Depression Predicts All-Cause Mortality

Epidemiological evaluation from the ACCORD HRQL substudy

MARK D. SULLIVAN, MD, PHD[1]
PATRICK O'CONNOR, MD, MPH[2]
PATRICIA FEENEY, MS, MA[3]
DON HIRE, MS[3]
DEBRA L. SIMMONS, MD[4,5]
DENNIS W. RAISCH, PHD, MS, RPH[6,7]
LAWRENCE J. FINE, MD, DRPH[8]
K.M. VENKAT NARAYAN, MD[9]
MOHAMMAD K. ALI, MB, CHB[9]
WAYNE J. KATON, MD[1]

OBJECTIVE—Depression affects up to 20–25% of adults with type 2 diabetes and may increase all-cause mortality, but few well-designed studies have examined the effects of depression on the full range of cardiovascular disease outcomes in type 2 diabetes.

RESEARCH DESIGN AND METHODS—A total of 2,053 participants in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Health-Related Quality of Life substudy completed the Patient Health Questionnaire (PHQ)-9 measure of depression symptoms at baseline and 12, 36, and 48 months. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) (95% CI) for the time-varying impact of depression on protocol-defined clinical outcomes with and without adjustment for demographic, trial-related, clinical, and behavioral variables.

RESULTS—In fully adjusted models, depression was not significantly related to the ACCORD primary composite outcome (cardiovascular death, nonfatal heart attack, or stroke) (HR 1.53 [95% CI 0.85–2.73]) or to the ACCORD microvascular composite outcome (0.93 [0.53–1.62]), but all-cause mortality was significantly increased both in those with PHQ-assessed probable major depression (2.24 [1.24–4.06]) and PHQ score of ≥10 (1.84 [1.17–2.89]). The effect of depression on all-cause mortality was not related to previous cardiovascular events or to assignment to intensive or standard glycemia control. Probable major depression (by PHQ-9) had a borderline impact on the ACCORD macrovascular end point (1.42 [0.99–2.04]).

CONCLUSIONS—Depression increases the risk of all-cause mortality and may increase the risk of macrovascular events among adults with type 2 diabetes at high risk for cardiovascular events.

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Patients with diabetes are approximately twice as likely to meet DSM-IV criteria for major depression than the general medical population, with depressive symptoms affecting up to 20–25% of these patients (1,2). Patients with diabetes and depression have younger age of diabetes onset; poor adherence to diet, exercise, and disease control medications; poorer glycemic control; and an increased risk of macrovascular and microvascular complications (3–5). Six prospective epidemiologic studies have shown that after controlling for sociodemographic factors and clinical severity of illness, comorbid depression in patients with diabetes compared with diabetes alone was associated with a 33–52% increased risk of all-cause mortality (6–11). One recent study of >4,000 patients with diabetes found that probable major depression assessed by Patient Health Questionnaire (PHQ)-9 was associated with a more than twofold risk of non–cancer and non–atherosclerotic associated mortality (6). However, few studies have examined specific effects of depression on macrovascular and microvascular complications. Studies have also not examined the moderating role of preexisting cardiovascular disease (CVD) or intensity of glucose control (9,12).

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial offers a unique opportunity to examine the relationship between depression, mortality, and cardiovascular events in a sample receiving standardized diabetes care. The ACCORD trial also includes rigorous criteria for defining macrovascular and microvascular complications and cause of death. It also allowed us to examine how the effect of depression on mortality and CVD differs between those with and without previous CVD and examine whether any effect of depression on mortality or CVD is modified by randomization to intensive versus standard glucose control. Specific hypotheses from the ACCORD Health-Related Quality of Life (HRQL) substudy examined in this epidemiological analysis are as follows (13). After controlling for baseline factors, depression will be associated with the following: *1*) primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke); *2*) all-cause mortality; *3*) composite macrovascular outcome (primary outcome plus any revascularization plus hospitalization for congestive heart failure [CHF]); and *4*) composite microvascular outcome (fatal or nonfatal renal failure or retinal photocoagulation or vitrectomy for diabetic retinopathy). We further hypothesize that these associations will not be affected by preexisting CVD or by randomization to intensive versus standard glucose control. We have previously reported that randomization to intensive glycemic control did not lead to benefits in HRQL in ACCORD but was associated with modest improvement in diabetes treatment satisfaction (14).

