The Bidirectional Association Between Depression and Severe Hypoglycemic and Hyperglycemic Events in Type 1 Diabetes

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OBJECTIVE

Severe hyperglycemia and hypoglycemia ("severe dysglycemia") are serious complications of type 1 diabetes (T1D). Depression has been associated with severe dysglycemia in type 2 diabetes but has not been thoroughly examined specifically in T1D. We evaluated bidirectional associations between depression and severe dysglycemia among older people with T1D.

RESEARCH DESIGN AND METHODS

We abstracted depression and severe dysglycemia requiring emergency room visit or hospitalization from medical health records in 3,742 patients with T1D during the study period (1996–2015). Cox proportional hazards models estimated the associations between depression and severe dysglycemia in both directions, adjusting for demographics, micro- and macrovascular complications, and HbA_{1c}.

RESULTS

During the study period, 41% had depression and 376 (11%) and 641 (20%) had hyperglycemia and hypoglycemia, respectively. Depression was strongly associated with a 2.5-fold increased risk of severe hyperglycemic events (hazard ratio [HR] 2.47 [95% CI 2.00, 3.05]) and 89% increased risk of severe hypoglycemic events (HR 1.89 [95% CI 1.61, 2.22]). The association was strongest within the first 6 months ($HR_{hyperglycemia}$ 7.14 [95% CI 5.29, 9.63]; $HR_{hypoglycemia}$ 5.58 [95% CI 4.46, 6.99]) to 1 year ($HR_{hyperglycemia}$ 5.16 [95% CI 3.88, 6.88]; $HR_{hypoglycemia}$ 4.05 [95% CI 3.26, 5.04]) after depression diagnosis. In models specifying severe dysglycemia as the exposure, hyperglycemic and hypoglycemic events were associated with 143% (HR 2.43 [95% CI 2.03, 2.91]) and 74% (HR 1.75 [95% CI 1.49, 2.05]) increased risk of depression, respectively.

CONCLUSIONS

Depression and severe dysglycemia are associated bidirectionally among patients with T1D. Depression greatly increases the risk of severe hypoglycemic and hyperglycemic events, particularly in the first 6 months to 1 year after diagnosis, and depression risk increases after severe dysglycemia episodes.

Maintaining healthy blood glucose levels is critical for people with type 1 diabetes (T1D) to reduce risk of diabetic microvascular (e.g., retinopathy) and macrovascular (e.g., cardiovascular disease) complications. Hypoglycemia (e.g., blood glucose levels <54 mg/dL) (1) can interfere with brain glucose supply, balance, and coordination (2). Hyperglycemia occurs at the other end of the spectrum (e.g., blood glucose

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levels >250 mg/dL) (3) and is associated with endothelial dysfunction, arterial stiffness, and neuropathy (4). Severe cases of hypoglycemia and hyperglycemia are defined by the need for intervention by another person (5), and both types of severe dysglycemia can result in coma, ventricular premature beats, or death (6). Moreover, both types are strongly associated with rates of hospital readmission (7). Severe hypoglycemia is associated with triple the risk of mortality (8) and strongly linked to poorer quality of life in older patients with diabetes (9). Diabetic ketoacidosis (DKA) is the most common form of severe hyperglycemia among people with T1D and is triggered by reduced effective insulin and increased counterregulatory hormones. DKA is the leading cause of mortality among children and young adults with T1D (6). Unfortunately, both types of severe dysglycemia are common; severe hypoglycemia occurs 110–320 times per 100 patients years (10), and DKA is estimated to occur up to 12 times per 100 patients years in children and adolescents with T1D (3).

Depression is approximately two to three times more common among adults with T1D than those without (11,12). Prevalence estimates vary from 5 to 32% depending on the study design and how depression was defined (12,13). Studies show that depression is associated with nonadherence to diabetes treatment (14,15) and worse glycemic control (16). The vast majority of research on depression and severe dysglycemic events has had samples comprised of people exclusively (17–19) or predominantly with type 2 diabetes (T2D) (20,21) even though these events are much more common among people with T1D. People with T1D are up to four times more likely to experience severe hypoglycemia (6) and about three times more likely to experience DKA than those with T2D (3). To our knowledge, no previous study has examined the longitudinal associations between depression and severe dysglycemic events in a large sample of well-characterized people with T1D.

