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Does Emotional Distress Predict Worse Glycemic Control Over Time? Results From the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

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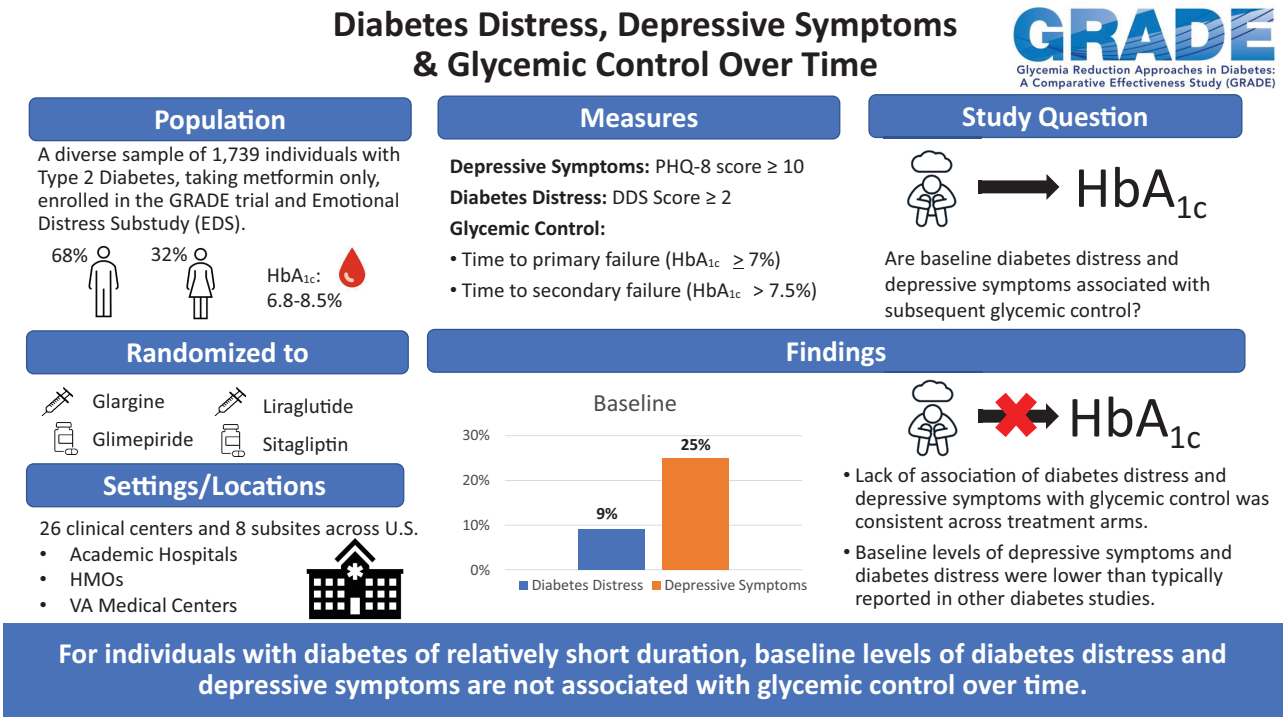

DDS, Diabetes Distress Scale; PHQ-8, eight-item Patient Health Questionnaire; VA, Veterans Affairs.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To examine whether baseline levels of distress are associated with subsequent glycemic control in a diverse sample of 1,739 individuals with type 2 diabetes mellitus enrolled in Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE).

- **What is the specific question(s) we wanted to answer?**
  Are baseline levels of depressive symptoms and diabetes-specific distress associated with glycemic control in GRADE participants?

- **What did we find?**
  Participants were within 10 years of diabetes diagnosis, on metformin monotherapy, and had HbA_{1c} in the range of 6.8%–8.5% at the time of randomization to one of four common glucose-lowering medications. Baseline levels of distress were lower than those typically reported in other diabetes studies.

- **What are the implications of our findings?**
  There were no significant associations between the depressive symptoms or diabetes distress and the subsequent risk of metabolic outcomes, and there were no treatment differences in these relationships.

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**A complete list of members of the GRADE Research Group can be found in the supplementary material online.*

This article is part of a special article collection available at https://diabetesjournals.org/collection/2066/Reports-from-the-GRADE-Study.

This article is featured in podcasts available at diabetesjournals.org/care/pages/diabetes_care_on_air.

OBJECTIVE

To evaluate whether baseline levels of depressive symptoms and diabetes-specific distress are associated with glycemic control in Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), a large randomized controlled trial comparing the metabolic effects of four common glucose-lowering medications when combined with metformin in individuals with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

The primary and secondary outcomes were defined as an HbA_{1c} value ≥7%, subsequently confirmed, and an HbA_{1c} value >7.5%, subsequently confirmed, respectively. Separate Cox proportional hazards models assessed the association between baseline levels of each exposure of interest (depressive symptoms measured with the eight-item Patient Health Questionnaire and diabetes distress measured with the Diabetes Distress Scale) and the subsequent risk of metabolic outcomes.