RESEARCH DESIGN AND METHODS

—The rationale, study design, and entry criteria for the ACCORD

From the [1]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington; [2]HealthPartners, Minneapolis, Minnesota; the [3]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [4]Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas; the [5]John L. McClellan Memorial Veterans Hospital, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas; the [6]College of Pharmacy, University of New Mexico, Albuquerque, New Mexico; the [7]Veterans Affairs Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico; the [8]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and the [9]Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia.
Corresponding author: Mark D. Sullivan, sullimar@uw.edu.
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trial have been described elsewhere and the randomized trial results published (8–10). In brief, this was a multicenter randomized controlled treatment trial testing independent effects of two strategies of control of blood glucose, blood pressure, and lipids on CVD in patients with type 2 diabetes. The glycemia trial randomized 10,251 participants with type 2 diabetes to intensive (goal HbA_{1c} <6%) or standard (goal HbA_{1c} 7.0–7.9%) glucose control. All participants were also randomized within either the blood pressure or the lipid trial arms, resulting in assignment to one of eight treatment cells as follows: *1*) intensive glucose/intensive blood pressure, *2*) intensive glucose/standard blood pressure, *3*) standard glucose/intensive blood pressure, *4*) standard glucose/standard blood pressure, *5*) intensive glucose/fibrate, *6*) intensive glucose/placebo, *7*) standard glucose/fibrate, and *8*) standard glucose/placebo.

The primary outcome of the ACCORD trial is a composite of death from CVD, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes include the following: *1*) all-cause mortality, *2*) composite macrovascular outcome (major coronary artery disease events, specifically fatal events, nonfatal myocardial infarction, and unstable angina), and *3*) composite microvascular outcome (fatal or nonfatal renal failure, retinal photocoagulation, or vitrectomy for diabetic retinopathy). These outcomes are not exclusive of each other.

The goal of the ACCORD HRQL investigation is to assess the overall effect of the ACCORD interventions from the patient's point of view in 2,053 participants randomly sampled from the eight ACCORD treatment groups. Measurements were taken at baseline and at 12, 36, and 48 months. Mean follow-up time was 4.67 ± 1.45 years.

Because of the documented relationship between depression and cardiovascular events and glycemic control (3–7), depressive symptoms were measured in the ACCORD study using the nine-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is the self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD), a well-validated psychiatric diagnostic interview for use in primary care settings (9). The PHQ-9 depression measure provides diagnostic and severity information and is used serially to assess responsiveness to depression treatment. Since the PHQ-9 items mirror those of the major depression and minor depression diagnostic criteria in the DSM-IV (15), it is also possible to derive provisional diagnostic categories from PHQ-9 responses. Major depression requires five symptoms scored ≥2, at least one of which is depressed mood or lack of pleasure. A score of ≥10 on the PHQ-9 has been shown to have 77% sensitivity and 94% specificity to the diagnosis of major depression by structured psychiatric interview (16). In patients with type 2 diabetes, a PHQ-9 score of ≥10 has been associated with higher risk of mortality and dementia, as well as macrovascular and microvascular complications (17). A recent review of the reliability and validity of depression screening tools in patients with diabetes gave the PHQ-9 generally high rates of sensitivity (66–100%) but lower rates of specificity (52–85%) (18). Minor depression is listed as a provisional diagnosis for further study in DSM-IV and requires three to four symptoms scored ≥2, at least one of which is depressed mood or lack of pleasure.