The association between depression and glycemic control is posited to be bidirectional (16,22,23) and can result in a harmful cycle in which poor glycemic control leads to a depressed mood, further exacerbating poor self-care (16). A cross-sectional study also found an association between severe hypoglycemic events and depression (24), and it is critical to identify if severe hypo- and hyperglycemic events could trigger a similar harmful cycle between depression and future repeat severe dysglycemic events.

In this study, we examine the longitudinal associations between depression and severe hypo- and hyperglycemic events that required hospitalization or an emergency room visit in a cohort of older individuals with T1D. Additionally, we examine if this relationship is bidirectional by determining if severe dysglycemic events elevate the risk of depression.

RESEARCH DESIGN AND METHODS

Study Population

This study examines a dynamic cohort of Kaiser Permanente Northern California (KPNC) members with T1D who were at least 50 years old during the study period (1 January 1996 to 30 September 2015) as part of an aging and diabetes study. KPNC is an integrated health care delivery system serving over 3 million members, who are representative of the population of the geographic region with the exceptions of the extremes of income (25–27). KPNC maintains the Diabetes Registry that encompasses all members with diabetes identified through laboratory data, pharmacy records, and inpatient and outpatient diagnoses of diabetes (28,29). A review of the Diabetes Registry identified individuals with T1D using the following three criteria, all of which had to be met: *1*) having at least two T1D ICD-9 codes without a T2D code or 75% or more of their diagnostic codes indicated T1D, *2*) filled an insulin prescription at any point between 1996 and 2015, and *3*) did not fill prescriptions of any hypoglycemic agents other than insulin (30). Individuals entered the cohort (i.e., their baseline date) at the first date between 1 January 1996 and 30 September 2015 that an individual was at least 50 years old and met the above criteria for T1D. The final analytic sample included 3,742 individuals with T1D.

Depression

The following ICD-9 codes were used to identify time-updated depression throughout the study period in the electronic medical records: major depressive disorder (296.2x and 296.3x), depressive type psychosis (298.0x), dysthymic disorder (300.4x), adjustment disorder with depressed mood (309.0x) or with mixed anxiety and depressed mood (309.28), and depressive disorder not otherwise classified (311). In sensitivity analyses, a more narrow definition of depression was used, including only diagnosis of major depressive disorder, depressive type psychosis, and dysthymic disorder. An individual was considered depressed from the date of diagnosis onward.

Severe Hyper- or Hypoglycemic Events

Severe dysglycemic events were defined as episodes of hyperglycemia or hypoglycemia that resulted in hospital admission or emergency room care. Hyperglycemic episodes between 1996 and 2015 were identified as the following ICD-9, Clinical Modification (ICD-9-CM) codes: 249.2 (secondary diabetes mellitus with hyperosmolarity), 250.1 (diabetes with ketoacidosis), and 250.2 (diabetes with hyperosmolarity). The following set of ICD-9-CM codes was used to identify hypoglycemic episodes between 1996 and 2015 (these codes were validated in a prior study compared with medical record review) (31): 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), and 251.2 (hypoglycemia, unspecified). The following ICD-9-CM codes were not used to identify hypoglycemic episodes: 250.3 diabetes mellitus with coma (because it does not distinguish between hypoglycemia and DKA), 250.8 diabetes mellitus with other specified manifestations (because it does not specify hypoglycemia), 270.3 leucine-induced hypoglycemia, 775.6 neonatal hypoglycemia, and 775.0 hypoglycemia in an infant born to a mother with diabetes.

Death

Dates of death were extracted from medical records, Social Security Administration data sets, and California death certificates between 1996 and 2015.

Covariates

All covariates were from a participant's baseline (i.e., the participant's time of entry into the cohort). Demographic information, including age, sex, and race, was obtained from the KPNC membership database. Glycosylated hemoglobin (HbA_{1c}) measurements and the following microvascular and macrovascular complications were abstracted from the start of the electronic medical records (1996) to participant entry date (ICD-9 code definition in Supplementary Table 1): neuropathy, peripheral artery disease, myocardial

infarction, and stroke. In sensitivity analyses allowing for a nonlinear association between HbA_{1c} and severe dysglycemic events, baseline HbA_{1c} was grouped into quintiles, with the third quintile serving as the reference group. The 1,068 individuals missing baseline values of HbA_{1c} were flagged by a missing indicator and assigned to the reference group of the quintile variable and the mean for the continuous variable.