RESULTS

This substudy included 1,739 participants (56% of whom were non-Hispanic White, 18% non-Hispanic Black, 17% Hispanic, and 68% male; mean [SD] age 58.0 [10.2] years, diabetes duration 4.2 [2.8] years, and HbA_{1c} 7.5% [0.48%]). A total of 1,157 participants reached the primary outcome, with time to event of 2.1 years on average, while 738 participants reached the secondary outcome at 3 years on average. With adjustment for sex, race/ethnicity, treatment group, baseline age, duration of T2DM, BMI, and HbA_{1c}, there were no significant associations between the depressive symptoms or diabetes distress and the subsequent risk of the primary or secondary outcomes.

CONCLUSIONS

The current findings suggest that, at least for individuals with diabetes of relatively short duration, baseline levels of emotional distress are not associated with glycemic control over time.

Emotional distress, including depression and diabetes-related distress (e.g., feeling overwhelmed by diabetes, feelings of failure related to self-care), is a significant and

THE GRADE STUDY

prevalent problem for individuals with type 2 diabetes mellitus (T2DM). Depression is up to twice as common among adults with diabetes compared with those without diabetes (1,2), and 36% of patients treated for diabetes experience moderate to severe levels of diabetes distress (3–5). In cross-sectional studies, both depression and diabetes distress have been associated with glycemic control, diabetes-related complications, and quality of life (5–7). The results of longitudinal studies assessing these relationships are mixed (5,8–10). In a recent meta-analysis investigators examining the longitudinal association between depressive symptoms and glycemic control identified a modest but significant association between baseline depressive symptoms and subsequent glycemic levels, supporting a temporal relationship (11). However, the limited number of studies precluded sensitivity analyses discriminating between type of diabetes, differences in treatment regimens (i.e., insulin vs. noninsulin), or adjustment for diabetes distress. A better understanding of the connection between emotional distress and diabetes control, including causal mechanisms, could support targeted interventions that improve diabetes-related outcomes as well as emotional health.

Both behavioral and biologic mechanisms could contribute to the association between emotional distress and glycemic control (12,13). For example, a meta-analysis showed that higher depressive symptoms are consistently associated with poorer diabetes self-management across a variety of indicators, including medication adherence (14). There is also evidence that biological pathways may be involved. For example, a proinflammatory effect of depressive symptoms has been documented among treated adults with T2DM (15). hs-CRP has been positively correlated with both depression and glycemia (16–19) and thereby has been proposed as a candidate biomarker of the biological processes that may explain how depression/distress could influence blood glucose control and subsequent diabetes health outcomes. Although these causal mechanisms are consistently hypothesized in the literature, they are rarely directly tested prospectively.

This study leveraged the infrastructure of Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), a large randomized controlled trial comparing the metabolic effects of four common glucose-lowering medications when combined with metformin (20). Random assignment to treatment and validated measures of emotional distress, medication adherence, hs-CRP, and glycemic control provided a unique opportunity to evaluate the independent impact of emotional distress on glycemic control, while controlling for important confounders (12). The overarching goal of this study was to evaluate whether baseline levels of emotional distress, including both depressive symptoms and diabetes-specific distress, predict glycemic control over time. We hypothesized that both baseline depressive symptoms and diabetes distress would be associated with reaching the GRADE primary outcome ($HbA_{1c} \geq 7\%$ [53 mmol/mol]) and/or secondary outcome ($HbA_{1c} > 7.5\%$ [58 mmol/mol]). We further hypothesized that the relationships would be mediated by medication nonadherence and/or systemic inflammation (hs-CRP).

RESEARCH DESIGN AND METHODS

Study Design and Overview of GRADE

Details regarding GRADE have previously been published (20,21). The objective of GRADE was to study the comparative effectiveness of four commonly used glucose-lowering medications (basal insulin glargine U-100, sulfonylurea glimepiride, glucagon-like peptide 1 agonist liraglutide, or dipeptidyl peptidase 4 inhibitor sitagliptin) for use with metformin to maintain target glycated hemoglobin levels in individuals with T2DM. The primary and secondary outcomes are defined above. For the current study, analyses include baseline data, collected after final run-in (see below), and subsequent outcome data related to achievement of primary and secondary outcomes.

GRADE Sample, Inclusion Criteria, and Procedures

In total, 5,047 patients with T2DM were enrolled from 36 clinical centers and 9 additional subsites across the U.S. Inclusion criteria included age $\geq$30 years, except for American Indian and Alaska Natives, who were eligible if $\geq$20 years old, and diagnosis of T2DM $<$10 years prior. Eligible participants completed a run-in period lasting 6–14 weeks, during which the metformin dose was titrated to 1,000 (minimum)–2,000 (goal) mg/day, and centrally measured HbA_{1c} at the final run-in visit was between 6.8% and 8.5% (51 and 69 mmol/mol) for study entry. The randomly assigned treatment doses were then added with subsequent adjustment in accordance with their labeling. Participants were evaluated quarterly. The assigned treatment was continued until participants had a confirmed HbA_{1c} level $>$7.5% ($>$58.5 mmol/mol) (the secondary metabolic outcome). At that time, glargine was added to the three assigned noninsulin treatments. Among participants assigned to receive glargine who reached the secondary outcome, prandial rapid-acting insulin aspart was added. The full protocol is available online from https://grade.bsc.gwu.edu.

