Longitudinal Changes in Depression Symptoms and Glycemia in Adults With Type 1 Diabetes

Paula M. Trief,[1] Nicole C. Foster,[2] Naomi Chaytor,[3] Marisa E. Hilliard,[4] Julie M. Kittelsrud,[5] Sarah S. Jaser,[6] Shideh Majidi,[7] Sarah D. Corathers,[8] Suzan Bzdick,[1] Deanna W. Adkins,[9] and Ruth S. Weinstock[1]

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OBJECTIVE

This study assessed longitudinal change in depression symptoms over ≥4 years in adults with type 1 diabetes and examined the association between change in depression symptom status and glycemia.

RESEARCH DESIGN AND METHODS

Adults in the T1D Exchange registry with HbA_{1c} and Patient Health Questionnaire (PHQ-8) at 1 year (baseline) and 5 years post-enrollment (follow-up; n = 2,744, mean age, 42 years; 57% female, 92% white; mean HbA_{1c}, 7.6% [58 mmol/mol]) were included. Depression status was defined as Persistent Elevated Depression Symptoms (EDS) (EDS at baseline and follow-up), Resolved EDS (EDS at baseline, no EDS at follow-up), New Onset EDS (no EDS at baseline, EDS at follow-up), and Not Depressed (no EDS at baseline or follow-up).

RESULTS

Overall, 131 (5%) had Persistent EDS, 122 (4%) had Resolved EDS, 168 (6%) had New Onset EDS, and 2,323 (85%) were Not Depressed. Of those with EDS (PHQ ≥ 10) at baseline, 53% had EDS at follow-up; of those not depressed at baseline, 7% had EDS at follow-up. An increase in PHQ-8 was associated with an increase in HbA_{1c} ($P < 0.001$). Although HbA_{1c} increased in all groups, the increase was less in the Resolved EDS and Not Depressed groups ($P = 0.001$). Persistent EDS and New Onset EDS groups were more likely to experience diabetic ketoacidosis (DKA) ($P < 0.001$).

CONCLUSIONS

T1D Exchange registry data provide evidence for relationships over time between persistently, and newly developing EDSs and worsening glycemic control, and suggest relationships between depression symptoms and the occurrence of severe hypoglycemia and DKA. Successful treatment of depression symptoms may lead to better long-term diabetes outcomes.

Studies have shown that the prevalence of clinically significant symptoms of depression is two times higher in people with diabetes than it is in the general population (1–4). However, most studies combine people with type 1 and type 2 diabetes or report only on people with type 2 diabetes. Few studies have assessed only individuals with a diagnosis of type 1 diabetes (T1D).

In prior work, assessments of depressive symptoms (eight-item Patient Health Questionnaire depression scale [PHQ-8]) in adults (n = 6,172; median age, 34 years)

[1]State University of New York Upstate Medical University, Syracuse, NY
[2]Jaeb Center for Health Research, Tampa, FL
[3]Elson S. Floyd College of Medicine, Washington State University, Spokane, WA
[4]Baylor College of Medicine and Texas Children's Hospital, Houston, TX
[5]Avera McKennan Hospital and University Health Center, Sioux Falls, SD
[6]Vanderbilt University Medical Center, Nashville, TN
[7]Barbara Davis Center for Diabetes, Aurora, CO
[8]Cinncinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH
[9]Duke Children's Hospital and Health Center, Durham, NC

Corresponding author: Nicole C. Foster, t1dstats3@jaeb.org

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participating in the T1D Exchange clinic registry identified probable major depression, defined as elevated depressive symptoms (EDS), in 10.3% of registry participants using traditional scoring criteria (i.e., PHQ score ≥10) or 4.6% of participants using more conservative scoring criteria (5). These rates are comparable to adults in the general population. Fisher et al. (6) reported similar prevalence data (*n* = 368). We also reported that the group with EDS had higher HbA_{1c} levels (not found by Fisher et al.), and worse clinical outcomes: the EDS group was more likely than the not depressed group to report at least one diabetes-related complication, to report episodes of diabetic ketoacidosis (DKA) and severe hypoglycemic (SH) events within the prior 3 months, to exercise less often, and to miss insulin doses.

A significant limitation of most prior work is that the data were cross-sectional and, thus, could not differentiate between poorer glycemic control and self-care relating to the development of depression symptoms over time and the presence of significant depression symptoms relating to poorer self-care and glycemic control over time. Also, previous data sets did not report the course of depression symptoms over time. Not surprisingly, others have reported that some get worse, some stay the same, and some improve (7,8), but little is known about how these different patterns of depressive symptoms relate to diabetes outcomes.

The aims of this study were *1*) to assess change in depression symptoms over ≥4 years in adults with T1D and *2*) to examine the association between change in depression symptoms and glycemic outcomes. We hypothesized that improvement in depression symptoms would be related to improved glycemic outcomes over time.