Statistical Analysis

We examined the baseline characteristics of members with and without depression during follow-up. Cox proportional hazards models were specified to evaluate if depression during follow-up (i.e., time-varying exposure) was associated with elevated risk of severe dysglycemia, examining severe hyperglycemic and hypoglycemic events in separate models. Individuals with baseline values (i.e., between 1996 and cohort entry) of the outcome were excluded. For example, individuals with baseline hyperglycemia were excluded from analyses examining the association between depression and hyperglycemia during follow-up. Individuals were censored on the date of the first severe hyper- or hypoglycemic event (depending on the model's outcome of interest), the beginning of a gap in membership >90 days, or death, or at the end of the study period on 30 September 2015.

To assess if the association between depression and severe dysglycemic events varied by time since depression, we compared the risk of dysglycemic events occurring within 6 months, within 1 year, and >1 year after depression with those without depression. Covariates were added to the model in groups: demographics (baseline age, race, and sex), microvascular complications (neuropathy and peripheral artery disease), and macrovascular complications (myocardial infarction and stroke). In fully adjusted models, we also controlled for HbA_{1c}, which likely serves as a mediator of the depression-dysglycemia relationship in both directions.

We conducted four sets of sensitivity analyses examining depression as a risk factor for severe dysglycemic events. First, we used the narrower definition of depression and examined its association with severe dysglycemic events any time after depression. Second, we allowed for a nonlinear association between HbA_{1c} and severe dysglycemic events by using quintiles of baseline HbA_{1c} in fully adjusted models with the third quintile as the reference group. Third, we further adjusted for baseline values of the dysglycemic event of interest when examining the association between our original definition of depression and severe dysglycemic events during the four time periods. This was the only analysis for which individuals with baseline dysglycemic events were included in the sample. Last, we examined a possible effect modification of the relationship between depression and time to a severe dysglycemic event by race, sex, baseline HbA_{1c} status, and micro- or macrovascular complications using interaction terms and stratified models.

Cox proportional hazards models were also implemented to examine if severe dysglycemic events during follow-up were associated with risk of depression during follow-up, excluding those with baseline depression. Hyperglycemia and hypoglycemia were separately examined as exposures and covariates were added to the models in the same order as before (demographics, microvascular complications, macrovascular complications, and HbA_{1c}). Last, for each set of dysglycemia models, we further adjusted for the baseline values of the other form of dysglycemia. All analyses were conducted on SAS statistical software version 9.3 (SAS Institute Inc., Cary. NC).

RESULTS

Overall, the sample had a mean age of 56 years and was 79% white, 4% Asian, and 15% black/Hispanic/other (Table 1). Depression was present among 20% of the sample at baseline and an additional 21% was diagnosed during the study. A narrow definition of depression (i.e., major depressive disorder, depressive type psychosis, and dysthymic disorder) was present in 11% of the sample and 14% received a diagnosis during follow-up. There were 376 cases (11%) of severe hyperglycemia and 641 cases (20%) of severe hypoglycemia during follow-up; ~5% experienced both. The mean follow-up time was 5.9 years (SD 5.25; range 0.003–19.7) for analyses examining severe hyperglycemia as the outcome and 5.1 years (SD 4.80; range 0.003–19.7) for analyses examining severe hypoglycemia as the outcome. At the end of follow-up for the hyperglycemia analyses, 16% died without a severe hyperglycemic event during follow-up, 25% were censored due to a lapse in membership, and 48% were live members of KPNC without a severe hyperglycemic event during follow-up. At the end of follow-up for hypoglycemia analyses, 15% died without a severe hypoglycemic event during follow-up, 24% were censored due to a lapse in membership, and 40% were members of KPNC without a severe hypoglycemic event during follow-up.

