DEPRESSIVE SYMPTOM PRESENTATION IN ADOLESCENTS WITH AND WITHOUT TYPE 1 DIABETES

By

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DEDICATION

This research is dedicated to all the adolescents with chronic illness who navigate the choppy waters of adolescence while gracefully managing their illness. Also, to those caring for them who see the whole person and not the illness.

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

Introduction

Type 1 diabetes (T1D) is one of the most common chronic illnesses in children and adolescents accounting for 87% of all cases of diabetes in people 10 to 19 years of age (Imperatore et al., 2018). Although the etiology of T1D is multifactorial, the primary characteristic is insulin deficiency. This lack of insulin leads to hyperglycemia requiring administration of insulin (DiMeglio et al., 2018). Optimizing glucose control with intensive insulin therapy and minimizing risk for hypoglycemia have been associated with significant reductions in long-term complications, such as kidney disease, diabetic retinopathy, and diabetes ketoacidosis (Greening et al., 2007; Hood et al., 2009; Nathan, 2014; Nathan et al., 1993). For every 1% reduction in Hemoglobin A1c (HbA1c), complications such as cardiovascular disease by 21% (Benhalima et al., 2011). However, intensive insulin therapy, which is the current standard of care, has minimally reduced the average HbA1c levels in adolescents 13 to 17 years of age with only 17%–20% of youth meeting current recommendations for HbA1c (Foster et al., 2019; Miller et al., 2015; Nathan, 2014). Furthermore, only 21% of adults with T1D are meeting the recommended HbA1c (Foster et al., 2019). Psychosocial factors like depression, diabetes distress, and burnout contribute to poor self-management, glycemic control, and quality of life especially during adolescence (Hood et al., 2018; Jaser et al., 2017; Mulvaney et al., 2019; Silverstein et al., 2015; Young-Hyman et al., 2016).

Statement of the Problem

Increased rates of depression and suicidality in adolescents with T1D, compared to healthy adolescents (Silverstein et al., 2015), have prompted the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (Delamater et al., 2018) to recommend routine depression screening in adolescents with T1D, although no specific depression screening tool is endorsed by the ADA and International Society for Pediatric and Adolescent Diabetes. Studies describing depression screening in adolescents with T1D have used a variety of validated tools, but no tools have been specific to those with diabetes. Commonly used depression screening tools in this population include Children's Depression Inventory (CDI; Corathers et al., 2013; Hood et al., 2018; Weissberg-Benchell et al., 2016), Center for Epidemiologic Studies Depression Scale (CES-D; Baucom et al., 2015), the Patient Health Questionnaire–9 (PHQ-9; Iturralde et al., 2017; Marker et al., 2019; Mulvaney et al., 2019), and the Beck Depression Inventory (BDI; Kristensen et al., 2014).

Following recommendations from the U.S. Preventive Services Task Force and the American Academy of Pediatrics for depression screenings in adolescents 12–17 years of age, the number of adolescents being screened in primary care settings has increased (Siu, 2016; Zuckerbrot et al., 2018). A commonly used tool to screen for presence and severity of depressive symptoms in both primary care and pediatric specialty settings is the PHQ-9 (Kroenke et al., 2001, 2010; Marker et al., 2019). The PHQ-9 comprises nine items that represent somatic and cognitive/affective symptoms associated with depressive disorders as outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013; Kroenke et al., 2001). This self-report tool has been validated in adolescents, is brief, and

is simple to score (Richardson, McCauley, et al., 2010; Richardson, Rockhill, et al., 2010). Thus, administration in the clinical setting is feasible.

The PHQ-9 has been used to evaluate depressive symptoms in adults and youth diagnosed with various chronic illnesses, such as multiple sclerosis (MS; Sjonnesen et al., 2012), diabetes (Garey et al., 2021; Iturralde et al., 2017; Marker et al., 2019; Mulvaney et al., 2021; Wolfgram et al., 2020), lupus (Knight, Vickery, et al., 2015; Knight, Weiss, et al., 2015), inflammatory bowel disease (IBD; Mackner et al., 2020), and HIV (Crane et al., 2010). The burden of self-management associated with chronic illnesses and functional impairments due to disease progression can manifest in somatic and cognitive/affective symptoms resembling depressive symptoms. Researchers explored this overlap in symptoms associated with fatigue and difficulty concentrating observed in people with MS (Gunzler et al., 2015; Sjonnesen et al., 2012). Fatigue and poor appetite are among the depressive symptoms that were identified as overlapping with somatic symptoms observed in youth with IBD (Mackner et al., 2020). In people with T1D, some of the somatic and cognitive manifestations of hyperglycemia and hypoglycemia may present as similar to depressive symptoms assessed by the PHQ-9 including sleep disturbances (Monzon et al., 2019; Patel et al., 2019), trouble with concentration (Northam, 2020; Schwartz et al., 2014), fatigue, and feelings of failure and shame (Ivey et al., 2009; Main et al., 2014; Whittemore et al., 2014). The patterns of symptom endorsement using the PHQ-9 have been examined in adults with MS (Gunzler et al., 2015; Sjonnesen et al., 2012), HIV (Crane et al., 2010), and deaf and hard-of-hearing youth (Bozzay et al., 2017) compared to their healthy counterparts with similar findings.

However, previous research findings have not clearly identified specific items that may have a significant role in driving positive PHQ-9 scores in adolescents with T1D. Moreover,

previous findings have not addressed how patterns of depressive symptoms in adolescents without T1D may differ from those observed in adolescents with T1D. Identifying whether PHQ-9 items function differently in adolescents with T1D than those without T1D will provide critical data for interpreting and responding to the results of the screening. This knowledge may provide insights about over estimation of depressive symptoms due to the similarity of diabetes symptoms. By examining item-level responses, diabetes care teams may better individualize care to meet each adolescent's unique needs based on symptom differentiation leading to a mental health referral or discussion about changes in diabetes management.

Purpose of the Study and Long-Term Goals

The purpose of this retrospective case-control study was to (a) examine the severity of depressive symptoms and differences in symptom presentation using the PHQ-9 between adolescents with and without T1D, (b) examine the relationship of item to total scores using the PHQ-9 in adolescents with and without T1D, and (c) examine the association between identified item-level drivers of depression symptoms with diabetes-related variables.