RESEARCH DESIGN AND METHODS

The T1D Exchange Clinic Network and registry includes >80 U.S.-based pediatric and adult endocrinology practices. To be enrolled in the clinic registry, participants must have a clinical diagnosis of presumed autoimmune T1D and islet cell antibodies present or insulin must have been started at or shortly after diagnosis and used continually thereafter. Details on the eligibility criteria and informed consent process for the T1D Exchange clinic registry have been published previously (9). Data (questionnaires and medical data from patient records) were collected from >26,000 children and adults with T1D enrolled between September 2010 and December 2012. At 1 year after enrollment (referred to as "baseline") and ~5 years after enrollment (referred to as "follow-up"; April 2016 through April 2018), adult registry participants (aged ≥18 years at baseline) also completed the PHQ-8. This report includes data on the 2,744 adult participants who met inclusion criteria and who completed the PHQ-8 at baseline and follow-up.

Measures

Depression Symptoms

The PHQ-8 is a standardized and validated measure of self-reported depression symptoms and their severity (10,11) that has been used in numerous patient-related studies (12), including with patients with diabetes (5,13). The PHQ-8 asks, on how many days in the past 2 weeks the individual has experienced eight of the nine symptoms of major depressive disorder defined in the DSM-IV (14). The ninth criterion assesses thoughts of suicide and self-harm, which is often omitted from the PHQ-9 when used for research purposes. This yields the PHQ-8 and does not affect scoring validity (10). Respondents indicate (0–3 point scale) whether they have experienced the symptom "not at all" (0), "on several days" (1), "more than half the days" (2), or "nearly every day" (3); thus, the total PHQ-8 score has a possible range of 0–24.

Versions of the PHQ are commonly used for depression screening, and the American Diabetes Association recommends the PHQ as a valid and relevant depression screening and monitoring tool for people with diabetes (15,16). A PHQ-8 cutoff score of ≥10 is most commonly used to define a clinically relevant level of major depression symptoms, as it has been demonstrated that this scoring threshold has a sensitivity and specificity of 88% for the diagnosis of major depression (10–12) and thus is a valid proxy for probable major depression.

An alternative approach is to use the scoring algorithm used in the Behavioral Risk Factor Surveillance Survey (BRFSS) (17). With this algorithm, respondents are identified as having probable major depression if they meet at least five of the eight DSM-IV–defined depression criteria for "more than half the days" (i.e., rated the symptom a 2 or 3) and at least one of those criteria is depressed mood or loss of interest (anhedonia). The algorithm is more akin to results one might obtain from a structured clinical interview, which is considered the gold standard of depression diagnosis. Algorithm results can be compared with BRFSS results for the general population. Probable major depression was defined in two ways in these analyses: *1*) using the PHQ-8 cutoff of ≥10 and *2*) using the BRFSS algorithm. Results using these methods were in the same direction, but not always identical; therefore, we report results using both methods.

A Note About Language. The PHQ-8, scored via algorithm or cutoff, is used to screen for probable major depression, but it does not confirm a diagnosis of major depression. Given the high rate of false positives identified with the PHQ-8, if someone screens positive, practitioners should follow-up with a structured clinical interview to establish a diagnosis before intervening. Therefore, we use the term "elevated depression symptoms (EDS)" to label our groups of interest. We labeled the group of those with EDS at both baseline and follow-up as "Persistent EDS," those with EDS at baseline but not at follow-up as "Resolved EDS," those without EDS at baseline but with EDS at follow-up as "New Onset EDS," and those without EDS at both baseline and follow-up as "Not Depressed," recognizing that these terms may lack specificity and do not describe the true course of depression symptoms over a 5-year span given the episodic nature of depression symptoms. We urge the reader to consider this report with these caveats about language.

Demographic Data

Sex, race/ethnicity, household income, and insurance status were collected through participant questionnaire. Information about age, duration of diabetes, insulin modality (pump or injections), use of continuous glucose monitor (CGM), and BMI (height/weight) was collected from medical record data extraction.

Diabetes Outcomes

HbA_{1c} was obtained from medical record data extraction (median [interquartile

range]). The duration from PHQ to HbA_{1c} measurement was 13 days (0, 77) at baseline and 0 days (−3, 49) at follow-up. HbA_{1c} values were measured by a point-of-care device or local laboratory. Results were similar when restricting the data set to records with HbA_{1c} measured within 3 months of the PHQ at both time points. Information on the occurrence of severe hypoglycemia (SH; defined as an episode of low blood glucose resulting in seizure and/or loss of consciousness) and diabetic ketoacidosis (DKA; defined as the occurrence of ketoacidosis resulting in hospitalization) within the prior 3 months was obtained by participant self-report on the baseline and follow-up questionnaires.

Statistical Methods

Participants were defined as having, or not having, EDS using the two definitions described above (i.e., PHQ-8 ≥10 or by the BRFSS algorithm). Continuous PHQ-8 score and change in continuous PHQ-8 score between baseline and follow-up (positive value indicating increase in score) were also used to define depression symptom status.