Table 1—Baseline characteristics by time-updated depression

	No depression during study	Depression during study	Total sample	*P* value
Number of people	2,200 (58.8)*	1,542 (41.2)*	3,742	
Demographics				
Age at cohort entry, mean (SD)	57.0 (9.1)	54.7 (7.3)	56.1 (8.5)	<0.0001
Male	1,304 (59.3)	666 (43.2)	1,970 (52.7)	<0.0001
White	1,702 (77.4)	1,254 (81.3)	2,956 (79.0)	0.23
Asian	99 (4.5)	47 (3.1)	146 (3.9)	0.05
Other	317 (14.4)	224 (14.5)	541 (14.5)	0.10
Missing	82 (3.7)	<20	<102	<0.0001
Baseline health conditions				
Neuropathy	214 (9.7)	301 (19.5)	515 (13.8)	<0.0001
PAD	115 (5.2)	149 (9.7)	264 (7.1)	<0.0001
MI	38 (1.7)	57 (3.7)	95 (2.5)	<0.0001
Stroke	64 (2.9)	86 (5.6)	150 (4.0)	<0.0001
Hyperglycemia	118 (5.4)	198 (12.8)	316 (8.4)	<0.0001
Hypoglycemia	263 (12.0)	279 (18.1)	542 (14.5)	<0.0001
HbA_{1c}, mean (SD)	8.3 (2.0)	8.3 (1.9)	8.3 (1.9)	0.88
Depression	0 (0)	752 (48.8)	752 (20.1)	<0.0001

Data are *n* (%) unless stated otherwise. MI, myocardial infarction; PAD, peripheral artery disease.
*Row percent.

Depression and Severe Glycemic Event Onset

After controlling for demographics, HbA_{1c}, and microvascular and macrovascular complication, depression was associated with more than double the risk of severe hyperglycemic events (hazard ratio [HR] 2.47 [95% CI 2.00, 3.05]) and almost a doubling of risk of severe hypoglycemic events (HR 1.89 [95% CI 1.61, 2.22]) at any point after depression diagnosis (Table 2). The association between depression and risk of severe dysglycemic events was substantially stronger within the first 6 months and within the first year than in the later time period. Compared with people without depression, those with depression had over sevenfold and fivefold risk of severe hyper- and hypoglycemic events within the first 6 months, respectively ($HR_{hyperglycemic\ event}$ 7.14 [95% CI 5.29, 9.63]; $HR_{hypoglycemic\ event}$ 5.58 [95% CI 4.46, 6.99]). Compared with people without depression, people with depression had over five times the risk of a severe hyperglycemic event (HR 5.16 [95% CI 3.88, 6.88]) and over four times the risk of a severe hypoglycemic event (HR 4.05 [95% CI 3.26, 5.04]) in the first year. In fully adjusted models, the risk of hyperglycemia after the first year was less elevated but significantly higher for those with depression compared with those without (HR 1.44 [95% CI 1.14, 1.83]). Depression was not significantly associated with an elevated risk of a severe hypoglycemic event occurring more than 1 year or more later (HR 1.10 [95% CI 0.91, 1.32]).

Sensitivity Analyses of Depression as a Risk Factor for Severe Dysglycemic Events

In models adjusting for demographics, depression defined more narrowly (i.e., diagnosis of major depressive disorder, depressive type psychosis, or dysthymic disorder) was associated with more than double the risk (HR 2.46 [95% CI 1.97, 3.08]) of a severe hyperglycemic event and almost double the risk (HR 1.98 [95% CI 1.66. 2.37]) of a severe hypoglycemic event any time after depression (Supplementary Table 2). These associations persist after adjusting for micro- and macrovascular complication ($HR_{hyperglycemic\ event}$ 2.49 [95% CI 1.98, 3.12]; $HR_{hypoglycemic\ event}$ 1.95 [95% CI 1.63, 2.32]). Effect estimates of the relationship between depression and dysglycemic events remained similar when adjusting for quintiles of HbA_{1c} (versus a linear form) (Supplementary Table 3) and after further adjustment for baseline dysglycemia (Supplementary Table 4). In models adjusting for baseline severe dysglycemic events, risk for either dysglycemic event was greatest during the first 6 months after depression diagnosis (fully adjusted $HR_{severe\ hyperglycemic\ event}$ 7.82 [95% CI 6.15, 9.94]; $HR_{severe\ hypoglycemic\ event}$ 5.68 [95% CI 4.77, 6.76]). Effect estimates were lowest, but still significant, for dysglycemic events occurring more than 1 year after depression diagnosis (fully adjusted $HR_{severe\ hyperglycemic\ event}$ 1.38