Statistical methods

For each of the four depression measures (PHQ-9 ≥10, probable major depression, probable minor depression, and continuous PHQ-9 score), we ran a series of separate proportional hazards regressions models where the outcome is the time until first occurrence of each event and the predictor of interest is the measure of depression. In each model, depression was a dichotomous, time-varying indicator measured at baseline, year 1, year 3, and year 4. We report rates at which patients met any depression criteria at any time point ("ever depressed") versus not meeting any depression criteria at any time point ("never depressed"). The first series of models contained the depression measure as well as variables indicating the randomization assignments for the main glycemia trial, with stratification for the blood pressure and lipid trial arms, and primary versus secondary prevention status. As specified in the ACCORD protocol, these models also included adjustments for the following baseline factors: demographics (age, sex, race/ethnicity, BMI, weight, waist circumference, and duration of diabetes), blood pressure (systolic and diastolic), laboratory values (triglycerides, LDL and HDL cholesterol, serum creatinine, HbA_{1c}, and fasting glucose), presence of microvascular complications, and blood pressure and lipid medications. A second series of models contained all of the above adjustments, plus factors known to be related to both depression and mortality in patients with diabetes: education, smoking, alcohol, and living alone. We also divided PHQ-9–assessed depression symptoms into somatic and psychological subsets and assessed whether each was related to all-cause mortality. All models used Cox proportional hazards regression model analyses to obtain hazard ratios (HRs) (95% CI) of the measure of depression. These analyses combined participants from the randomized groups and are thus epidemiologic in nature. There were no adjustments made for postrandomization events or measures. Participants with missing data were omitted from the models, resulting in ~4% loss in the most complex models. Since we conducted 12 statistical tests of hypotheses related to secondary end points and subgroups, there was a 46% chance (i.e., $1 - [1 - 0.05]^{12}$) that at least one of these tests would be statistically significant at an α level of 0.05, assuming independence between tests.

RESULTS—Table 1 compares the demographic and clinical characteristics of ACCORD HRQL substudy participants compared with the full ACCORD sample. As expected, because of randomization, there are no significant differences between the groups.

Table 2 displays the rates at which ACCORD HRQL participants screened positive for depression (PHQ score ≥10) or met criteria for probable major depression or minor depression based on responses to the PHQ. Nearly 20% of participants screened positive for clinically significant depressive symptoms (PHQ-9 ≥10) at baseline, with 8% meeting DSM-IV probable major depression criteria and another 7% meeting DSM-IV probable minor depression criteria. Approximately 31% of participants screened positive for depression at one of the four assessments, with 15% meeting major depression and 18% meeting minor depression criteria at least at one assessment.

Table 3 displays the baseline characteristics of the subjects based on whether they ever met any of the depression criteria. As would be expected from the epidemiology of depression, ever depressed patients were more likely to be younger, female, less educated, cigarette smokers, obese, and have higher HbA_{1c}, higher pulse, lower HDL cholesterol, and higher total cholesterol and triglycerides. They were also more likely to be treated with insulin or sulfonylureas.

Table 1—*Demographic and clinical characteristics of ACCORD HRQL substudy participants compared with full ACCORD sample*