Multivariable linear regression models were used to assess the association between change in HbA_{1c} between baseline and follow-up (positive value indicating increase in HbA_{1c}) and depression symptoms status (separately for the two binary depression symptoms status definitions and the continuous PHQ-8 score). Linear regression models also were used to assess the association between change in the sex- and age-adjusted BMI *z*-score from baseline to follow-up (positive value indicating an increase in the BMI *z*-score) and depression symptom status. Separate multivariable logistic regression models were used to assess the associations between EDS and SH at follow-up and between EDS and DKA at follow-up. Multinomial logistic regression models with stepwise selection procedure were used to assess the association between depression symptom status (separate models for PHQ-8 ≥10 and BRFSS definitions) and the following participant characteristics: age at baseline, sex, race/ethnicity, BMI *z*-score at baseline, insurance status at baseline, pump use at baseline, and CGM status (from baseline to follow-up).

Results are expressed as mean ± SD for normally distributed variables or median (interquartile range) for nonnormally distributed variables. To account for possible confounding, the following covariates were assessed for association with each outcome (excluding the multinomial models for depression symptom status) through bivariate analysis and selection models: age (at baseline), sex, race/ethnicity, duration of diabetes (at baseline), CGM status (from baseline to follow-up), pump status (from baseline to follow-up), insurance status (at baseline and follow-up), annual income (at baseline and follow-up), and clinic site. The following additional covariates were assessed for specific analyses: HbA_{1c} at baseline (for change in HbA_{1c} outcome), BMI *z*-score at baseline (for change in BMI outcome), report of SH at baseline (for SH at follow-up outcome), and report of DKA at baseline (for DKA at follow-up outcome). If an association with an outcome was present, the covariate was included in the model for that outcome.

Data analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). In view of multiple comparisons, only *P* values <0.01 were considered suggestive of a true association. All *P* values are two-sided.

RESULTS

The 2,744 participants ranged in age from 18 to 85 years at baseline (mean 42 ± 16 years); 57% were female, and 92% were non-Hispanic white. Median duration of diabetes at baseline was 21 (11, 32) years. CGM use was 22% at baseline and 30% at follow-up. Mean HbA_{1c} was 7.6% (60 mmol/mol) at baseline and 7.7% (61 mmol/mol) at follow-up. Additional participant characteristics are described in Table 1. Compared with the larger group of all other adult clinic registrants (1 April 2016 –31 March 2018, *n* = 6,444), this analysis cohort (*n* = 2,744) was older (mean 47 vs. 41 years), more likely to be female (57% vs. 51%), more likely to be non-Hispanic white (92% vs. 87%), more likely to use technology (67% vs. 62%

Table 1—Participant characteristics

N = 2,744	Baseline (year 1)	Follow-up (year 5)
Age (years)	42 ± 16	47 ± 16
Female	1,556 (57)	
Race/ethnicity		
White non-Hispanic	2,518 (92)	
Black non-Hispanic	62 (2)	
Hispanic or Latino	88 (3)	
Other race/ethnicity	75 (3)	
Duration of T1D (years)	21 (11, 32)	25 (16, 37)
BMI *z*-score[a]	−0.02 ± 0.86	−0.04 ± 0.76
BMI (kg/m^2)[a]	27 ± 8	28 ± 6
Insurance status		
Private	2,194 (83)	2,106 (79)
Medicaid	119 (4)	153 (6)
Other insurance	294 (11)	388 (15)
No insurance	38 (1)	9 (<1)
Annual household income		
<$35,000	366 (16)	385 (17)
$35,000 to <$75,000	682 (30)	592 (26)
≥$75,000	1,221 (54)	1,282 (57)
CGM used	616 (22)	815 (30)
Pump used	1,749 (64)	1,813 (67)
HbA_{1c}, %	7.6 ± 1.3	7.7 ± 1.2
≥1 Severe hypoglycemia event[b]	240 (9)	216 (8)
≥1 DKA event	76 (3)	67 (2)
PHQ-8 ≥10	253 (9)	299 (11)
PHQ-8 score	3.3 ± 4.2	3.8 ± 4.5
BRFSS	124 (5)	152 (6)

Data are presented as the mean ± SD, median (25th percentile, 75th percentile), or *n* (%). [a]BMI and BMI *z*-score are sex and age adjusted. [b]Severe hypoglycemia defined as seizure and/or loss of consciousness within the prior 3 months.

pump; 39% vs. 31% CGM), and had lower HbA_{1c} (7.7% vs. 8.0% [61 vs. 64 mmol/mol]).

Depression Symptom Status From Baseline to Follow-up

Of the 2,744 participants, 253 (9%) were defined as having EDS at baseline according to the PHQ-8 ≥10 definition and 124 (5%) according to the BRFSS algorithm. All participants defined as having EDS according to the BRFSS algorithm also were defined as having EDS according to the PHQ-8 cutoff score. At follow-up, 299 (11%) and 152 (6%), respectively, were defined as having EDS according to the PHQ-8 ≥10 criterion and BRFSS algorithm. The mean PHQ-8 score was 3.3 ± 4.2 at baseline and 3.8 ± 4.5 at follow-up.