Study results may guide future research on alternative casual pathways for symptoms of depression in T1D. Specifically, depressive symptoms endorsed by adolescents with T1D, may be attributed to diabetes symptoms. These findings may change how health care providers interpret PHQ-9 items associated with glycemic control indicators by not only relying on and reporting the total scores but closely examining items endorsement in those with T1D. Moreover, because the PHQ-9 was developed and validated in healthy adolescents, this case-control study compared an age-, sex-, and race-matched cohort with and without T1D to compare response patterns and identify any weakness in the PHQ-9 as used in adolescents with diabetes.

Specific Aims and Hypotheses

Aim 1

Aim 1 was to examine the severity of depressive symptoms and differences in symptom presentation using the PHQ-9 between age-, sex-, and race-matched adolescents in a primary care setting to those administered to adolescents with T1D.

Hypothesis A. The severity of total PHQ-9 scores will be higher in adolescents with T1D than age-, sex-, and race-matched adolescents without T1D.

Hypothesis B. Items that resemble diabetes symptoms, such as difficulty sleeping, fatigue, inability to concentrate, and feelings of failure and guilt, will most commonly be endorsed with higher scores by adolescents with T1D.

Aim 2

Aim 2 was to evaluate the relative contribution of each of the items comprising the PHQ-9 on the total scores for adolescents with and without T1D.

Hypothesis. A higher total score on the PHQ-9 in adolescents with T1D will be associated with higher scores of items resembling diabetes symptoms in comparison to PHQ-9 items endorsed by those from a general pediatric population without T1D.

Aim 3

Aim 3 was to examine associations of diabetes-related clinical variables with PHQ-9 total scores and PHQ-9 items resembling somatic and cognitive/affective diabetes-related symptoms.

Hypothesis. There will be positive associations of HbA1c, frequency of hospitalizations and clinic visits, and time in range (for adolescents with continuous glucose monitoring [CGM] only) and a negative association of frequency of blood glucose monitoring (BGM) with PHQ-9

total scores and PHQ-9 item responses resembling somatic and cognitive/affective diabetes symptoms.

Significance

The central focus of the study was to critically examine depressive symptom endorsement in adolescents with T1D using the PHQ-9 compared to adolescents without T1D. Moreover, to determine whether items endorsed by adolescents with T1D may be those representing physical and emotional manifestation of diabetes. Similar symptom presentations between depressive symptoms and consequences of health conditions have been identified in other conditions such as MS (Sjonnesen et al., 2012), IBD (Mackner et al., 2020), and HIV (Crane et al., 2010). Moreover, others have reported similarities in people with diabetes in select depressive symptoms that resemble symptoms attributed to diabetes (Bächle et al., 2015). However, differential symptom profiling at the item level has not been conducted in adolescents with T1D, nor has symptom presentation been compared to a group of adolescents without T1D. Although there are prevalence estimates indicating higher prevalence of depression in those with chronic illnesses such as T1D, no previous studies provide insights on what drives an elevated score on the PHQ-9 in adolescents with T1D in comparison to those without T1D. This project uniquely explored whether some depressive symptoms may be associated with T1D. If confirmed, future research could distinguish between symptoms possibly linked to the consequences of living with T1D and not directly to depression itself.

CHAPTER 2

Theoretical Framework and Literature Review

Concepts relevant to this study are described in Table 1. A more detailed description of these concepts in the context of diabetes and adolescents follows.

Table 1

Summary of Conceptual Definitions

Concept	Conceptual definition
Depression	Mood disorder characterized by feelings of sadness, hopelessness, and anhedonia, or loss of interest in activities that were once enjoyable (APA, 2013).
Diabetes distress	Diabetes distress is associated to disease burden and refers to negative emotions arising from living with diabetes and the work of self-management (Hagger et al., 2016).
Self-management	A dynamic process including adolescent and parent collaborative decision making and shared responsibility for diabetes-related tasks requiring negotiating roles and emotions surrounding illness (Lorig & Holman, 2003; Schilling et al., 2002).
Primary consequences of diabetes	Physical consequences and complications associated with diabetes
Secondary consequences of diabetes	Psychosocial burdens associated with diabetes

Depression

Depression is a mood disorder characterized by feelings of sadness, hopelessness, and anhedonia, or loss of interest in activities that were once enjoyable (APA, 2013). Depressive symptoms are outlined in the latest *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; APA, 2013). To confirm a diagnosis of depression, an individual must have

experienced five or more of the following nine symptoms for 2 weeks nearly every day: (a) feeling down, (b) anhedonia, (c) insomnia or hypersomnia, (d) poor or excessive appetite, (e) slowness of thinking and physical movement, (f) fatigue, (g) reduced self-worth and feelings of guilt, (h) difficulty with concentration, or (i) suicidal ideation.

Diagnosis entails further evaluation by a mental health provider once screening has identified the presence and severity of depressive symptoms. Screening alone does not lead to a diagnosis and treatment. The National Institute of Mental Health (2022) estimated close to 60% of adolescents with a major depressive disorder (MDD) did not receive any treatment in 2020. Ninety percent of those who die by suicide suffer from depression, supporting the push for increased screening of and treatment for depression.

Depression in children and adolescents can negatively impact functional ability, school performance, and social interactions (Siu, 2016). In 2018, 1 in 7, or 3.5 million, adolescents in the United States had an MDD (Substance Abuse and Mental Health Services Administration, 2019). Undiagnosed and untreated depression can worsen overtime, diminish quality of life, and decrease one's contribution in school or work (Williams et al., 2017). Timely diagnosis and treatment of depression can improve health outcomes at the individual and societal levels; however, two thirds of people with depression in the United States are not diagnosed.

The etiology of depression is not fully understood and may involve a combination of risk factors such as genetics and other mental, behavioral, or physical comorbid and social conditions (Siu, 2016). Studies have shown an increased likelihood of depression related to stressful experiences such as a diagnosis of a chronic illness (Grey et al., 2002; Hood et al., 2006). Therefore, given the increased risk of depression in adolescents with T1D, screening is an integral part of routine diabetes care. Researchers in neurobiology have posited dysregulation of

the body's response to stress may be the underlying factor in depression, which can be a complicating factor in diabetes as the body's response to stress is increased inflammation leading to insulin resistance which in turn increases blood glucose (BG) levels (Moulton et al., 2015).

