, history of coronary heart disease and history of stroke

Table 3.

Hazard ratios (HR) and 95% CI for the association of elevated depressive symptoms with cardiovascular disease mortality for participants with and without diabetes, the REGARDS Study

	No Prediabetes/Diabetes (N=14,229)	Prediabetes (N=3,986)	Diabetes (N=4,592)
	HR (95% CI)		
Model 1	1.54 (1.24-1.93)	1.55 (1.07-2.23)	1.28 (1.02-1.60)
Model 2	1.50 (1.20-1.90)	1.71 (1.18-2.47)	1.35 (1.08-1.70)
Model 3	1.40 (1.12-1.74)	1.54 (1.06-2.22)	1.31 (1.04-1.65)
Model 4	1.32 (1.05-1.64)	1.55 (1.07-2.24)	1.17 (0.93-1.47)

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race, geographic region, marital status, education and health insurance

Model 3: Model 2 variables plus BMI, smoking status, physical activity and alcohol use

Model 4: Model 3 variables plus systolic blood pressure, antihypertensive medication use, total cholesterol, HDL cholesterol, LDL cholesterol, statin use, estimated glomerular filtration rate, albumin-to-creatinine ratio, C-reactive protein, history of coronary heart disease and history of stroke