Emotional Distress Substudy: Study Overview and Design

Substudy Sample

Details regarding the Emotional Distress Substudy (EDS) have previously been published (22). Briefly, all participating GRADE sites were invited but not required to participate in the substudy; 26 of the 36 GRADE centers and 8 of 9 subsites obtained institutional review board approval and chose to participate. Research coordinators at participating sites completed training and certification prior to local EDS implementation. The informed consent of the parent study was amended to include EDS as an embedded substudy. As a result, participants enrolling in GRADE were also enrolled in the substudy; the inclusion/exclusion criteria were the same for the parent and substudy. Recruitment for EDS began more than halfway through the GRADE recruitment period, and enrollment ranged by site from 4 to 138 participants, with a total of 1,739 participants enrolled from 2015 to 2017. Participants completed the EDS assessments, consisting of a self-administered questionnaire battery and collection of a blood sample, at either the final run-in visit or at the baseline visit.

Measures

Depression Symptom Severity. The eight-item Patient Health Questionnaire (PHQ-8) was administered for assessment of participants' depressive symptoms. Reliability and validity are well established (23,24).

The total PHQ-8 scores range between 1 and 24 with a higher score indicating more depressive symptoms. Clinical levels of depressive symptoms, or a positive screen, were defined as a PHQ ≥10. The PHQ-8 consists of four somatic and four cognitive-affective symptoms items; sum scores were calculated and analyzed for symptom profiles separately. Internal reliability for the PHQ-8 in the current sample measure was good (Cronbach α = 0.81).

Diabetes Distress. Diabetes distress was assessed with the 17-item Diabetes Distress Scale (DDS) (25). The measure includes four subscales focused on different sources of distress: emotional burden captures the burden of living with diabetes, regimen distress represents the burden of diabetes self-management, interpersonal distress represents perceived lack of support and empathy from friends and family, and physician distress captures perceived inadequacy of expertise, positive regard, and clear direction from health providers. The full scale and subscales have excellent internal reliability (25) and are sensitive to treatment regimen differences in T2DM (26). The DDS average score is treated as a continuous indicator of diabetes distress severity. A mean score of ≥2 indicates significant diabetes distress (4). Internal reliability for the total scale was excellent (Cronbach α = 0.84).

Medication Adherence. We measured adherence using three items previously validated in HIV/AIDS research (27,28). The three items referenced the last 30 days and included, "On how many days did you miss at least one dose of any of your diabetes medicines?", "How good a job did you do at taking your diabetes medicines in the way you were supposed to?", and "How often did you take your diabetes medicines in the way you were supposed to?" This measurement approach is supported by previous research demonstrating that single item scales (29) with longer assessment time frames (30) have good validity. A total score was calculated for these three items ranging from 0 to 100, with higher scores signifying better adherence.

Demographics and Other Participant Characteristics. Medical history, current medications, alcohol intake, smoking status, race/ethnicity, and educational attainment were self-reported and obtained by staff through interviews. All physical and metabolic measurements were performed by centrally trained certified staff. Medications for depression and anxiety were self-reported. Diabetes-related complications included prior amputation, retinopathy, nephropathy, diabetic peripheral neuropathy (DPN) or cardiovascular autonomic neuropathy (CAN); data on prior myocardial infarction (MI) or stroke were also collected.

HbA_{1c}. Whole blood samples were collected at quarterly visits for measurement of glycated hemoglobin (HbA_{1c}) with a high-performance liquid chromatography method. All measurements were performed at the central laboratory at the Advanced Research and Diagnostic Laboratory (ARDL) at the University of Minnesota.

hs-CRP. hs-CRP is measured in serum with a latex-particle enhanced immunoturbidimetric assay on the Roche cobas c502 chemistry analyzer by the ARDL central laboratory.

Statistical Analyses

Baseline participant characteristics were summarized by means (SD) for quantitative variables (e.g., age) and percentages for categorical variables (e.g., sex) both in the overall cohort and separately by whether a participant ever reached the primary outcome, defined as an HbA_{1c} value ≥7% (53 mmol/mol), subsequently confirmed. The secondary outcome was time to reaching an HbA_{1c} value >7.5% (58 mmol/mol), subsequently confirmed. Associations between the baseline characteristics and the risk of metabolic outcomes were assessed with unadjusted Cox proportional hazards (PH) models.

The primary exposures of interest are the PHQ-8 total score and the DDS average score, as quantitative indicators of depressive symptoms and diabetes distress, respectively. Secondary exposures of interest include PHQ-8 total score ≥10 vs. <10, DDS average score ≥2 vs. <2, and individual subdomains for PHQ-8 (i.e., somatic symptom score and cognitive-affective symptom score) and DDS (i.e., emotional distress, regimen-related distress, physician-related distress, and interpersonal distress).