When the PHQ-8 ≥10 definition was used to compare baseline to follow-up depression symptom scores, 131 participants (5%) were categorized as having Persistent EDS, 122 (4%) as having Resolved EDS, 168 (6%) as having New Onset EDS, and 2,323 (85%) as Not Depressed (Fig. 1). Results were similar when EDS was defined according to the BRFSS algorithm, with slightly more in the Not Depressed group (91%) (Fig. 1). Of the 253 participants with EDS at baseline, 131 (52%) also were classified as having EDS at follow-up (Persistent EDS); of the 2,491 participants not depressed at baseline, 168 (7%) had EDS at follow-up (New Onset EDS).

Association Between Depression Symptom Status From Baseline to Follow-up and Participant Characteristics

Using the multinomial regression stepwise procedures, we found an association between depression symptom status from baseline to follow-up and age at baseline, sex, insurance status at baseline, and CGM status from baseline to follow-up (Table 2). Participants in the Not Depressed group were older, more likely to be male, more likely to have private insurance at baseline, and more likely to have started a CGM between baseline and follow-up (Table 2). Participants in the New Onset EDS group were younger and more likely to be female (Table 2). Participants in the Persistent EDS and New Onset EDS groups were less likely to be using a CGM at baseline or follow-up (Table 2).

Association Between Change in HbA_{1c} and Depression Symptom Status From Baseline to Follow-up

There was an association between change in HbA_{1c} from baseline to follow-up and in depression symptom status from baseline to follow-up for all three metrics (binary EDS using PHQ-8 ≥10, BRFSS algorithm, and continuous change in PHQ-8 score from baseline to follow-up; adjusted $P < 0.001$ for all) (Table 3). Change in HbA_{1c} was similar in the Persistent EDS and New Onset EDS groups and similar in the Resolved EDS and Not Depressed groups. HbA_{1c} increased from baseline to follow-up; however, the increase was smaller in the Resolved EDS and Not Depressed groups (Table 3). An increase in the PHQ-8 score was associated with an increase in HbA_{1c} (Table 3).

Association Between SH at Follow-up and Depression Symptom Status From Baseline to Follow-up

Participants with Persistent EDS and New Onset EDS defined according to the PHQ-8 ≥10 criterion were marginally more likely to report SH at follow-up, and participants with Resolved EDS were marginally less likely to report SH at follow-up (17.6% and 11.9% in Persistent EDS and New Onset EDS groups vs. 10.7% and 6.9% in Resolved EDS and Not Depressed groups; adjusted $P = 0.11$) (Table 3). A similar trend was seen for binary BRFSS algorithm depression symptom status ($P = 0.21$) (Table 3). An association between SH at follow-up and continuous change in the PHQ-8 score was not observed (adjusted $P = 0.70$) (Table 3).

Association Between DKA at Follow-up and Depression Symptom Status From Baseline to Follow-up

Participants with Persistent EDS and New Onset EDS were more likely to experience DKA at follow-up (10.0% and 6.5% in Persistent EDS and New Onset EDS groups vs. 4.1% and 1.6% in Resolved EDS and Not Depressed groups; adjusted $P < 0.001$ for depression symptom status defined according to PHQ-8 ≥10 and defined according to BRFSS algorithm) (Table 3). Participants with an increase in the continuous PHQ-8 score from baseline to follow-up were marginally more likely to report DKA at follow-up (adjusted $P = 0.03$) (Table 3).

Association Between Change in BMI *z*-Score and Depression Symptom Status From Baseline to Follow-up

An association between change in BMI *z*-score and depression symptom status from baseline to follow-up was not observed ($P > 0.40$ for all three metrics) (Table 3).

CONCLUSIONS

Cross-sectional studies of adults with T1D report that "depression" (typically defined by cutoff scores on self-report screening tools) is associated with

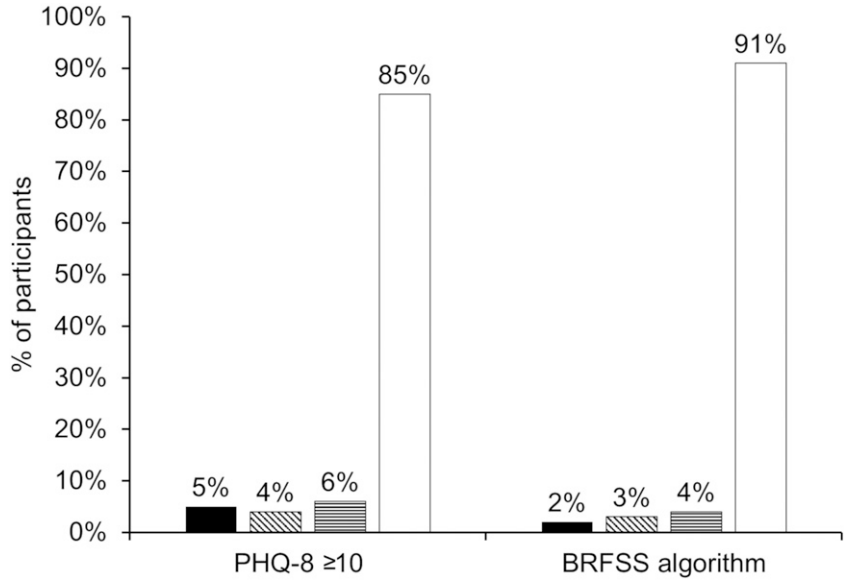

Figure 1—EDS from baseline to follow-up (■Persistent EDS, ▨Resolved EDS, ▤New Onset EDS, □Not Depressed).