The Centers for Disease Control and Prevention (2020) reported the second leading cause of death in adolescents is suicide. Wang et al.'s (2017) meta-analysis revealed an increased risk of suicide in adults with Type 2 diabetes (T2D; RR = 1.56; 95% CI: 1.23–1.57; $p < 0.001$) with gender not being a significant contributing factor. Wang et al. reported an even higher risk of suicide in adults with T1D (RR = 2.25; 95% CI: 1.5–3.38; $p < 0.001$). Prevalence of depressive symptoms is 2 to 3 times greater with double the rates of suicide in adolescents with T1D than healthy adolescents, with approximately 20% of the variance in metabolic control attributed to depression (Buchberger et al., 2016; Grey et al., 2002; Herzer & Hood, 2010). Hence, routine depression screening is an important strategy in accurately identifying possible psychological causes associated with poor management of T1D.

Depression is associated with increased morbidity and mortality across a wide range of physical conditions (Zheng et al., 2020). In the context of managing a chronic illness like T1D, increased morbidity is associated with development of comorbid conditions (e.g., retinopathy, nephropathy), complicating the clinical course and management of the disease (de Groot et al., 2001) and decreasing adherence (Gonzalez et al., 2008); increasing health care utilization (McEwen & Herman, 2018; Wiltink et al., 2014); and increasing financial burden on the individual, family, and society (McEwen & Herman, 2018). Depression screening is critical in identification of presence and severity of depressive symptoms, which have a bidirectional association with poor diabetes management (Golden et al., 2008). Although the prevalence of MDD in people with diabetes is elevated compared to those without diabetes, even more people

experience subclinical depression (i.e., not meeting the threshold for MDD) and diabetes distress (Gonzalez et al., 2018; Nicolucci et al., 2016).

Most studies on the prevalence of depression in diabetes have focused on adults with T2D. A systematic review in adults with T1D found a higher prevalence in this group compared to a matched control (Barnard et al., 2005); this finding was supported in the second global Diabetes, Attitudes, Wishes, and Needs (DAWN2) study (Barnard et al., 2016). In this large multisite DAWN2 study, 32% of those with T1D and 30% of those with T2D reported being depressed. Emotional distress related to the burdens of managing a chronic condition such as diabetes (i.e., diabetes distress) complicates depression screening. Findings from the DAWN2 study indicated 13.8% of those with diabetes (T1D and T2D) had a positive depression screen but 44.6% reported diabetes distress (Nicolucci et al., 2013). Diabetes management and sociodemographic characteristics of those with T1D and T2D are not identical, and findings associated with T2D cannot be generalized to T1D. Given the similarity of depressive symptom presentations with somatic and emotional symptoms of diabetes, accurate measurement of depression in people with diabetes is challenging (Gonzalez et al., 2018).

Although general psychometric strengths and weaknesses of various depression screening measures have been reported (Smarr & Keefer, 2011), this study focused on the PHQ-9 and its utility in accurately identifying depressive symptoms in adolescents with T1D. Each of the nine items of the PHQ-9 represent a symptom of depression identified by the DSM-5 (APA, 2013). The primary focus of this study was to describe the depressive symptom presentation in adolescents with T1D. Several of the nine depressive symptoms included in the PHQ-9 resemble somatic and affective symptoms associated with T1D. Additionally, symptoms of inadequate glycemic control resemble some of the symptoms assessed in the PHQ-9, such as sleep

disturbances, fatigue, and inability to concentrate. In addition, feelings of guilt or shame may be a result of pressure to attain a high level of self-management success. Similarly, the specificity of symptom presentation and association with health outcomes has been investigated in other adult and pediatric chronic illnesses such as HIV (Crane et al., 2010), MS (Sjonnesen et al., 2012), lupus (Knight, Vickery et al., 2015; Knight, Weiss et al., 2015), inflammatory bowel disease (IBD; Stapersma et al., 2018), cystic fibrosis (CF; Quittner et al., 2016), and in people who are deaf and hard of hearing (Bozzay et al., 2017). These studies indicated a higher prevalence of depression and anxiety in adolescents and adults with chronic illness than the general population. These studies reported using various screening measures with different cutoff points. Regarding symptom endorsement, adolescents with lupus reported feelings of uncomfortable completing PHQ-9 surveys and indicated they concealed their emotions or were not truthful in reporting symptoms (Knight, Vickery, et al., 2015). Certain depressive symptoms functioned differently in respect to certain demographic characteristics such as race, age, and sex in adults with HIV (Crane et al., 2010). Although fatigue, agitated/slow movement, and poor appetite were more likely to be endorsed by youth who were deaf or hard of hearing, hearing adolescents were more likely to endorse feeling bad about themselves (Bozzay et al., 2017).

Diabetes Distress

Although the focus of this study was depression in the context of T1D, diabetes distress is a common phenomenon in T1D. Diabetes distress is associated with disease burden and refers to negative emotions arising from living with diabetes and the work of self-management (Hagger et al., 2016). Although distress is directly related to the burden of living with and managing diabetes, depression can be both a consequence of diabetes or a contributing factor to poor self-management (Polonsky et al., 2005). The high correlation of diabetes distress and depression

raises the question of accuracy of self-report measures used to assess for depression and whether they are actually highlighting the burden of illness (i.e., distress) rather than depression (Fisher et al., 2016). Therefore, distinguishing these two concepts is critical in informing how to best support adolescents who have a difficult time managing diabetes (Gonzalez et al., 2018).

Primary and Secondary Consequences of Diabetes

T1D is associated with primary and secondary consequences. Among the primary consequences of T1D are acute life-threatening episodes of diabetic ketoacidosis (DKA) and severe hypoglycemia (DiMeglio et al., 2018). DKA is diagnosed based on: (a) elevated BG (> 200 mg/dL), (b) venous pH < 7.3, and (c) moderate to large ketones (Wolfsdorf et al., 2018). Hypoglycemia is considered a BG of ≤ 70 mg/dL (International Hypoglycemia Study Group, 2017), but severe hypoglycemia is an event with severe cognitive compromise, such as seizures, and requires immediate medical management by someone other than the patient (Abraham et al., 2018). Long-term complications like cardiovascular disease, retinopathy, and nephropathy can potentially shorten the life of those with T1D (Chiang et al., 2018).

Secondary consequences of T1D are associated with the psychosocial burden of managing a chronic illness. Living with T1D is relentless, including daily tasks that require constant vigilance and attention such as frequent BG monitoring, carbohydrate counts, and appropriate dosing of insulin at mealtime. Among these consequences are depression, anxiety, diabetes distress, and burnout (Delamater et al., 2018). Additionally, family conflict (Ingerski et al., 2010; Trojanowski et al., 2021), social consequences (e.g., stigma and isolation; Montali et al., 2022), increased health care utilization, cognitive deficits, and academic performance (Cooper et al., 2016) have also been reported.