Baseline characteristics	HRQL substudy Yes	HRQL substudy No	*P*
N	2,053	7,583	
Demographic			
Age (years)	62.2 ± 6.7	62.1 ± 6.8	0.5454
Female	39.6	38.4	0.3171
Non-Hispanic white	65.1	64.5	0.6520
Black	19.5	19.1	0.6818
Hispanic	6.8	7.3	0.3829
Education			
Highest level of education			0.5130
Less than high school	13.9	14.8	—
High school graduate (or GED)	26	26.7	—
Some college	33.2	33	—
College graduate or more	26.9	25.5	—
Lifestyle			
Living with someone	80	79.7	0.7713
Drinking	22.5	24.1	0.1358
Cigarette smoker			0.1973
Current	13.3	14.5	—
Former	45.6	43.7	—
Never	41.2	41.9	—
Comorbidities			
Weight (kg)	94.1 ± 18.9	93.6 ± 18.6	0.2735
BMI (kg/m^2)	32.4 ± 5.5	32.3 ± 5.5	0.2153
Waist circumference (cm)	107.1 ± 13.9	106.8 ± 13.9	0.4899
Peripheral neuropathy	43	42.6	0.7782
Macroalbuminuria	7.3	6.3	0.1266
Microalbuminuria	30.1	31.4	0.2395
Laser photo or vitrectomy	8.6	8.7	0.9436
Diabetes profile			
Duration of diabetes (years), median	10	9	0.0536
HbA_{1c} (%)	8.3 ± 1.1	8.3 ± 1	0.5014
HbA_{1c} (%), median	8.1	8.1	0.5712
Fasting plasma glucose (g/dL)	177.1 ± 57.5	174.9 ± 56	0.1266
Other biomarkers			
SBP (mmHg)	136.2 ± 17.1	136.2 ± 17.2	0.8398
DBP (mmHg)	74.5 ± 10.9	75 ± 10.6	0.0837
LDL (mg/dL)	104.3 ± 34	104.3 ± 33.9	0.9987
HDL among females (mg/dL)	47.3 ± 12.6	46.9 ± 12.6	0.4812
HDL among males (mg/dL)	38.7 ± 9.7	38.7 ± 9.7	0.8937
Total cholesterol (mg/dL)	182.8 ± 41.3	182.8 ± 42.1	0.9858
Triglycerides (mg/dL), median	156	155	0.6812
Potassium (mg/dL)	4.5 ± 0.4	4.5 ± 0.6	0.4836
Serum creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.2837
Medications			
On insulin	35.9	34.8	0.3233
On any HTN medications	85.5	85.8	0.6968
On any ACE inhibitors	52	52.9	0.4560
On β-blockers	30.3	29.8	0.6396
On statins	63.5	63.1	0.7048
Secondary status	36.1	35.2	0.4647

Data are means ± SD or percent unless otherwise indicated. DBP, diastolic blood pressure; GED, General Educational Development; HTN, hypertension; SBP, systolic blood pressure.

The primary composite outcome was reached by 2.1% per year (6,000 person-years observed) in the never-depressed group and 1.9% per year (3,239 person-years observed) in the ever depressed group. All-cause mortality was 1.4% per year in both the never-depressed (6,313 person-years observed) and ever-depressed (3,438 person-years observed) groups. The macrovascular composite outcome was reached by 5.2% per year (5,552 person-years observed) in the never-depressed group and 5.9% per year (2,908 person-years observed) in the ever-depressed group. The microvascular composite outcome was achieved by 2.6% per year (5,573 person-years observed) in the never-depressed group and 3.2% per year (2,999 person-years observed) in the ever-depressed group. Outcome rates are similar between the ever- versus never-depressed groups, but these results do not account for other clinical differences between these groups.

Table 4 displays the HRs for different measures of PHQ-assessed depression as a time-dependent covariate for time to the ACCORD primary and secondary end points. The first set of models was adjusted for the demographic, trial, and clinical variables described as follows. *1)* Probable major depression did not significantly increase the risk for the primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. The point estimate for major depression is HR 1.53, but the effect is not statistically significant. Neither PHQ score ≥10 nor the PHQ continuous score was significant. *2)* Both PHQ score of ≥10 (HR 1.84 [95% CI 1.17–2.89]) and PHQ-assessed probable major depression (2.24 [1.24–4.06]) increased risk for the secondary outcome of all-cause mortality after controlling for age, sex, race/ethnicity, primary/secondary CVD prevention, HbA_{1c}, lipids, blood pressure, BMI, smoking, alcohol consumption, living alone, blood pressure, presence of microvascular complications, CHF, education, duration of diabetes, antidepressant medications, glucose, blood pressure and lipid medications, and assignment to one of eight study intervention arms. The continuous PHQ-9 score was also a significant predictor of all-cause mortality (1.05 [1.01–1.09]). For each point increase on the PHQ-9, all-cause mortality increased by 5%. The increase in absolute risk for all-cause mortality associated with probable major depression at any time point is estimated to be 0.92%.