Kaplan-Meier estimates described the cumulative incidence of the primary and secondary outcomes separately by PHQ-8 total score ≥10 vs. <10 and DDS average score ≥2 vs. <2 status. In separate Cox PH models, each emotional distress predictor was examined as a predictor for primary and secondary metabolic outcomes following three steps: *1*) as an unadjusted predictor; *2*) as a predictor with adjustment for sex, race/ethnicity, randomized treatment group, and baseline values of age, duration of T2DM, BMI, and HbA_{1c} (preplanned); and *3*) as a predictor including step 2 covariates plus education and income (requested post hoc). Joint models were also run that included both depressive symptoms and diabetes distress as predictors and followed the same three steps of adjustment outlined above for the separate models. Additional Cox PH models assessed whether any observed associations were independent of systemic inflammation and medication adherence with further adjustment for hs-CRP and medication adherence.

Heterogeneity of the association between the emotional distress measures (i.e., PHQ-8 total score and DDS average score) and the subsequent risk of outcomes across the four treatment groups was assessed with testing for an interaction between the emotional distress measure and treatment assignment.

All tests were two sided and conducted at a prespecified 0.01 significance level to account for multiple testing.

Given a lower than anticipated prevalence of emotional distress and the relatively confined HbA_{1c} range (6.8%–8.5%) for study inclusion, post hoc power calculations were conducted as requested by a reviewer. The power to detect associations in Cox PH models is a function of the number of events observed. For the main primary metabolic outcome, the observed n = 1,157 events provide ∼80% power to detect an 8.6% increase in risk (i.e., a hazard ratio [HR] of 1.086) associated with 1 SD in a quantitative exposure (such as the PHQ-8 total score or the DDS average score) with use of a two-sided score at level 0.05 in a Cox PH model. The SD for the PHQ-8 total score was ∼4, while that for the DDS average score was 0.74. Therefore, there was ∼80% power to detect 2.2% (= 8.6 / 4) and 11.6% (= 8.6 / 0.74) increases in risk per 1-unit increase in the PHQ-8 total score and the DDS average score, respectively. Likewise, for the secondary metabolic outcome, the 738 observed events provide ∼80% power to detect 2.7% and 14.7% (= 8.6 / 0.74) increases in risk per 1-unit increase in the PHQ-8 total score and the DDS average score.

Data and Resource Availability

This article is based on follow-up data and outcome assessments from the 1,739 participants enrolled into the EDS of GRADE. The GRADE and EDS database will be available in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository in 2024.

RESULTS

Baseline characteristics for the GRADE-EDS sample have previously been reported in detail (31). Briefly, mean age of participants was 58 years and diabetes duration just over 4 years, 68% were male, and 56% were non-Hispanic White, 18% non-Hispanic Black, 9% non-Hispanic other, and 17% Hispanic. Of participants, 30% had a high school degree, GED, or less and 17% had a reported income of USD ≤20,000 (Table 1). At baseline, mean BMI was 34 kg/m^2 and HbA_{1c} 7.5% (58 mmol/mol), with 59% reporting no prior diabetes complications. Mean PHQ-8 score was 3.4, with 9% of participants scoring ≥10 suggesting high risk for clinical depression. Mean DDS score was 1.67, with 25% scoring ≥2 (Supplementary Table 2). Compared with participants who never reached the primary outcome, those with confirmed HbA_{1c} ≥7% (53 mmol/mol) at any point were younger, with a shorter duration of diabetes, and a higher proportion were women, Hispanic participants, nonsmokers, employed, and had higher HbA_{1c} and hs-CRP levels at baseline. Additionally, they reported slightly worse medication adherence and higher levels of diabetes distress. These demographic and metabolic differences were similar in comparing those who reached secondary end point of >7.5% (58 mmol/mol) with those who did not (Supplementary Table 1).

Figure 1 shows the unadjusted cumulative incidence of the primary and secondary outcomes by PHQ-8 total score ≥10 vs. <10 and DDS average score ≥2 vs. <2. The number of events, average length of follow-up, and rates for these outcomes are presented in Supplementary Table 2 both overall and separately by PHQ-8 total score ≥10 vs. <10 and DDS average score ≥2 vs. <2. Briefly, 1,157 participants reached the primary metabolic outcome over an average follow-up of 2.1 years (crude rate 31 events per 100 participants at risk for 1 year) and 738 participants reached the secondary outcome over an average follow-up of 3 years (rate 14.2 events per 100 participants at risk for 1 year).

Depression Symptoms and Metabolic Outcomes

Unadjusted models showed no significant association between depressive symptoms and the primary outcome, as did subsequent models with adjustment for preplanned and post hoc covariates (Table 2).

Unadjusted models also showed no significant association between depressive symptoms and the secondary outcome (Table 3). After adjustment for preplanned covariates, associations of small magnitude of the PHQ-8 total score and the PHQ-8 somatic depression score with subsequent risk of reaching the secondary end point (HR 1.02, P = 0.014, and HR 1.18, P = 0.016, respectively) were noted but failed to meet the prespecified 0.01 level of significance.