The emotional burden of managing diabetes affects not only the adolescent with T1D, but also the family caregivers who share the responsibilities of diabetes management. Some families may have difficulty communicating about and addressing diabetes-related burdens such as single-parent homes in which there is more conflict and less parental involvement (Lord et al., 2015). Adolescents from lower socioeconomic and racial and ethnic minority backgrounds are more vulnerable to the psychosocial burdens of T1D (Hilliard et al., 2016; Lord et al., 2015; Walker et al., 2015).

Theoretical Framework

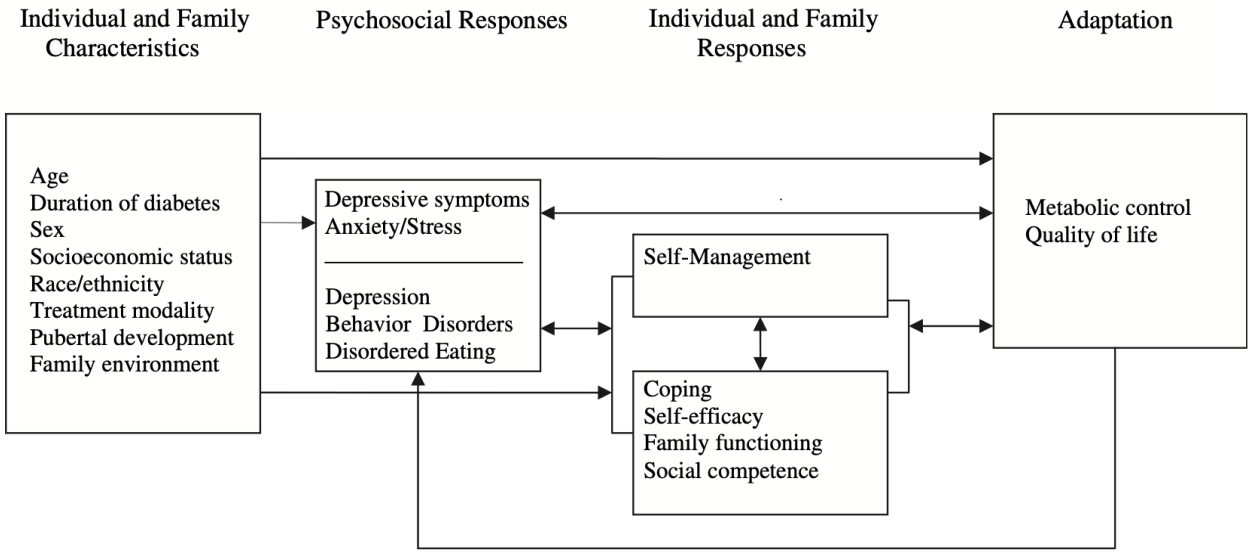
There is not a theoretical framework to address screening for depression and the primary and secondary consequences of depression in adolescents in the context of T1D or chronic illness management. However, this study focused on identifying key drivers of depressive symptom endorsement in adolescents with T1D using the PHQ-9. This study tested the hypothesis that the similarity of some depression and diabetes symptoms may result in over diagnosis of depression when the cause of the depressive symptom endorsement may, in fact, be diabetes. For example, difficulties with sleep have been attributed to glucose variability and mild depressive symptoms in adolescents with diabetes (Hamburger et al., 2020; Rechenberg et al., 2020). Therefore, the underlying reason for endorsement of sleep disturbances as a depressive symptom may be glucose variability and not depression.

Among existing conceptual and theoretical frameworks, the most fitting is the model of childhood adaptation to T1D (see Figure 1; Whittemore et al., 2010). This model presents psychosocial attributes of living with and adapting to T1D. Originally developed in 1991 (Grey & Thurber, 1991), this model was updated to include changes in treatment supported by the Diabetes Control and Complications Trial Research Group's (1994) landmark study. The model

suggests psychosocial attributes of the individual with T1D and their family have a critical influence on adaptation to illness. Although narrow in scope, the model of childhood adaptation to T1D describes the impact of individual and family characteristics and psychosocial state on (a) self-management and adaptation to T1D and quality of life (Whittemore et al., 2010). The inclusion of family functioning and social competence in this model recognizes adolescents' need for autonomy and parents' need to remain involved while allowing adolescents to take a more active role in self-management.

Figure 1

Model of Childhood Adaptation to T1D



Note. From "A Conceptual Model of Childhood Adaptation to Type 1 Diabetes," by R. Whittemore, S. Jaser, J. Guo, & M. Grey, 2010, *Nursing Outlook*, *58*(5), p. 244. Copyright 2010 by Mosby.

Although this model includes treatment modality, it does not specifically account for the more advanced glucose monitoring systems currently available to people with diabetes, including continuous glucose monitoring (CGM) that provides critical information on daily management of diabetes and glycemic control (Ng et al., 2019) Traditionally, HbA1c (measure of glycemic control over a period of 3 months) has been used to monitor glycemic control. Although HbA1c will continue to be used as an indicator of risk for developing long-term complications of diabetes, CGMs provide the added benefit of providing information regarding: (a) blood glucose time in range (BG: 70–180 mg/dL), (b) daily mean glucose, (c) glucose variability, and (d) number of daily hypoglycemia and hyperglycemia episodes (Chiang et al., 2018). These data points are increasingly used as complimentary or additional indicators of glycemic control.

The model of childhood adaptation to T1D guided this study conceptually. Given the focus of this study was depression and depression screening, only some of the constructs in this model were examined. The emphasis of this study was individual psychological response (i.e., depression and depressive symptoms) and self-management as an individual response using variables related to regimen adherence, such as BG readings (glucometers) and bolus insulin administration (insulin pumps). As a distal outcome, metabolic control was evaluated with HbA1c levels obtained from medical records of adolescents with T1D and time in range from a subsample with CGM reports. Given this study used data from electronic health records (EHR), the dataset did not contain contextual factors included in the model that may have impacted adolescents' life with T1D, such as family dynamics, coping, and adolescent self-efficacy.