Table 2—*Subjects meeting depression criteria at assessment points throughout ACCORD trial*

Visit	*N*	Definition 1: PHQ-9 ≥10	Definition 2: major depression	Definition 3: minor depression
Baseline	1,953	381 (19.5)	158 (8.1)	139 (7.1)
12 months	1,860	241 (13)	96 (5.2)	122 (6.6)
36 months	1,753	239 (13.6)	97 (5.5)	102 (5.8)
48 months	1,691	201 (11.9)	84 (5)	91 (5.4)
Ever	2,038	624 (30.6)	301 (14.8)	368 (18.1)

Data are *N* (%) unless otherwise indicated.

3) Probable major depression was associated with borderline significant increased risk for the secondary outcome of macrovascular events, including fatal myocardial infarction, nonfatal myocardial infarction, and unstable angina (1.42 [95% CI 0.99–2.04], $P = 0.0552$). PHQ score ≥10 was not significantly associated, but the continuous PHQ-9 score was significantly associated with increased risk of macrovascular events (1.02 [1.00–1.04]). 4) Probable major depression (0.93 [0.53–1.62]), PHQ score ≥10 (1.27 [0.90–1.80]), and continuous PHQ score were not associated with increased risk for the secondary outcome of microvascular events.

The models in the second set of Table 4 were adjusted for demographic, trial, clinical, and behavioral variables. The additional adjustment for these potentially confounding or mediating variables slightly attenuated the risk associated with depression. Effects of depression on all-cause mortality remained significant, though the marginal effects of depression on the macrovascular outcome became nonsignificant.

In order to verify that the effects of probable major depression on mortality and the primary outcome were similar in both glycemia arms, we fit a model for each outcome controlling for the randomization factors and including an interaction term between glycemia arm and major depression. We fit the same set of models to see if the effects were the same for participants with prior CVD at baseline. None of the interaction terms of interest in the four models were significant, indicating that effect of probable major depression was consistent across the groups. While some studies of patients post–myocardial infarction have found that only the somatic symptoms of depression (e.g., fatigue, insomnia) are associated with subsequent mortality, we found that both psychological and somatic symptoms of depression as assessed by the PHQ-9 were significantly (and nearly equally) associated with all-cause mortality (19).

CONCLUSIONS—This epidemiological analysis of data from the ACCORD trial revealed that depression, defined as PHQ-assessed probable major depression, PHQ score of ≥10, or continuous PHQ-9 score, was associated with increased risk of all-cause mortality regardless of whether previous CVD was present and regardless of randomization to intensive versus standard glycemia control. Depression marginally increased the risk of the combined macrovascular outcome. Depression was not significantly associated with the primary composite ACCORD outcome or the secondary composite microvascular outcome. In ACCORD, probable major depression was associated with an approximate two-fold risk of all-cause mortality. This is somewhat higher than in previous studies and might be due to the increased capability in ACCORD to control for other clinical variables or due to the fact that study subjects were selected for high risk for cardiovascular events. It is notable that this risk was observed in the context of good glucose control in all groups, since poor adherence and poor glucose control have been proposed to account for the effect of depression on mortality in patients with diabetes (11).

The point prevalence of major depression in primary care patients is between 5 and 10% (20), whereas prevalence rates of major depression in patients with diabetes and coronary heart disease (CHD) have been estimated to be 12–18% (21) and 15–23% (22,23), respectively. The relationship between major depression and diabetes and/or heart disease appears to be bidirectional. A recent meta-analysis of 13 studies found that the pooled relative risk for depressed patients subsequently developing diabetes was 1.60 (95% CI 1.37–1.88) (24). This meta-analysis also found modest evidence that diabetes was a risk factor for subsequent major depression (relative risk 1.15 [1.02–1.30]) (24). Major depression following myocardial infarction is also very common, occurring in up to 25% of patients (22,23). Recent data suggest that approximately one-half of patients who developed major depression post–myocardial infarction had recurrent depressive episodes and that half had their first depressive episode post–myocardial infarction (23).