Table 2—EDS from baseline to follow-up by participant characteristics[a]

	Depression status from baseline to follow-up							
	PHQ-8 ≥10				BRFSS			
	Persistent EDS *n* = 131	Resolved EDS *n* = 122	New Onset EDS *n* = 168	Not Depressed *n* = 2,323	Persistent EDS *n* = 42	Resolved EDS *n* = 82	New Onset EDS *n* = 110	Not Depressed *n* = 2,510
Age at baseline (years)	**40 ± 13**	**41 ± 15**	**37 ± 16**	**43 ± 16**	**38 ± 13**	**41 ± 14**	**35 ± 14**	**43 ± 16**
Female	**79 (60)**	**82 (67)**	**123 (73)**	**1,272 (55)**	**25 (60)**	**57 (70)**	**76 (69)**	**1,398 (56)**
Race/ethnicity								
White non-Hispanic	113 (86)	109 (89)	152 (90)	2,144 (92)	36 (86)	71 (87)	98 (89)	2,313 (92)
Black Non-Hispanic	2 (2)	6 (5)	6 (4)	49 (2)	1 (2)	3 (4)	3 (3)	56 (2)
Hispanic or Latino	9 (7)	6 (5)	7 (4)	66 (3)	2 (5)	6 (7)	6 (5)	74 (3)
Other race/ethnicity	7 (5)	1 (<1)	3 (2)	64 (3)	3 (7)	2 (2)	3 (3)	67 (3)
BMI *z*-score at baseline[b]	0.14 ± 0.89	−0.02 ± 0.74	0.06 ± 0.77	−0.04 ± 0.88	0.05 ± 0.75	−0.03 ± 0.74	0.15 ± 0.90	−0.03 ± 0.87
BMI at baseline (kg/m^2)[b]	29 ± 6	27 ± 5	27 ± 5	27 ± 8	28 ± 6	27 ± 6	27 ± 6	27 ± 8
Insurance status at baseline								
Private	**87 (67)**	**87 (74)**	**121 (77)**	**1,899 (85)**	**28 (68)**	**59 (75)**	**80 (75)**	**2,027 (84)**
Medicaid	**21 (16)**	**13 (11)**	**13 (8)**	**72 (3)**	**5 (12)**	**12 (15)**	**13 (12)**	**89 (4)**
Other insurance	**18 (14)**	**15 (13)**	**21 (13)**	**240 (11)**	**7 (17)**	**8 (10)**	**10 (9)**	**269 (11)**
No insurance	**3 (2)**	**3 (3)**	**2 (1)**	**30 (1)**	**1 (2)**	**0**	**3 (3)**	**34 (1)**
Pump use at baseline	81 (62)	80 (66)	102 (61)	1,486 (64)	24 (57)	53 (65)	58 (53)	1,614 (65)
CGM use from baseline to follow-up								
CGM at both	**13 (10)**	**16 (13)**	**12 (7)**	**325 (14)**	4 (10)	7 (9)	5 (5)	350 (14)
Stopped CGM	**11 (8)**	**21 (17)**	**15 (9)**	**203 (9)**	2 (5)	13 (16)	8 (7)	227 (9)
Started CGM	**13 (10)**	**10 (8)**	**24 (14)**	**402 (17)**	6 (14)	5 (6)	13 (12)	425 (17)
No CGM at either	**94 (72)**	**75 (61)**	**117 (70)**	**1,393 (60)**	30 (71)	57 (70)	84 (76)	1,508 (60)

Data are presented as the mean ± SD or as *n* (%). [a]Bold values indicate the factor remained after stepwise selection using a multinomial logistic regression model. Owing to multicollinearity, BMI *z*-score, not BMI, was included in the selection model. [b]BMI and BMI *z*-score are sex and age adjusted.

complications (5,18), diabetes distress (19), physical inactivity (20), and other diabetes-related outcomes. Studies of the relationship of depression (thus defined) to glycemic control in adults with T1D have yielded mixed results (5,18,21–23). Ehrmann et al. (24) recently reported that the affective subtype of depression (e.g., feeling blue) had a negative relationship to HbA_{1c}, the somatic subtype (e.g., poor appetite) had a positive relationship, and anhedonia had no relationship to glycemic control, demonstrating the complexity of this issue. However, there are limited data that provide longitudinal assessments to examine changes in depression symptom status and their relationship to glycemic outcomes in adults with T1D. Our findings suggest that a relationship exists between depression symptom status and glycemia-related outcomes over time that deserves attention.