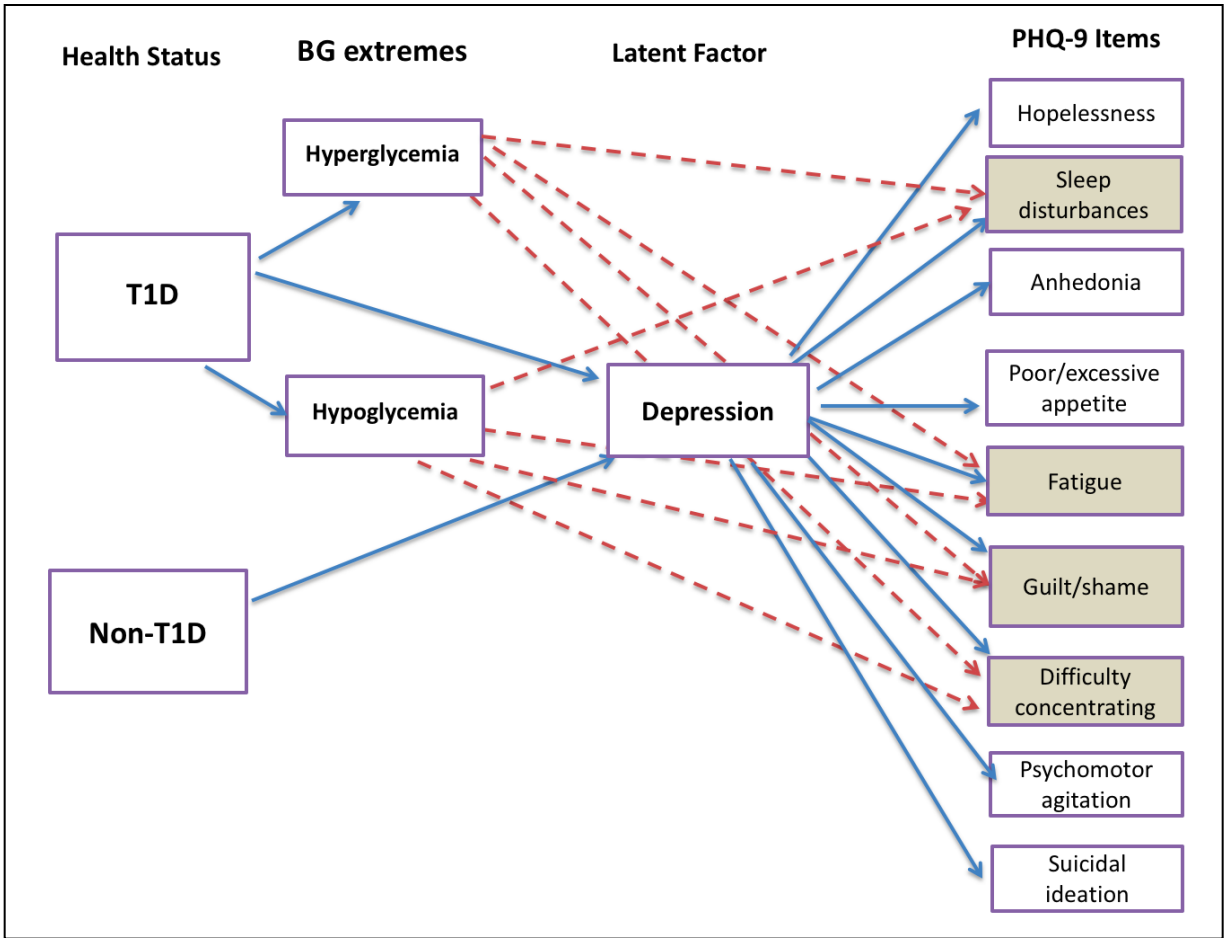
Critical Analysis of Relevant Literature

For this study, we investigated the precision of the PHQ-9 as a depression screening tool in identifying depressive symptoms in adolescents with T1D. Group differences in response to

the PHQ-9 between adolescents with and without T1D were examined and, more specifically, item-level responses to determine differential item response patterns. Given Aim 3 was psychometric in nature, the model depicted in Figure 2 shows the hypothesized differential item response patterns and the relationship of select depressive symptoms to hypoglycemia and hyperglycemia. The selection of these items is supported by current literature in T1D as described in more detail.

Figure 2

Hypothesized Differential Item Response Patterns of the PHQ-9



Sleep Disturbances

American Academy of Sleep Medicine recommends adolescents sleep 8–10 hours every night (Paruthi et al., 2016). However, many adolescents do not meet this recommendation, especially youth with chronic illnesses such as T1D (Eaton et al., 2010; Jaser & Ellis, 2016; Monzon et al., 2019). Short sleep durations (≤ 8 hours) have been self-reported by more than two thirds of youth with T1D (Estrada et al., 2012). In addition, researchers who conducted studies using objective measures based on polysomnography indicated youth with T1D have poorer sleep quality and spend less time in the deep stage of sleep than healthy youth (Perfect et al., 2012; Reutrakul et al., 2016). Sleep quality influences cognitive functioning (e.g., academic performance), memory (Cusick et al., 2018; Maski & Kothare, 2013), and executive functioning (e.g., problem solving; Caruso, et al., 2014). Factors contributing to sleep disturbances in T1D include: (a) glucose variability and poor glycemic control resulting in alteration of the hypothalamic-pituitary-adrenal axis (Monzon et al., 2019), (b) increases in cortisol levels stemming from hypoglycemia, (c) diabetes device alarms, (d) need for overnight BG monitoring, and (e) treatment of nocturnal hypoglycemia (Patel et al., 2019).

Impaired Concentration

The daily management of T1D requires frequent BG monitoring and treatment of episodes of hyperglycemia or hypoglycemia. People with diabetes have trouble with concentration during episodes of hyperglycemia and hypoglycemia. Researchers have found brain development can be interrupted at the time of diagnosis and during acute episodes of hyperglycemia and hypoglycemia, impacting those who are in earlier developmental stages when diagnosed (Schwartz et al., 2014). Although less is understood of cognitive outcomes in adolescence than younger children or older adults (Northam, 2020; Schwartz et al., 2014;

Wysocki et al., 2003), neuropsychological studies have found subtle changes beginning in childhood in cognition and mental flexibility in individuals with diabetes when compared to their healthy counterparts (Koekkoek et al., 2015). One of the more acute symptoms experienced during these glycemic extremes is difficulty concentrating; however, asymptomatic hypoglycemia may contribute to slow response rates, reasoning issues, and trouble with memory impacting academic performance in children and adolescents with T1D (McCarthy et al., 2003). In addition, children with T1D have reduced executive functioning, ability to regulate behaviors, and use problem-solving skills (Caruso et al., 2014; Perez et al., 2017).