In post hoc analyses with further adjustment for education and income, there were significant associations of the PHQ-8 total score and the PHQ-8 somatic depression score with subsequent risk of reaching the secondary end point (HR 1.03, P = 0.007, and HR 1.22, P = 0.009, respectively).

Diabetes Distress and Metabolic Outcomes

In unadjusted models, diabetes distress (average and dichotomous) and two DDS subscores (emotional distress and regimen-related distress) were significantly associated with the primary outcome (Table 2), with increased risk of 9%–13% for continuous measures of diabetes distress and subscores and 21% for elevated distress versus no distress. However, diabetes distress was not significantly associated with the primary outcome after adjustment for preplanned and post hoc covariates (Table 2).

Unadjusted models also showed a significant association of diabetes distress (average and dichotomous) and two DDS subscores (emotional distress and interpersonal distress) with the secondary outcome (Table 3). After adjustment for preplanned and post hoc covariates, these associations were no longer significant.

Independent Effects of Depressive Symptoms and Diabetes Distress

In unadjusted analyses, when depressive symptoms and diabetes distress were included in the same model as predictors of primary and secondary outcomes, only diabetes distress showed an independent relationship with the primary outcome (Table 2). However, this independent association was no longer significant with adjustment for prespecified and post hoc covariates. In considering the secondary outcome, there were no significant associations between depressive symptoms or diabetes distress in unadjusted or adjusted analyses.

Results were similar in models with adjustment for medication adherence, hs-CRP, and the combination of the two (Supplementary Table 3). There was no significant heterogeneity in the association between the emotional distress measures (i.e., PHQ-8 total score and DDS average score) and the subsequent risk of outcomes across the four treatment groups (Supplementary Table 4).

CONCLUSIONS

In this sample of 1,739 individuals with T2DM duration <10 years at baseline, clinically meaningful levels of depressive symptoms and diabetes distress were lower than those seen in many previous studies of individuals with T2DM. Both diabetes distress and medication adherence were modestly associated with time to primary outcome defined as reaching an HbA_{1c} of ≥7% (53 mmol/mol) in unadjusted models. However, after adjustment for sex, race/ethnicity, treatment group, duration of diabetes, and baseline values for age, BMI, and HbA_{1c}, there were no significant associations between the baseline depressive symptoms or diabetes distress levels and the subsequent risk of either the primary or the secondary outcome. Notably, there were no treatment group differences in these relationships, including for insulin.

Previous studies have documented a positive association between depressive symptoms/emotional distress and higher HbA_{1c}. However, most of these studies included individuals with no specification of diabetes duration, treatment regimen, or level of glycemic control and were not designed to distinguish the impacts of worsening disease, increasing rates of complications, and treatment effects. The

Table 1—Baseline characteristics

		Ever confirmed primary outcome (HbA_{1c} ≥7%)		
	Overall	No (*n* = 582)	Yes (*n* = 1,157)	*P**
Age (years)	57.97 (10.21)	60.47 (9.35)	56.71 (10.39)	**<0.0001**
T2DM duration (years)	4.21 (2.81)	4.36 (2.87)	4.13 (2.78)	0.2821
Sex (%)				
Male	68	71	66	
Female	32	29	34	**0.0074**
Race/ethnicity				
Non-Hispanic White	56	58	54	
Hispanic	17	12	19	
Non-Hispanic Black	18	20	17	
Non-Hispanic other	9	9	10	**0.0001**
Smoking status				
Never smoked	52	44	56	
Past smoker	35	40	33	
Current smoker	13	16	11	**<0.0001**
BMI (kg/m^2)	34.09 (6.47)	34.04 (6.08)	34.12 (6.67)	0.7472
Education				
High school/GED or less	30	30	30	
Some college	29	30	29	
College/graduate school	41	40	41	0.5713
Income (USD)				
<10,000	6	6	7	
10,000–20,000	11	10	11	
20,000–50,000	32	29	33	
≥50,000	51	55	49	0.0383
Living status				
Living alone	17	19	16	
With another adult	79	78	80	
With children only	4	3	4	0.3981
Employment				
Employed	56	50	59	
Retired	26	35	22	
Other	18	15	19	**<0.0001**
Any diabetes-related complications				
No	59	54	62	
Yes	41	46	38	0.0455
Any macrovascular disease				
No	93	92	93	
Yes	7	8	7	0.1829
Medication adherence	89.88 (11.05)	91.13 (10.24)	89.26 (11.39)	**0.0004**
HbA_{1c} (%)	7.51 (0.48)	7.34 (0.43)	7.59 (0.48)	**<0.0001**
HbA_{1c} (mmol/mol)	59 (5)	57 (5)	59 (5)	**<0.0001**
hs-CRP (mg/L)**	4.17 (4.60); 2.61 (1.22, 5.26)	4.19 (4.85); 2.46 (1.16, 5.21)	4.15 (4.47); 2.66 (1.30, 5.26)	0.2100
PHQ-8 total	3.44 (3.96)	3.30 (3.91)	3.51 (3.98)	0.1225
DDS average	1.67 (0.74)	1.61 (0.68)	1.70 (0.77)	**0.0011**