Peyrot and Rubin (8) first looked at depression over time in 1999 when they reported a combined sample of adults with T1D and type 2 diabetes who completed a depression questionnaire before, immediately after, and 6 months after participation in a 1-week outpatient diabetes program. They found that factors that predicted "persistent disturbance" differed somewhat from those that predicted initial disturbance, but that neither related to HbA_{1c}. The type of diabetes (type 1 vs. type 2) did not relate to initial disturbance, but those with type 2 diabetes were at greater risk of persistent disturbance; however, the sample only included 35 individuals with T1D.

A more recent study examined depression "trajectories" by assessing depression symptoms in adults with newly diagnosed T1D annually for 5 years. They reported that 5 years after diagnosis, 7.8% were "moderately depressed," and 10.2% were "severely depressed." as defined by scores on the Symptom Checklist-90 (25). They identified three trajectories: "no depressive symptoms" (79% of their sample), "worsening depressive symptoms that improved after 2 years" (7%), and "worsening depressive symptoms" (14%). After 5 years, the group with worsening depressive symptoms had higher HbA_{1c} values than the other two groups. This group also reported worsening quality of life and increasing diabetes distress (7).

Our prospective data from a large national clinic registry provided a unique opportunity to examine depression symptom trajectories for adults, most of whom were not newly diagnosed: they had been living with T1D for a mean of 21 years. Looking at individuals with similar trajectories (i.e., those with persistent depressive symptoms, those who improved, and those not depressed), the finding that a full 53% of those who had elevated depression symptoms at baseline continued to report elevated depression symptoms 5 years later, while 7% developed elevated depression symptoms by follow-up, and 15% were dealing with elevated depression symptoms at some time during the 5 years, is noteworthy. Although all groups showed an increase in HbA_{1c} over time, we also found evidence for a clear relationship between persistently elevated depression symptoms, or development of significant depression

Table 3—Clinical outcomes by EDS status from baseline to follow-up

Depression status from year 1 to year 5	Adjusted change in HbA_{1c} from year 1 to year 5 (%)[a]	*P* value[a]	SH at follow-up[b]	*P* value[c]	DKA at follow-up	*P* value[d]	Adjusted change in BMI *z*-score from year 1 to year 5 (%)[e]	*P* value[e]
PHQ-8 ≥10		0.001		0.11		<0.001		0.84
Persistent EDS	0.6 ± 0.1		23 (17.6)		13 (10.0)		−0.10 ± 0.11	
Resolved EDS	0.3 ± 0.1		13 (10.7)		5 (4.1)		−0.09 ± 0.11	
New Onset EDS	0.6 ± 0.1		20 (11.9)		11 (6.5)		−0.04 ± 0.11	
Not Depressed	0.4 ± 0.1		160 (6.9)		38 (1.6)		−0.10 ± 0.09	
BRFSS		0.004		0.21		<0.001		0.93
Persistent EDS	0.7± 0.2		7 (16.7)		8 (19.5)		−0.09 ± 0.13	
Resolved EDS	0.3 ± 0.2		12 (14.6)		5 (6.1)		−0.06 ± 0.12	
New Onset EDS	0.7 ± 0.2		10 (9.1)		10 (9.1)		−0.06 ± 0.12	
Not Depressed	0.4 ± 0.1		187 (7.5)		44 (1.8)		−0.10 ± 0.09	
Change in PHQ-8 score[f]		<0.001		0.70		0.03		0.48
<−1.0	0.4 ± 0.1		54 (10.1)		15 (2.8)		−0.09 ± 0.10	
−1.0 to <0.0	0.4 ± 0.1		22 (6.9)		4 (1.3)		−0.06 ± 0.10	
0.0 to <2.0	0.5 ± 0.1		66 (6.1)		17 (1.6)		−0.13 ± 0.09	
≥2.0	0.5 ± 0.1		74 (9.1)		31 (3.8)		−0.06 ± 0.09	

Data are presented as the mean ± SE or *n* (%). [a]Change in HbA_{1c} was calculated as (HbA_{1c} at follow-up – HbA_{1c} at baseline), in which positive values indicate an increase in HbA_{1c}; adjusted values and *P* values from linear regression model adjusted for age at baseline, race/ethnicity, and CGM status at baseline vs. follow-up, pump status at year vs. follow-up, insurance status at baseline, insurance status at follow-up, annual income at baseline, annual income at follow-up, clinic site, and HbA_{1c} at baseline; model for change in PHQ-8 score used continuous score. [b]SH defined as seizure or loss of consciousness in the prior 3 months. [c]*P* values from logistic regression model adjusted for report of SH at baseline, diabetes duration at baseline, race/ethnicity, insurance status at baseline, and insurance status at follow-up; model for change in PHQ-8 score used continuous score. [d]*P* values from logistic regression model adjusted for report of DKA at baseline, annual income at baseline, and annual income at follow-up; model for change in PHQ-8 score used continuous score. [e]Change calculated as (BMI *z*-score at year 5 – BMI *z*-score at baseline) in which negative values indicate a decrease in BMI; adjusted values and *P* values from linear regression model adjusted for age at baseline, diabetes duration at baseline, race/ethnicity, and pump status at baseline vs. follow-up, insurance status at baseline, insurance status at follow-up, clinic site, and BMI *z*-score at baseline; model for change in PHQ-8 score used continuous score. [f]Change in PHQ-8 score calculated as (PHQ-8 score at follow-up – PHQ-8 score at baseline) in which positive values indicate an increase in the PHQ-8 score.