In the general population, both diabetes and depression increase mortality. They exert a greater than additive effect when both are present. A large prospective study of an aging Hispanic population found that lifetime major depression was associated with a 1.64 (95% CI 1.17–2.28) and diabetes a 1.51 (1.23–1.86) HR for all-cause mortality, respectively, compared with those without history of depression or diabetes (9). When combined, depression and diabetes had an HR of 4.59 (2.12–9.93) of all-cause mortality compared with control subjects without history of diabetes or depression (9). Another study that followed >10,000 participants for 8 years found that subjects with significant depressive symptoms (Center for Epidemiologic Studies Depression Scale ≥16) but no diabetes had a 1.20 (1.03–1.40) increase in all-cause mortality, those with diabetes but no depression had a 1.88 (1.55–2.27) increase, and those with both depression and diabetes had a 2.50 (2.04–3.08) increase in all-cause mortality compared with subjects without depression or diabetes (10).

Recent prospective studies have also examined the association of depression with subsequent development of macrovascular and microvascular complications in patients with diabetes. A 5-year prospective study of >4,000 diabetic patients found that comorbid probable major depression on PHQ-9 was associated with a 24% increased risk of macrovascular complications and a 36% increased risk of microvascular complications (11). ACCORD showed a 42% increase in risk of macrovascular complications, but this was of borderline significance, possibly due to the smaller sample. In ACCORD, there was not a significant effect of depression on microvascular complications. It is possible that some previous studies may have overestimated

Table 3—*Baseline characteristics by depression status*

Baseline characteristics	Overall	Ever depressed by any definition	Never depressed by all definitions	*P*
N	2,038	712	1,326	
Demographic				
Age (years)	62.2 ± 6.7	61.2 ± 6.8	62.8 ± 6.5	<0.0001
Female	39.5	46.2	35.8	<0.0001
Non-Hispanic white	65.2	64.9	65.3	0.8490
Black	19.4	18.8	19.8	0.6097
% Hispanic	6.7	7.7	6.2	0.1854
Education				
Highest level of education				0.0031
Less than high school	13.9	17.1	12.2	
High school graduate (or GED)	26.1	26.3	26	
Some college	33.2	33.4	33	
College graduate or more	26.9	23.2	28.9	
Lifestyle				
Cigarette smoker				0.0011
Never	41.1	39.3	42	
Former	45.7	43.7	46.8	
Current	13.2	17	11.2	
Living with someone	80.1	79.2	80.5	0.4737
Drinking at least 1 alcoholic drink per week	22.6	18.4	24.8	0.0010
Comorbidities				
CHD present	36	38.2	34.8	0.1319
Heart failure	5.2	6.7	4.3	0.0236
Amputation resulting from diabetes	2	2.5	1.7	0.2238
Weight (kg)	94.1 ± 18.9	97.1 ± 20	92.5 ± 18.1	<0.0001
BMI (kg/m^2)	32.4 ± 5.5	33.7 ± 5.8	31.7 ± 5.2	<0.0001
Waist circumference (cm)	107.1 ± 13.9	109.6 ± 14.4	105.7 ± 13.4	<0.0001
Peripheral neuropathy	42.9	43.9	42.4	0.5067
Macroalbuminuria	7.2	8.1	6.7	0.2603
Microalbuminuria	30.1	30.2	30	0.9502
Laser photo or vitrectomy	8.7	8.1	9	0.4678
Diabetes profile				
Duration of diabetes (years), median	10	10	10	0.9449
HbA_{1c} (%)	8.3 ± 1.1	8.4 ± 1.1	8.2 ± 1	<0.0001
HbA_{1c} (%), median	8.1	8.2	8	<0.0001
Fasting plasma glucose (mg/dL)	177 ± 57.5	182 ± 61.7	174.4 ± 55	0.0063
	9.7 ± 3.2	10 ± 3.4	9.6 ± 3	
Other biomarkers				
SBP (mmHg)	136.3 ± 17	136.3 ± 16.7	136.3 ± 17.2	0.9734
DBP (mmHg)	74.5 ± 10.9	75.2 ± 11.2	74.1 ± 10.6	0.0389
Pulse	72.4 ± 11.8	73.6 ± 12	71.8 ± 11.7	0.0010
LDL (mg/dL)	104.3 ± 33.9	106.1 ± 35.1	103.3 ± 33.2	0.0842
	2.7 ± 0.9	2.8 ± 0.9	2.7 ± 0.9	
HDL among females (mg/dL)	47.3 ± 12.6	46 ± 11.7	48.2 ± 13.1	0.0115
	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	
HDL among males (mg/dL)	38.8 ± 9.7	37.8 ± 9.8	39.2 ± 9.6	0.0269
	1 ± 0.3	1 ± 0.3	1 ± 0.3	
Total cholesterol (mg/dL)	182.8 ± 41.2	187.4 ± 43	180.3 ± 39.9	0.0003
	4.8 ± 1.1	4.9 ± 1.1	4.7 ± 1	
Triglycerides (mg/dL)	156	172	147	<0.0001
	1.7	1.9	1.6	
Potassium (mg/dL)	4.5 ± 0.4	4.5 ± 0.4	4.5 ± 0.4	0.7106
Serum creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.0025
	79.8 ± 21	77.9 ± 20.1	80.8 ± 21.4	
Estimated GFR	91.7 ± 30.9	92.1 ± 27	91.4 ± 32.8	0.5938