Data are percent for categorical variables and mean (SD) for quantitative variables, unless otherwise indicated. Employment: employed, currently employed full- or part-time, full-time homemaker, or seasonally employed; retired, currently retired; other, currently not employed, student, never worked or disabled, or other. Any diabetes-related complication: prior amputation, retinopathy, nephropathy (presence of either albumin-to-creatinine ratio ≥30 mg/g or estimated glomerular filtration rate <60 $mL/min/m^2$), or neuropathy (presence of either diabetic peripheral neuropathy, with use of a composite cutoff including both the Michigan Neuropathy Screening Instrument questionnaire score and the clinical examination, or cardiovascular autonomic neuropathy defined according to two heart rate variability (HRV) indices: SD of normally conducted R-R intervals <8.2 ms and root mean square of successive differences between normal-to-normal R-R intervals <8 ms). Any macrovascular disease: prior MI or stroke. Bold type represents $P < 0.01$. **P* values from unadjusted Cox PH models. **hs-CRP has a distribution skewed to the right (Supplementary Fig. 1), and both mean (SD) and median (1st, 3rd quartiles) are reported.

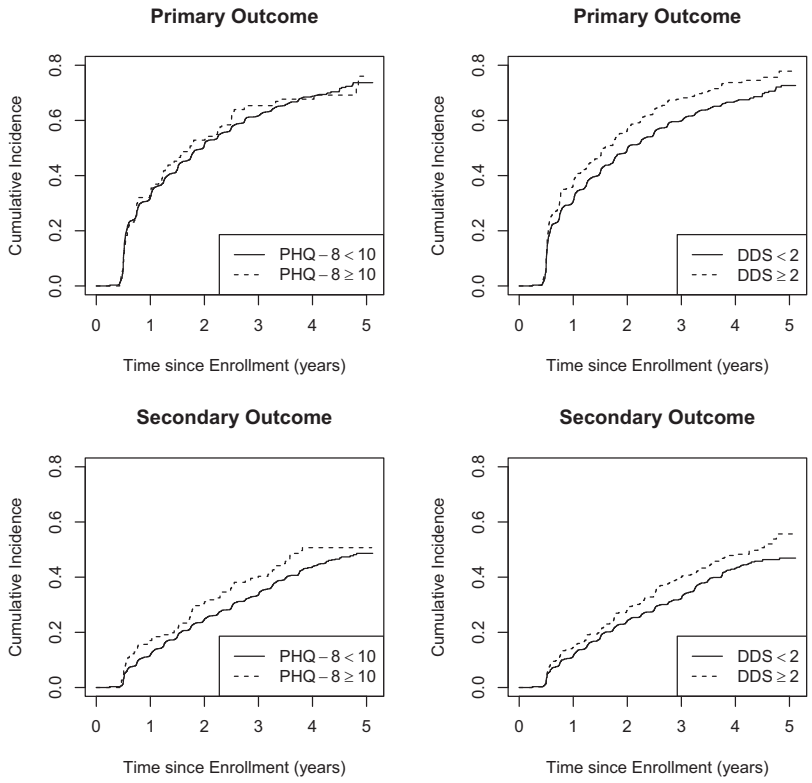

Figure 1—Cumulative incidence of the primary outcome (HbA_{1c} ≥7% subsequently confirmed [top]) and secondary outcome (HbA_{1c} >7.5% subsequently confirmed [bottom]) separately by PHQ-8 total score (left) and DDS average score (right).

study design of GRADE, with random assignment to one of four different treatments and the focus on individuals within 10 years of diagnosis with an HbA_{1c} range of 6.8%–8.5% (51–69 mmol/mol), allowed for a rigorous assessment of the relationship between measures of emotional distress and glycemic control. The null findings in preplanned analyses suggest that for individuals whose characteristics match those of the GRADE sample, baseline emotional distress is not an independent driver of glycemic control. It is interesting that post hoc analyses with further adjustment for education and income demonstrated a modest but significant association between higher baseline depressive symptoms (as in PHQ total score and somatic subscore) and subsequent risk for reaching an HbA_{1c} of 7.5% (58 mmol/mol). This finding is consistent with the findings described in the recent meta-analysis by Beran et al. (11), who identified a temporal association between depressive symptoms and subsequent glycemic control. However, as post hoc analyses these findings should be interpreted with caution and confirmed in future prospective studies.

It is important to note that the current results are limited to this study scenario. The constrained HbA_{1c} inclusion criteria (6.8%–8.5% [51–69 mmol/mol]) precluded examination of these relationships for individuals with higher levels of chronic hyperglycemia. It is possible that emotional distress would predict changes in HbA_{1c} over time had individuals with poorer initial glycemic control (higher baseline HbA_{1c}) been included. It is also possible that other factors specific to participation in GRADE, including free medication, quarterly visits, close follow-up, and provision of standard diabetes education materials, which included information about diabetes distress, could have mitigated the impact of baseline emotional distress over time. The level of care provided in GRADE may not reflect the reality of diabetes care across the U.S., and thus results should be interpreted with caution. Finally, depressive symptoms and distress levels are known to fluctuate over time. Future studies should include evaluation of whether changes in emotional distress over time are related to changes in glycemic control and the extent to which one may predict the other. Nevertheless, results from our study suggest that initial levels of emotional distress have little bearing on glycemic benefits derived from treatment intensification with any of the treatments investigated in GRADE, at least in the supportive context provided by the study.