Fatigue

Fatigue is common in those with MDD. Adolescents with depression describe fatigue as feeling weighed down and describe a lack of motivation and energy to even get out of bed (Dundon, 2006). Fatigue is also a symptom commonly experienced during hypoglycemia and hyperglycemia (Driscoll et al., 2016). Fatigue can also be a result of diabetes-related sleep disturbances described earlier. Fatigue was associated with missed self-monitoring blood glucose (SMBG) and skipped administration of insulin at mealtimes (Mulvaney et al., 2019).

Guilt and Stigma

As adolescents become more autonomous in diabetes management, the quality and tone of parental communication influences treatment adherence and self-management (DeBoer et al., 2017; Young et al., 2014). Parental involvement perceived by adolescents as intrusive (e.g., parents inquiring about completion of diabetes tasks, blaming adolescent for poor management) can exacerbate feelings of inadequacy (Young et al., 2014). During life transitions, young women with T1D have reported feeling guilty burdening their mothers, prompting them to become less reliant on parental support in managing diabetes (Rasmussen et al., 2008).

Managing T1D is complex and demanding. Adolescents with T1D must monitor BG several times a day as recommended before meals, but also at times when they may be experiencing physical symptoms of hypoglycemia or hyperglycemia. Adolescents must frequently make decisions to treat or prevent acute conditions like hypoglycemia requiring problem-solving skills and completing self-management tasks at school, with friends, and at social gatherings.

Fear of hypoglycemia may prompt adolescents to engage in hypoglycemic avoidance behaviors, including intentional insulin omission or underdosing, which can result in hyperglycemia (Driscoll et al., 2016; Starkman et al., 2019). The increase of BG can be denied or not disclosed by adolescents to avoid conflict with parents who become angry (Starkman et al., 2019). These complex psychological responses may give rise to feelings of guilt related to uncontrolled diabetes (Schneider et al., 2009).

Management of T1D poses challenges during adolescence, many of which are psychosocial in nature and involve the adolescent, their social network, and their family (Chao et al., 2016; Foster et al., 2016; Gonzalez et al., 2018; Hilliard et al., 2016). Self-management of T1D requires unrelenting vigilance to prevent acute and long-term complications through adherence to an intensive insulin regimen and maintaining optimal glycemic control (Atkinson et al., 2014). The work of a patient with diabetes includes managing and interpreting a constant stream of data, including BG levels, meal and snack carbohydrates, insulin dosing, and problem solving (Miller et al., 2020; Mulvaney et al., 2014). Treatment burden, severity of illness, and functional impairment related to diabetes complications are risk factors associated with depression in people with diabetes (Gonzalez et al., 2018; Trief et al., 2014).

Concerns about overdiagnosis due to the overlap of some of the depressive symptoms with physical manifestations of hyperglycemia and hypoglycemia have been reported (Fisher et al., 2016). Fisher et al. (2016) reported a 52%–71% false positive rate when using the PHQ-9 compared to the clinical interview. In another study, comparisons between the PHQ-9 results and semi-structured interviews for depression screening indicated adolescents with T1D endorsed depressive symptoms like difficulty sleeping, difficulty with concentration, anhedonia, motor disturbances, and thoughts of self-harm more frequently on the PHQ-9 and less so in the interviews (Vassilopoulos et al., 2020).

Fisher et al. (2016) used different strategies to reduce this measurement limitation and conducted their analysis in a sample of adults with T1D using different scoring methods for the Patient Health Questionaire-8. They report using cutoff scores of ≥ 10, ≥ 12, ≥ 15, and using a DSM-5 algorithm to categorize participants into depressed or not depressed. Using a more conservative criterion for scoring reduced the prevalence of adults with depression in this study from use of the DSM-5 algorithm to the cutoff score ≥ 10 (11.4% vs. 4.6%, respectively).

Given the recommendation for depression screening in adolescents with T1D, appraising the operational characteristics of depression screening tools administered to this population is important. Gold standard depression screening is a formal structured clinical interview by a mental health professional that is challenging to implement during a busy clinic visit. Some have suggested increasing the cutoff score for the PHQ-9 when screening people with diabetes to allow more accurate discrimination between diabetes-related and depressive symptoms (Holt & Van der Feltz-Cornelis, 2013; Trief et al., 2014). Other studies have included researchers administering the PHQ-2 first to determine the presence of the two core symptoms of depression

(i.e., anhedonia and feeling down and hopeless) to identify if further evaluation is warranted (Marker et al., 2019).

The primary gaps identified in the review of the relevant literature were (a) studies that had tested whether the depression measures can accurately distinguish between depressive symptom presentations in the adolescent population with T1D and (b) studies comparing depressive symptom presentations of adolescents with T1D and those without T1D. The goal of this study was to explore the PHQ-9 as a measure of depressive symptom in adolescents with T1D and to examine differential item response patterns considering similarities between symptoms of diabetes and depression. Studies using the PHQ-9 have reported using different cutoff scores of the PHQ-9 in distinguishing depression in the T1D population. It is unclear what the ideal cutoff score should be as there are no comparative studies in this population. Measures of diabetes distress have been developed and validated in the T1D population (e.g., the Diabetes Distress Scale and the Problem Areas in Diabetes; Markowitz et al., 2015; Polonsky et al., 2005). However, there are no validated measures of depression in diabetes. We specifically examined depression screening in adolescents with and without T1D using the PHQ-9. Furthermore, we explored the hypothesis that some depressive symptoms (i.e.., PHQ-9 items) may be more sensitive to symptoms of diabetes.

CHAPTER 3

Methodology

Research Design

The study used a retrospective case-control design. The cases were adolescents 13–18 years of age with T1D receiving care in the Eskind Pediatric Diabetes Clinic at Vanderbilt University Medical Center (VUMC). The controls were adolescents 13–18 years of age who did not have T1D and were receiving primary care services in the General Pediatrics Clinic at VUMC.

Sample and Setting

The T1D sample (case) comprised adolescents 13–18 years of age who received diabetes care at the Eskind Pediatric Diabetes Clinic from 2016 to 2020 for whom age, sex, and race information and a completed PHQ-9 survey were available. The Eskind Pediatric Diabetes Clinic is a VUMC specialty clinic that serves more than 3,000 children with diabetes in Tennessee and surrounding areas. This selection process resulted in a total sample of 1,403 adolescents with T1D. A subset of 500 of those T1D case subjects were randomly selected for analyses of diabetes device outcome data from the EHR which served as self-management indicators for Aim 3. Of those selected, 432 contained data for key variables in the analyses [BG meters (n = 267): frequency of daily BG readings, CGM (n = 69): time in range, and insulin pumps (n = 93): number of daily insulin boluses].