Continued on p. 1713

Table 3—*Continued*

Baseline characteristics	Overall	Ever depressed by any definition	Never depressed by all definitions	*P*
Medications				
Insulin	35.9	41.2	33	0.0003
Sulfonylureas	49.7	44.1	52.6	0.0002
Metformin	59.4	59.4	59.4	0.9795
TZD	20.3	22.3	19.2	0.0972
Any antihypertensive medicine	85.6	85.4	85.7	0.8648
ACE inhibitors	52	52.8	51.6	0.5976
β-Blockers	30.4	30.6	30.3	0.8879
ARBs	16.6	15.2	17.4	0.1930
Thiazide diuretic	26.6	25.4	27.3	0.3604
Calcium channel blocker	18.4	17.1	19.2	0.2622
α-Blockers	2.7	2.5	2.8	0.7276
Statins	63.5	60.5	65.2	0.0386
Other lipid-lowering medicine	10	11	9.5	0.2975
Aspirin	55.7	53.1	57.2	0.0775

Data are means ± SD or percent unless otherwise indicated. ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; GED, General Educational Development; GFR, glomerular filtration rate; SBP, systolic blood pressure; TZD, thiazolidinedione.

the impact of depression on microvascular complications by not establishing whether the depression antedated the microvascular complication or whether the microvascular complication may have contributed to the subsequent onset of depression. One strength of our study is its clear ascertainment of both microvascular complication status and depression status at fixed time intervals during the study period.

Our study adds to the above studies in a number of ways. First, we were able to control for a wide range of baseline clinical characteristics related to cardiovascular risk including age, sex, race/ethnicity, CHD status, HbA_{1c}, lipids, systolic and diastolic blood pressure, BMI, presence of microvascular complications, CHF status, and duration of diabetes. We were also able to control for a number of social and behavioral factors that might confound the depression effect, including smoking, alcohol consumption, living alone, and education. Second, all subjects had reasonably well-controlled glucose, blood pressure, and lipids. Third,