Table 2—HR (95% CI) of depression predicting time to dysglycemic events adjusting for baseline covariates

	Severe hyperglycemic event	Severe hypoglycemic event
Adjusted for severe dysglycemic events any time after depression		
Number of eligible severe glycemic events	376	641
Demographics	2.38 (1.93, 2.94)	1.89 (1.61, 2.22)
Demographics and microvascular complications	2.40 (1.95, 2.94)	1.88 (1.60, 2.20)
Demographics and macrovascular complications	2.39 (1.94, 2.95)	1.87 (1.60, 2.20)
Demographics and micro- and macrovascular complications	2.40 (1.94, 2.97)	1.86 (1.58, 2.19)
Demographics, micro- and macrovascular complications, and HbA_{1c}	2.47 (2.00, 3.05)	1.89 (1.61, 2.22)
Adjusted for severe dysglycemic events within 6 months of depression		
Number of eligible severe glycemic events	244	447
Demographics	7.13 (5.29, 9.62)	5.72 (4.57, 7.15)
Demographics and microvascular complications	7.01 (5.19, 9.45)	5.66 (4.52, 7.09)
Demographics and macrovascular complications	7.13 (5.29, 9.62)	5.69 (4.55, 7.12)
Demographics and micro- and macrovascular complications	7.01 (5.19, 9.45)	5.36 (4.49, 7.05)
Demographics, micro- and macrovascular complications, and HbA_{1c}	7.14 (5.29, 9.63)	5.58 (4.46, 6.99)
Adjusted for severe dysglycemic events within first year of depression		
Number of eligible severe glycemic events	251	456
Demographics	5.18 (3.90, 6.90)	4.18 (3.36, 5.18)
Demographics and microvascular complications	5.11 (3.84, 6.81)	4.14 (3.33, 5.14)
Demographics and macrovascular complications	5.18 (3.89, 6.89)	4.15 (3.34, 5.15)
Demographics and micro- and macrovascular complications	5.11 (3.84, 6.80)	4.10 (3.30, 5.10)
Demographics, micro- and macrovascular complications, and HbA_{1c}	5.16 (3.88, 6.88)	4.05 (3.26, 5.04)
Severe dysglycemic events 1+ years after depression		
Number of eligible severe glycemic events	306	524
Demographics	1.40 (1.11, 1.77)	1.11 (0.93, 1.34)
Demographics and microvascular complications	1.39 (1.10, 1.76)	1.09 (0.91, 1.32)
Demographics and macrovascular complications	1.42 (1.12, 1.80)	1.10 (0.92, 1.33)
Demographics and micro- and macrovascular complications	1.41 (1.11, 1.79)	1.09 (0.90, 1.31)
Demographics, micro- and macrovascular complications, and HbA_{1c}	1.44 (1.14, 1.83)	1.10 (0.91, 1.32)

Demographics included age, sex, and race. Microvascular complications included neuropathy and peripheral artery disease. Macrovascular complications included myocardial infarction and stroke.

[95% CI 1.13, 1.69]; $HR_{severe\ hypoglycemic\ event}$ 1.17 [95% CI 1.01, 1.37]). There was no evidence of effect modification of the relationship between depression and severe glycemic events by race, sex, baseline macrovascular or microvascular complications, or baseline HbA_{1c} (Supplementary Table 5).

Severe Dysglycemic Events and Risk of Depression

Among those who did not have depression at the start of the study, individuals who experienced a severe hyperglycemic event during the study had more than double (HR 2.39 [95% CI 2.00, 2.84]) the risk of future depression than their counterparts who did not experience a hyperglycemic event, adjusting for demographics (Table 3). This association was similar after adjusting for baseline HbA_{1c}, microvascular and macrovascular complications, and baseline hypoglycemia (HR 2.43 [95% CI 2.00, 2.99]). Among those without depression at baseline, those with a severe hypoglycemic episode had a 75% greater risk of depression, adjusting for demographics (HR 1.75 [95% CI 1.50, 2.05]). This association persisted in models further adjusting for microvascular and macrovascular complications, HbA_{1c}, and baseline hyperglycemia (HR 1.74 [95% CI 1.48, 2.05]).