In the current study, the proportion of individuals reaching a clinically meaningful cut point for depressive symptoms and diabetes distress, 9% and 25%, respectively, is lower than those reported in other studies. In a 2006 meta-analysis, Ali et al. (1) reported a higher prevalence of comorbid depression among adults with T2DM in comparison with those without (17.6% vs. 9.8%), with some evidence of increased risk for depression for individuals on insulin (32) and those with higher rates of complications (6,33). In all of the studies, patients with diabetes had higher rates of comorbid conditions, including hypertension and cardiac disease, compared with those without diabetes; however, only one study reported prevalence rates adjusted for multiple confounders (comorbid disease, age, sex, BMI), limiting the authors' ability to conduct a rigorous meta-analysis for specific risk factors. In a subsequent review published in 2021 (34) investigators found similar results, with prevalence rates nearly twice as high for individuals with T2DM compared with those without (19.1% vs. 10.7%). While results of both reviews suggest that the prevalence of depression is higher for individuals with T2DM, precise estimates are unavailable due to the lack of reporting and adjustment for important confounders.

Similar to the depression findings, the prevalence of clinically significant diabetes distress in GRADE was lower compared with previous studies. In 2017, a meta-analysis of 55 studies (n = 36,998) demonstrated an overall prevalence of 36% for clinically significant diabetes distress in people with T2DM (3). Authors noted a higher prevalence of distress in studies with a majority of female participants and in studies with a higher prevalence of comorbid depression. The relatively low levels of emotional distress in the current study may be explained by GRADE's focus on individuals with relatively short duration of diabetes (<10 years since T2DM diagnosis, mean time with T2DM <4.5 years) with low rates of existing complications (e.g., 7% baseline prevalence of either MI and/or stroke), supporting the hypothesis that the prevalence of emotional

Table 2—Association of depression symptoms and diabetes distress with subsequent risk of GRADE primary metabolic outcome (HbA_{1c} ≥7% subsequently confirmed)

	Primary metabolic outcome (unadjusted)		Primary metabolic outcome (model 1*)		Primary metabolic outcome (model 2**)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Separate models						
Depression symptoms						
PHQ-8 total score	1.01 (1.00–1.03)	0.123	1.01 (1.00–1.03)	0.076	1.01 (1.00–1.03)	0.110
PHQ-8 total score (≥10 vs. <10)	1.03 (0.84–1.27)	0.747	1.09 (0.88–1.34)	0.422	1.13 (0.91–1.41)	0.272
PHQ-8 somatic depression score	1.09 (0.98–1.21)	0.105	1.10 (0.99–1.23)	0.080	1.10 (0.98–1.24)	0.113
PHQ-8 cognitive-affective depression score	1.06 (0.95–1.19)	0.266	1.09 (0.97–1.22)	0.146	1.09 (1.00–1.23)	0.193
Diabetes distress						
DDS average score	1.13 (1.05–1.22)	**0.001**	1.04 (0.96–1.12)	0.351	1.10 (1.01–1.20)	0.027
DDS average score (≥2 vs. <2)	1.21 (1.06–1.38)	**0.005**	1.08 (0.94–1.23)	0.287	1.16 (1.00–1.33)	0.050
DDS emotional distress	1.11 (1.05–1.18)	**0.001**	1.03 (0.97–1.10)	0.303	1.07 (1.00–1.15)	0.071
DDS regimen-related distress	1.09 (1.02–1.15)	**0.007**	1.03 (0.97–1.09)	0.310	1.07 (1.01–1.15)	0.033
DDS physician-related distress	1.07 (1.00–1.14)	0.054	1.03 (0.96–1.10)	0.448	1.08 (1.00–1.16)	0.058
DDS interpersonal distress	1.08 (1.01–1.15)	0.016	1.00 (0.94–1.07)	0.957	1.04 (0.96–1.11)	0.334
Joint model						
PHQ-8 total score	1.00 (0.99–1.02)	0.734	1.01 (1.00–1.03)	0.151	1.01 (1.00–1.02)	0.494
DDS average score	1.12 (1.04–1.22)	**0.004**	1.01 (0.93–1.10)	0.775	1.09 (0.99–1.19)	0.082

*Model 1, preplanned analyses, with adjustment for sex, race/ethnicity, randomized treatment group, and baseline values of age, duration of T2DM, BMI, and HbA_{1c}. **Model 2, post hoc analyses, with model 1 adjustments plus education and income. Bold type represents $P < 0.01$.

distress in T2DM is influenced by the presence of additional risk factors, such as diabetes complications and severity of illness. It is also possible that the study sample having a higher proportion of men (68%) compared with women (32%) contributed to a lower baseline level of distress. Finally, individuals who volunteer to participate in a long-term intensive intervention study may be less depressed and/or distressed than those who choose not to participate.