Table 4—*Proportional hazard models of depression predicting ACCORD outcomes*

	Model adjusted for demographic, trial, and clinical variables		Model adjusted for demographic, trial, clinical, and behavioral variables	
Predictor	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary composite outcome (cardiovascular mortality, nonfatal MI, or nonfatal stroke)				
Major depression	1.53 (0.85–2.73)	0.1527	1.47 (0.82–2.64)	0.1913
Minor depression	1.03 (0.56–1.92)	0.9168	0.99 (0.53–1.83)	0.9633
PHQ continuous	1.01 (0.98–1.05)	0.4179	1.01 (0.97–1.04)	0.6286
PHQ score ≥10	1.13 (0.73–1.75)	0.5842	1.07 (0.69–1.66)	0.7722
All-cause mortality				
Major depression	2.24 (1.24–4.06)	0.0078	2.14 (1.18–3.89)	0.0123
Minor depression	1.14 (0.59–2.21)	0.6907	1.08 (0.56–2.10)	0.8143
PHQ continuous	1.05 (1.01–1.09)	0.0096	1.04 (1.01–1.08)	0.0229
PHQ score ≥10	1.84 (1.17–2.89)	0.0078	1.76 (1.12–2.78)	0.0144
Macrovascular composite outcome (major coronary artery disease events, specifically fatal events, nonfatal MI, and unstable angina)				
Major depression	1.42 (0.99–2.04)	0.0552	1.36 (0.95–1.95)	0.0960
Minor depression	1.23 (0.85–1.78)	0.2762	1.23 (0.85–1.78)	0.2762
PHQ continuous	1.02 (1.00–1.04)	0.0247	1.02 (1.00–1.04)	0.0635
PHQ score ≥10	1.14 (0.88–1.49)	0.3261	1.10 (0.84–1.44)	0.4882
Microvascular composite outcome (fatal or nonfatal renal failure, retinal photocoagulation, or vitrectomy for diabetic retinopathy)				
Major depression	0.93 (0.53–1.62)	0.7929	0.97 (0.56–1.70)	0.9229
Minor depression	1.14 (0.70–1.85)	0.6011	1.14 (0.70–1.86)	0.5972
PHQ continuous	1.01 (0.98–1.04)	0.5197	1.01 (0.99–1.04)	0.3168
PHQ score ≥10	1.27 (0.90–1.79)	0.1804	1.31 (0.93–1.86)	0.1273

MI, myocardial infarction.

we were able to examine whether the depression effect on cardiovascular events and mortality differed by intensive versus standard use of glucose, blood pressure and lipid medications, clinical center network, and assignment to one of eight study intervention arms. None of these factors interacted significantly with depression status.

Several factors must be considered in interpreting the results of our study. First, study participants may have had less baseline depression and different subsequent depression trajectories based on the requirement to volunteer for the study and to provide informed consent at enrollment. Second, this analysis used a screening instrument (PHQ-9) to detect depression characterized by high sensitivity but low specificity. Up to one-half of patients with diabetes who score ≥10 on the PHQ-9 may not have major depression on structured interview. Patients with only minor depression tend to do as well with placebo as they do with antidepressant treatment. Third, this study does not consider depression treatment in detail, although the use of PHQ-9 scores obtained at four set time points may reflect the adequacy of depression treatment. Fourth, the composite microvascular end point we evaluated was comprised of advanced complications and we did not assess the impact of depression on early onset of microvascular complications, such as on new-onset microalbuminuria. Fifth, while we controlled for severity and duration of cardiometabolic disease, we did not control for all medical comorbidity. ACCORD did exclude patients with significant kidney or liver disease and cancer and those expected to live <3 years.

Despite these limitations, the results of this study highlight the importance of depression detection and effective depression treatment as key elements in quality diabetes care. Patients with diabetes and PHQ-9 scores of ≥10 randomized to collaborative depression and diabetes treatment showed greater improvements in depression, functioning, and quality of life than those randomized to usual care (25). However, no study has shown that depression treatment reduces mortality in patients with diabetes. Moreover, a recent study showed that the older tricyclic antidepressants may increase CVD with long-term use (26). This effect was not found for the more commonly used selective serotonin reuptake inhibitor antidepressants. The results we report here, in conjunction with data from other studies, support the need for a randomized controlled trial to assess the impact of depression care on mortality in adults with type 2 diabetes.

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M.D.S. researched data and drafted the manuscript. P.O. researched data and edited the manuscript. P.F. and D.H. performed statistical analyses. D.L.S., D.W.R., L.J.F., and K.M.V.N. researched data and edited the manuscript. M.K.A. and W.J.K. reviewed and edited the manuscript. M.D.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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