symptoms, and worsening glycemic control. And, we found suggestion of a relationship between depression symptom status and likelihood of SH and DKA. The latter, while not statistically significant in our sample, is consistent with data that found that, in a sample of adults with T1D, having elevated depression symptoms was associated with a 2.5-fold increased risk of severe hypoglycemic and hyperglycemic events (requiring an emergency department visit or hospitalization, extracted from medical records) (19). We note that our data provide evidence for relationships between depression symptom status and glycemic outcomes, but we cannot address causality; that is, whether improvements in depression symptoms lead to glycemic improvements, or whether improvements in glycemia lead to improvements in depression symptoms. However, the evidence for their association over time confirms that adults with T1D who have elevated depression symptoms are a highly vulnerable group that is at increased risk of serious short-term negative diabetes-related consequences as well as long-term complications.

We also found that those with persistently elevated depression symptoms or those who developed these symptoms over the 5 years were less likely to be using a CGM at either time point. It may be that people with depression symptoms are less likely to seek out, or accept, the technological challenges associated with CGM. Alternatively, perhaps providers were less likely to recommend a CGM if they noted symptoms of depression and were concerned about the potential of the individual to use, and benefit from, a CGM. Given the clinical benefits that may derive from use of a CGM (26–28), the relationship of probable depression to provider recommendations for, and patient acceptance of, CGM deserves further study.

Fisher et al. (6) point out that understanding the emotional side of T1D, and its potential relationship to glycemic outcomes, is important, but difficult to do, especially given the challenge of measurement (they found a high false-positive rate for major depressive disorder with the PHQ-8 when compared with a structured clinical interview). They also found a high level of shared variance between PHQ-8–defined probable major depression, diabetes distress, and other life stress and argued that the PHQ-8 may be measuring the "emotional impact of having a demanding, progressive chronic disease" rather than a "serious psychiatric condition" (6, p.1595). This is an important discussion to have, given the high rate of overdiagnosis and associated stigma attached to a mental illness diagnosis. Although we agree that some people develop symptoms of depression because of their life stressors (which could include those due to living with T1D), for others the cause may be biological/hormonal/genetic. For others, it may be related to problems with relationships, finances, and/or limited social support or coping skills available to cope with their individual stressors that are not directly related to having T1D. The true causes of depression are multifactorial and often difficult to discern at the individual level. However, any psychiatric diagnosis should be based on a thorough assessment, not on a screening result. If a patient screens positive for probable major depressive disorder on the PHQ-8, clinicians must provide additional, more comprehensive, assessments to guide their interventions.

Fisher et al. (6) also address treatment implications, and suggest that interventions should target diabetes/life stress "and not necessarily psychopathology" (p. 1596). We agree that it is important to appropriately tailor interventions. If the individual is reliably diagnosed with a depressive disorder, the most common treatment options are antidepressant medications, psychotherapy, or both. However, if the source of depression relates to living with T1D, this must be addressed. In these cases, the focus of psychotherapy may be helping the individual process his or her feelings about living with T1D, developing strategies to address T1D-related fears, ways to enlist family support, and other psychotherapeutic interventions tailored to diabetes distress. If the depression relates to other life stressors and/or lack of coping skills, this should also be addressed. Collaboration with diabetes educators (e.g., to address solutions to problems associated with monitoring, diet or injection therapy) and/or social workers (e.g., to address financial, insurance, or housing concerns) could also be important. In most cases, symptoms of depression are likely due to a combination of causative factors and will be addressed by various potential therapeutic targets and interventions. And, if a depressive disorder is reliably diagnosed, antidepressants may help the individual manage the anxiety and other symptoms (e.g., insomnia) that plague him or her.

The study has several limitations. First, we defined depression symptom status using a self-report survey, and using the cut point of 10, while considered valid and reliable as a screen for depression, may result in misclassification of depression status group based on small score changes. We addressed this concern somewhat by also scoring the PHQ-8 using the BRFSS algorithm, which is closer to interview criteria, and by reporting PHQ-8 scores as a continuous measure, and in general had the same results. Also, the very large sample size likely minimizes the effect of misclassification on the final results.

Second, the PHQ-8 asks about symptoms in the past 2 weeks. Although this is consistent with criteria for a depression diagnosis, it does not describe the course of depression symptoms over 5 years.

Third, the SH and DKA data were self-reported and not confirmed, and the time period for reporting such events was only the preceding 3 months.

Fourth, we did not administer a measure of diabetes distress, which may have been an even stronger predictor of poor outcomes, as reported by Fisher et al. (6).

Fifth, although the sample is large and heterogeneous, and participants are similar to adults with T1D from the registry clinics in race/ethnicity (77 vs. 82% non-Hispanic white), insulin pump use (41 vs. 50%), and access to private insurance (61 vs. 75%), the sample is not population-based, and thus may not be representative of all adults with T1D.