Strengths of this study include a relatively large, well-characterized, and diverse sample, with significant representation of Black and Hispanic or Latino participants, from across a range of socioeconomic strata recruited from all regions of the U.S. Random assignment to treatment regimens and the longitudinal follow-up with quarterly and semiannual assessments over 3 years are also strengths. The study also has several limitations. Participants in EDS were by definition enrolled in a randomized controlled trial and as such are not necessarily representative of all people with T2DM; care received as a part of GRADE (regular visits, free medication, etc.) does not reflect routine care for many individuals with T2DM. Further, the study sample is restricted by GRADE inclusion and exclusion criteria and results cannot be extrapolated to the entire population of individuals with T2DM. Although baseline levels of significant diabetes distress and clinically meaningful

Table 3—Association of depression symptoms and diabetes distress with subsequent risk of secondary metabolic outcome (HbA_{1c} >7.5% subsequently confirmed)

	Unadjusted		Model 1*		Model 2**	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Separate models						
Depression symptoms						
PHQ-8 total score	1.02 (1.00–1.04)	0.020	1.02 (1.00–1.04)	0.014	1.03 (1.01–1.05)	**0.007**
PHQ-8 total score (≥10 vs. <10)	1.20 (0.94–1.54)	0.146	1.22 (0.95–1.57)	0.126	1.31 (1.00–1.71)	0.051
PHQ-8 somatic depression score	1.16 (1.02–1.32)	0.025	1.18 (1.03–1.34)	0.016	1.22 (1.05–1.41)	**0.009**
PHQ-8 cognitive-affective depression score	1.15 (1.00–1.31)	0.043	1.16 (1.01–1.33)	0.037	1.20 (1.03–1.39)	0.021
Diabetes distress						
DDS average score	1.14 (1.04–1.25)	**0.004**	1.04 (0.95–1.15)	0.376	1.11 (1.00–1.23)	0.055
DDS average score (≥2 vs. <2)	1.19 (1.01–1.40)	0.037	1.04 (0.88–1.22)	0.676	1.14 (0.95–1.37)	0.148
DDS emotional distress	1.12 (1.04–1.21)	**0.003**	1.03 (0.95–1.12)	0.457	1.07 (0.99–1.17)	0.103
DDS regimen-related distress	1.08 (1.00–1.17)	0.039	1.03 (0.96–1.11)	0.426	1.07 (0.99–1.17)	0.081
DDS physician-related distress	1.07 (0.98–1.16)	0.125	1.03 (0.95–1.12)	0.512	1.04 (0.95–1.14)	0.357
DDS interpersonal distress	1.11 (1.03–1.20)	**0.009**	1.03 (0.95–1.12)	0.451	1.08 (0.99–1.18)	0.079
Joint model						
PHQ-8 total score	1.01 (0.99–1.03)	0.168	1.02 (1.00–1.04)	0.024	1.02 (1.00–1.05)	0.032
DDS average score	1.11 (1.01–1.23)	0.036	1.00 (0.90–1.11)	0.979	1.06 (0.95–1.19)	0.319

*Model 1, preplanned analyses, with adjustment for sex, race/ethnicity, randomized treatment group, and baseline values of age, duration of T2DM, BMI, and HbA_{1c}. **Model 2, post hoc analyses, with model 1 adjustments plus education and income. Bold type represents $P < 0.01$.

depressive symptoms were lower than anticipated, the large number of events (e.g., *n* = 1,157 primary and *n* = 738 secondary metabolic outcomes) provided adequate statistical power (i.e., 80%) to detect even very small HRs per 1-unit change in the exposures. As such, the clinical relevance of the modest but statistically significant associations observed in some unadjusted and post hoc analyses is unclear. The study included assessment of self-reported depressive symptoms and did not include a diagnostic interview for depression as a gold standard. As noted above, the study only includes an assessment of baseline levels of emotional distress.

Conclusion

In this study of 1,739 individuals with T2DM diagnosed within the last 10 years and HbA_{1c} between 6.8% and 8.5% (51 and 69 mmol/mol), baseline levels of emotional distress were not associated with reaching the primary or secondary outcome after adjustment for preplanned covariates. The modest association between glycemic outcomes and diabetes distress in unadjusted models was attenuated after the addition of demographic (sex, age, race/ethnicity) and clinical (duration of T2DM, BMI, and HbA_{1c}) characteristics. These findings suggest that, at least for this population with a relatively short duration of diabetes and low levels of depressive symptoms and diabetes distress, baseline levels of emotional distress do not independently drive glycemic control, regardless of which of the four study medications is added to metformin monotherapy. It is important to note that the lack of an association between emotional distress and glycemic control in this study does not detract from current recommendations to assess and address depressive symptoms and distress levels as important patient-reported outcomes (35,36).

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