CONCLUSIONS

In this large sample of older people with T1D, we found evidence that individuals with depression are considerably more likely to experience severe dysglycemic events, particularly within the first 6 months to 1 year after the diagnosis of depression. Depression was associated with more than double the risk of severe hyperglycemic events and 86% increased risk of severe hypoglycemic events any time after depression diagnosis, regardless of microvascular and macrovascular complications. The increased risk was particularly robust in the first 6 months when people with depression had more than five to seven times the risk of such a severe dysglycemic event even after accounting for microvascular and macrovascular complications. Depression was associated with increased risk of severe dysglycemic events at all time periods even after adjusting for baseline dysglycemic events, and the first 6 months continued to be associated with five to seven times the risk of such events. This suggests that there is a critical period shortly after depression diagnosis during which patients are at extremely high risk, and treatment of depression and glucose monitoring may be particularly important for preventing these dangerous episodes.

The relationship between depression and severe dysglycemic events was bidirectional. Compared with individuals who did not experience severe glycemic events, individuals who experienced severe hyperglycemic events had more than twice the risk of depression and those who experienced severe hypoglycemic events had a 75% elevated risk of depression. The bidirectional relationship likely enables a harmful feed-forward cycle, with depression and severe glycemic events increasing the risk of the other.

A meta-analysis has shown an association between depression and glycemic control (16), although some more recent studies have shown conflicting results (32,33). Severe hyper- and hypoglycemic events are common among people with T1D and increase the risk of neurological damage (34), coma (6), dementia (31), and mortality (6,8). Yet little research has been conducted examining the association between depression and severe dysglycemic events. To our knowledge, no study has previously examined the association between depression and severe hyperglycemic events, and only two prior studies have examined severe hypoglycemic events (20,21). Both studies predominantly included people with T2D and one was cross-sectional (20). In a 5-year study including 4,117 health care plan members with T1D and T2D (95.6% of the sample), depression was associated with a 78% increased risk of a severe hypoglycemic event (i.e., hypoglycemic episode requiring emergency room visits or hospitalizations) (21).

There is a large body of literature showing that depression in diabetes impacts self-care. Depression may lead to an increased risk of severe dysglycemic events through altered behaviors, e.g., worsening adherence to medication regimen, diet, physical activity, and self-monitoring of blood glucose (14,15,21,35,36). Poorer self-care may worsen glycemic control and put individuals at risk for severe dysglycemic events. Physiological changes due to depression may also mediate the depression–severe dysglycemic event relationship. Depression is associated with dysregulation of the hypothalamic-pituitary-adrenal axis (37). Increased levels of catabolic counterregulatory hormones increase blood glucose levels (37) and may make it harder to have appropriate glycemic control.

By definition, all cases of severe dysglycemic events captured in this sample had resulted in an emergency room visit or hospitalization and very likely were considered a stressful life event. Our finding that severe dysglycemic events predicted depression diagnosis is consistent with a body of literature linking stressful life events to depression onset (38,39). Our findings are also consistent with a body of

Table 3—HR (95% CI) of dysglycemic event predicting time to depression adjusting for baseline covariates

	Depression
Severe hyperglycemic events	
Demographics	2.39 (2.00, 2.84)
Demographics and microvascular complications	2.33 (1.95, 2.78)
Demographics and macrovascular complications	2.39 (2.00, 2.85)
Demographics and micro- and macrovascular complications	2.35 (1.97, 2.80)
Demographics, micro- and macrovascular complications, and HbA_{1c}	2.43 (2.03, 2.91)
Demographics, micro- and macrovascular complications, HbA_{1c}, and severe hypoglycemia	2.43 (2.00, 2.99)
Severe hypoglycemic event	
Demographics	1.75 (1.50, 2.05)
Demographics and microvascular complications	1.73 (1.47, 2.02)
Demographics and macrovascular complications	1.73 (1.48, 2.03)
Demographics and micro- and macrovascular complications	1.71 (1.46, 2.01)
Demographics, micro- and macrovascular complications, and HbA_{1c}	1.75 (1.49, 2.05)
Demographics, micro- and macrovascular complications, HbA_{1c}, and severe hyperglycemia	1.74 (1.48, 2.05)