Sixth, although statistically significant differences in HbA_{1c} were identified, these changes may not be clinically significant.

Finally, we did not have access to information about whether depression was treated during this time span, and treatment may have affected glycemic control.

In conjunction with the data on prevalence of elevated depression symptoms in adults with T1D (5), these findings represent another important step in understanding the course of depression symptoms and its relationship to diabetes outcomes for adults with T1D. These data support national clinical practice guidelines calling for routine depression screening among individuals with diabetes (16). Depression is a disabling, yet treatable, condition, and individuals with comorbid diabetes and depression deserve to be treated to improve their quality of life. For some, the underlying source of depression is diabetes distress, and screening to identify high levels of diabetes distress also appears warranted so that further assessments can lead to better understanding and interventions can be targeted and tailored to individual patient needs. Given the finding that over time elevated depression symptoms is associated with worse glycemic control and possibly SH and DKA, it is likely that successful diagnosis and treatment of depression symptoms will also lead to better long-term diabetes outcomes, but this will require further study.

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References

1. Centers for Disease Control and Prevention (CDC). *QuickStats*: percentage of adults aged ≥20 years reporting depressive symptoms in the past 2 weeks, by sex–National Health and Nutrition Examination Survey, United States, 2013-2016. MMWR Morb Mortal Wkly Rep 2018;67:287
2. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2006;23:1165–1173
3. Katon W, Maj M, Sartorius N. *Depression and Diabetes*. Hoboken, NJ, Wiley-Blackwell, 2010
4. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord 2012;142(Suppl.):S8–S21
5. Trief PM, Xing D, Foster NC, et al.; T1D Exchange Clinic Network. Depression in adults in the T1D Exchange Clinic Registry. Diabetes Care 2014;37:1563–1572
6. Fisher L, Hessler DM, Polonsky WH, et al. Prevalence of depression in type 1 diabetes and the problem of over-diagnosis. Diabet Med 2016; 33:1590–1597
7. Kampling H, Petrak F, Farin E, Kulzer B, Herpertz S, Mittag O. Trajectories of depression in adults with newly diagnosed type 1 diabetes: results from the German Multicenter Diabetes Cohort Study. Diabetologia 2017;60:60–68
8. Peyrot M, Rubin RR. Persistence of depressive symptoms in diabetic adults. Diabetes Care 1999; 22:448–452
9. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA; T1D Exchange Clinic Network. The T1D Exchange clinic registry. J Clin Endocrinol Metab 2012;97:4383–4389
10. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. Psychiatr Ann 2002;32:509–515
11. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114:163–173
12. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–613
13. Twist K, Stahl D, Amiel SA, Thomas S, Winkley K, Ismail K. Comparison of depressive symptoms in type 2 diabetes using a two-stage survey design. Psychosom Med 2013;75:791–797
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC, American Psychiatric Association, 2000
15. American Diabetes Association. 3. Comprehensive medical evaluation and assessment of comorbidities: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1): S28–S37
16. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140

17. Centers for Disease Control and Prevention (CDC). Current depression among adults–United States, 2006 and 2008. MMWR Morb Mortal Wkly Rep 2010;59:1229–1235
18. Rassart J, Luyckx K, Berg CA, Bijttebier P, Moons P, Weets I. Psychosocial functioning and glycemic control in emerging adults with type 1 diabetes: a 5-year follow-up study. Health Psychol 2015;34:1058–1065
19. Lloyd CE, Pambianco G, Orchard TJ. Does diabetes-related distress explain the presence of depressive symptoms and/or poor self-care in individuals with Type 1 diabetes? Diabet Med 2010;27:234–237
20. Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO. Depression, obesity, and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes. Eur J Endocrinol 2013;168:861–869
21. Berge LI, Riise T, Hundal O, Odegaard KJ, Dilsaver S, Lund A. Prevalence and characteristics of depressive disorders in type 1 diabetes. BMC Res Notes 2013;6:543
22. Roy MS, Roy A, Affouf M. Depression is a risk factor for poor glycemic control and retinopathy in African-Americans with type 1 diabetes. Psychosom Med 2007;69:537–542
23. Strandberg RB, Graue M, Wentzel-Larsen T, Peyrot M, Rokne B. Relationships of diabetes-specific emotional distress, depression, anxiety, and overall well-being with HbA1c in adult persons with type 1 diabetes. J Psychosom Res 2014;77:174–179
24. Ehrmann D, Schmitt A, Reimer A, Haak T, Kulzer B, Hermanns N. The affective and somatic side of depression: subtypes of depressive symptoms show diametrically opposed associations with glycemic control in people with type 1 diabetes. Acta Diabetol 2017;54:749–756
25. Pearson Assessments. Symptom Checkist-90-Revised (SCL-90-R) [Internet], 2018. Available from https://www.pearsonclinical.com/psychology/products/100000645/symptom-checklist-90-revised-scl-90-r.html. Accessed 19 November 2018
26. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378
27. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017;167:365–374
28. Bergenstal RM. Continuous glucose monitoring: transforming diabetes management step by step. Lancet 2018;391:1334–1336