Analyses exclude individuals with depression at baseline. Covariates from baseline included the following: demographics (age, sex, and race), microvascular complications (neuropathy and peripheral artery disease), and macrovascular complications (myocardial infarction and stroke).

literature providing evidence that poor glycemic control may worsen mood (22). Hyperglycemia has been shown to incite anxiety and, in a cross-sectional study, was associated with anger, tension, and sadness among people with T1D (22,40). A study including people with T1D and T2D found an association between severe hypoglycemic events and depression during a 1-year period but also did not establish temporal order (24). To our knowledge, our study is the first to examine severe dysglycemic events as a risk factor for depression and to examine the temporal ordering between severe dysglycemic events and depression during the follow-up period.

In general, people with diabetic complications are more likely to experience depression (37); thus, diabetic complications may mediate the association between hyper- and hypoglycemia and depression. However, in our study, the association persisted even when taking complications into account, suggesting that other unidentified pathways are also at play. Understanding the association between severe dysglycemic events and depression is critical to uncovering potential targets of intervention to break the cyclical association between them.

This study includes a well-characterized sample of people with T1D with prospectively identified depression diagnoses and severe dysglycemic events. As an integrated health care delivery system, the vast majority of care to members is provided at KPNC facilities and all diagnoses are captured by comprehensive electronic medical records. These records provide information on a wide range of complications related to T1D. Detailed information regarding date of depression diagnosis and severe dysglycemic events enabled us to implement time-dependent analyses. Unfortunately, we do not have measures of the severity of depressive symptoms and could not test for a dose-response association. However, we do use two different definitions of depression, the broader one of which includes less severe symptom levels, such as in dysthymic disorder. The timing of a depression diagnosis may lag considerably from the onset of depressive symptoms, and a severe dysglycemic event resulting in emergency department or hospital utilization could have been preceded by a longer history of less severe hypoglycemia or hyperglycemia. Thus, the time ordering of our analyses should be considered an approximation. Additionally, it is possible that there are cases of undiagnosed depression in our sample. If individuals with undiagnosed depression are also more likely to experience dysglycemic events than individuals without depression, we underestimate the effect of depression on dysglycemic events. Our findings show significant differences in severe dysglycemic events by depression status but no difference in baseline HbA_{1c} levels, suggesting that baseline HbA_{1c} levels may not adequately capture glycemic control. We did not have access to information regarding antidepressant use, which some studies have shown to be associated with increased risk of dysglycemic events (41, 42); thus, we do not know how antidepressant usage may impact associations between depression and risk of dysglycemic events in the current study. Our data also do not include brain imaging, so we are unable to examine the direct effect of depression and severe dysglycemic events on brain structure or integrity. We do not know if individuals who were censored due to lapse in membership or death would have experienced severe dysglycemic events had they remained alive and in the sample. Last, these analyses were restricted to individuals 50 years old and above as part of a study examining aging among people with T1D, which may limit the generalizability of these results to younger populations.

This is the first longitudinal study of the bidirectional relationship between severe dysglycemic events and depression in a large sample of older adults with T1D. Our study shows a substantially increased risk of severe hyperglycemic and hypoglycemic events overall and particularly in the first year after diagnosis of depression, highlighting the need for increased clinical vigilance for these patients during the vulnerable period after a depression diagnosis. This study also demonstrated an elevated risk of depression after severe hyperglycemic and hypoglycemic events. Together, these results suggest that people with T1D who are recently diagnosed with comorbid depression are at a very high risk of severe dysglycemic events and that any resulting severe dysglycemic events may be associated with greater risk of depression. Glycemic control is the cornerstone of prevention of acute and chronic diabetic complications, and it is critical that clinicians treating patients with diabetes mitigate obstacles to self-care, including depression. The relationship between depression and severe dysglycemic events is also important to study among younger populations, especially since some research has found depression to be most prevalent in the first years after diagnosis (43). Further research is needed to develop multifaceted interventions that address the intersection of physical and mental health of patients with T1D to reduce the morbidity and mortality attributed to either sphere of health. Given the danger of these severe dysglycemic events, patients with T1D with comorbid depression represent an extremely vulnerable population that requires increased vigilance in clinical care.

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