The sample of control participants was comprised of sex-, race-, and age- (+ or – 3 months) matched adolescents without T1D receiving care in the General Pediatrics Clinic with a completed PHQ-9 survey. The rationale for matching by race, sex, and age was to reduce

potential confounding of those variables with the PHQ-9 scores. The General Pediatrics Clinic began routine depression screening using the PHQ-9 in 2018; thus, the matched control sample received care between 2018 and 2020. The matching process resulted in matched pairs of 477 case and control participants.

Inclusion and Exclusion Criteria

The following inclusion criteria were used for both the cases and controls: (a) 13–18 years of age and (b) care provided by either the Eskind Pediatric diabetes clinic (case) or the General Pediatric Clinic with at least one completed PHQ-9 survey. For adolescents with T1D, additional inclusion criteria were used: (a) diagnosis of T1D confirmed by International Classification of Diseases-10 (ICD-10) code for T1D in the EHR, and (b) documented HbA1c in the EHR at the time of or up to 30 days before the date of PHQ-9 completion. The subsample of adolescents with T1D and device data were required to have at least one diabetes device report in the EHR, and the device report was required to be within 90 days prior to completing the PHQ-9.

The following subjects were excluded: (a) < 13 and >18 years of age at the time of completion of the first recorded PHQ-9, (b) a confirmed diagnosis of T2D based on ICD-10 code in the medical record (case), and (c) diagnosis of mental illnesses such as schizophrenia based on ICD-10 codes in the EHR (case). We did not exclude any adolescents with developmental delays or autism spectrum disorders. In addition, adolescents with attention deficit/hyperactivity disorders were not excluded as they are common diagnoses.

There were no missing PHQ-9 item responses as the survey is set up to require all questions to be completed by the adolescents in the Eskind Pediatric Diabetes Clinic. Adolescents from the Pediatrics Clinic with any missing responses were excluded from analyses.

Given the outcome of interest for Aim 3 was glycemic control, only subjects with a HbA1c in the EHR within 30 days of the PHQ-9 completion were included.

Strategies to Ensure Human Subjects Protection

Approval was obtained from the Vanderbilt University (VU) Institutional Review Board before any study activity including extraction of data from the EHR. The study met both human subjects protection and Health Insurance Portability and Accountability Act (HIPAA) privacy requirements. This study was designated as exempt as it posed minimal harm to subjects whose existing data were retrieved from the EHR. Existing data were deidentified with the removal of identifying variables or truncated including but not limited to name, address, social security number, and date of birth (reported as year/month only). A unique subject identification was assigned to each subject. The VUMC project management team matched the data pulled from the EHR to the identifier associated with the PHQ-9 survey in Research Electronic Data Capture (REDCap). REDCap is a widely used secure web-based application for developing and managing surveys and databases developed in 2004 at VU (Harris et al., 2009).

Data Collection Method

Procedures

Although the adolescents in both VUMC clinics (General Pediatrics and Eskind Pediatric Diabetes) completed the PHQ-9, the method used to administer the survey and how it was documented in the EHR were different. In the Eskind Pediatric Diabetes Clinic, adolescents 13–18 years of age with diabetes are screened every 6 months for depressive symptoms using the PHQ-9. The PHQ-9 is completed by adolescents during routine clinic visits using a tablet and a survey link in REDCap (Harris et al., 2009). In the General Pediatrics Clinic, adolescents 13–18 years of age are provided a hard-copy PHQ-9 survey during a routine annual clinic visit. This

completed survey was then scanned into the adolescent's medical records. Therefore, the PHQ-9 item scores from the T1D group were accessible in REDCap, but those for the control group had to be extracted from the EHR and scored.

The principal investigator (PI) collaborated with the research derivative (RD) team that was part of the Vanderbilt Institute for Clinical and Translational Research to obtain the data for the study. The PI worked closely with the RD project manager on the custom data pull for adolescents from both the Eskind Pediatric Diabetes and the General Pediatrics Clinics to ensure the study inclusion and exclusion criteria were met. Except for the PHQ-9 data for the cases from the Diabetes Clinic, the study variables listed in Table 2 were extracted from the EHR for both groups of adolescents.

Table 2

List of Variables Extracted From the EHR for Both the Adolescents With and Without T1D

T1D group	Control (pediatrics clinic group)
Demographics	Demographics
Age	Age
Sex	Sex
Race	Race
Ethnicity	Ethnicity
Insurance coverage (public vs. private)	Insurance coverage (public vs. private)
Health care utilization	
# Clinic visits (12 months before PHQ-9)	
Acute diabetes-related hospitalizations	
Clinical variables	
Glycemic control (HbA1c)	
Data from diabetes devices	
Glucometer: # daily BG checks	
CGM: Time-in-range	
Insulin pump: # daily insulin boluses	

The T1D cases' PHQ-9 responses were downloaded from the REDCap database used for collecting those data in the Eskind Pediatric Diabetes Clinic and those data were linked to the adolescents' respective EHR data by the RD team using the medical record number. Only the first completed PHQ-9 for each adolescent with T1D meeting the inclusion criteria was used in the study. Once the first instance of the PHQ-9 was determined, demographic characteristics and other study variables such as hospitalizations and clinic visits for the period of 12 months prior to completion of the first PHQ-9 on record were extracted from the respective EHR. The data dictionary used by the RD team is included in Appendix A.

The extracted case records were evaluated for duplicate records with duplicates being removed. The case records provided by the RD team were reviewed and subjects not meeting the inclusion criteria were excluded. Subjects were matched first by age and then sex and race. For age matching, a period of plus or minus 3 months was used as the criterion to match. Only the adolescents from the General Pediatrics Clinic with a complete PHQ-9 in the EHR were included in this matching. This process of matching continued until all possible matches were made.

Various sample device reports from commonly used manufactures of BG meters, CGMs, and insulin pumps were provided to the RD team after removal of patient identifiers with relevant variables from each report highlighted for the RD team. A list of requested variables for each device was included in the data dictionary provided to the RD team prior to extracting and coding data (see Appendix A).

The Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a brief 9-item self-report instrument developed from the Primary Care Evaluation of Mental Disorders instrument to screen for the presence and severity of depressive symptoms (Spitzer et al., 1999). The PHQ-9 was initially validated in the primary care and

obstetrics/gynecology settings and has since been used in a variety of adult and pediatric settings. The PHQ-9 is widely used in adult and pediatric primary and specialty care settings and is available in more than 49 languages (Arthurs et al., 2012). The PHQ-9 is at a fifth-grade reading level, publicly available, and free of charge on the internet. The PHQ may be implemented in the 2-item and 9-item versions (see Appendix B). The PHQ-9 is commonly used in the diabetes clinics for its brevity and ease of scoring and feasibility to administer during routine clinic visits (Garey et al., 2021; Iturralde et al., 2017; Marker et al., 2019; Mulvaney et al., 2021). The Eskind Pediatric Diabetes Clinic and the General Pediatric Clinic used the full PHQ-9 measure in routine care.

Respondents reported the severity of symptoms experienced in the past 2 weeks. Severity ratings on the PHQ-9 range from 0 (not at all) to 3 (nearly every day) for a total severity ranging from 0 to 27. Total scores of the PHQ-9 are interpreted based on these guidelines: 1–4 = minimal depressive symptoms, 5–9 = mild, 10–14 = moderate, 15–19 = moderately severe, and 20–27 = severe depression (Kroenke et al., 2001). The cutoff score of ≥ 10 indicates a positive screen (Costantini et al., 2021; Richardson, McCauley, et al., 2010). A positive screen has also been defined as the presence of five or more the depressive symptoms occurring at least more than half the days in the past 2 weeks (Johnson et al., 2002; Richardson, McCauley, et al., 2010). In this study the cutoff score of ≥ 10 was used as a positive score for depressive symptoms.

Internal consistency of the PHQ-9 in adults from primary care and obstetrics/gynecology settings was reported as Cronbach's $\alpha = 0.86–0.89$ (Kroenke et al., 2001; Spitzer et al., 1999). Test-retest was evaluated by correlating the self-reported PHQ-9 with phone interviews within 48 hours of completion of the survey resulting in correlations ranging from 0.86 to 0.89 (Pinto-Meza et al., 2005). Content validity of the measure is supported by the nine items that were

directly derived from the DSM-5 (APA, 2013). The sensitivity of the PHQ-9 as reported in systematic reviews in adults range from 0.77–0.88 and for its specificity 0.88–0.94 (Kroenke et al., 2010; Wittkampf et al., 2007). Additionally, the PHQ-9 correlated with the Beck depression inventory (BDI) $r = .73$, in a general population of adults (Martin et al., 2006). Although a recent study compared the PHQ-9 and the BDI in adults with T2D and found the PHQ-9 was better than the BDI in identifying mild depression which may lead to earlier identification of high-risk groups (Vaughan et al., 2019). In a recent meta-analysis of depression screening questionnaires in adults with diabetes, de Joode et al. (2019) reported the PHQ-9 sensitivity and specificity 81.5% (95% CI, 57.1–93.5%) and 79.7% (95% CI, 62.1–90.4%), respectively.

The first evaluation of the PHQ-9 for depression screening in healthy adolescents ages 13–17 years of age in a primary care setting in 2010 found, compared to the gold standard diagnostic interview, the PHQ-9 had a sensitivity of 89.5% and specificity of 78.8% (Richardson, McCauley, et al., 2010). This study evaluated construct validity by examining associations between the PHQ-9 with parental reports, internalizing behaviors, and adolescents' report of functional impairment. Richardson, McCauley, et al. (2010) reported a cutoff score of above 11 resulted in the best sensitivity (89.5%) and specificity (77.5%) in identifying adolescents with major depressive disorders.

Studies in adults and pediatric patients with T1D present a range of prevalence of depression in this population using a variety of screening measures. Studies using the Children's Depression Inventory reported depressive symptoms (moderate to high risk) were present in 12–22% of patients with diabetes (Corathers et al., 2013; Silverstein et al., 2015). In studies of late adolescents and emerging adults, the CES-D identified moderate-severe depression in 23.9% of the participants (Baucom et al., 2018; McGill et al., 2018). Prevalence of positive screens in

adolescents with T1D using the PHQ-9 using the criterion of ≥ 10 total score ranged from 6% to 21% (Garey et al., 2021; Iturralde et al., 2017; Mulvaney et al., 2021; Wolfgram et al., 2020). Reliability information was not presented in all studies using the PHQ-9 for depression screening in the T1D population. However, a retrospective multisite study reported Cronbach's $\alpha = 0.85$ for the PHQ-9 (Mulvaney et al., 2021). Comparison of PHQ-9 screening with semistructured interviews yielded some discrepancies in response patterns in a study of adolescents with T1D (Vassilopoulos et al., 2020). Vassilopoulos et al. (2020) indicated adolescents endorsed certain items on the PHQ-9 (e.g., sleep disturbance, trouble concentrating, motor disturbances) more so than during the interview. However, during the interview, adolescents endorsed depressed mood more readily.

Protocol for Data Management

Initially, a data use agreement (Contract: VUMC89123) was established between VUMC and VU for the transfer and use of data extracted from the VUMC EHR. A remote secure environment was set up for analyses by the VU Information Technology Service risk management team. Once this environment was established, staff working for the Vanderbilt RD team sent the extracted data to the PI in a password-protected file that was placed in the remote secure environment. All analyses and findings were conducted in that remote secure environment.

Data Analysis

Statistical analyses were performed using the latest version of IBM SPSS Statistics (Version 28). An alpha of 0.05 was used to determine statistical significance. Descriptive statistics were used to summarize the demographic and clinical characteristics of the samples

included in each study aim. Following are the descriptions of analyses conducted specific to each aim of the study.

Aim 1 Analytic Approach

The goal of Aim 1 was to compare the severity of depressive symptoms (Total PHQ-9) and depressive symptom presentation between the case and control participants. The PHQ-9 total scores were severely positively skewed, thus median and interquartile ranges (IQR, middle 50%), and frequencies of PHQ-9 categories (minimal to severe) were used to summarize the two groups. In addition, crosstabulations of individual item responses (0–3) by study group were used to generate summaries of those responses (counts and percentages). Logistic regression analyses were used to test the associations of the PHQ-9 total score and items with group membership (case vs. control).

Aim 2 Analytic Approach

The goal of Aim 2 was to evaluate the relative contribution of each of the PHQ-9 items on the total score for the adolescents with or without T1D. The effect of each of the PHQ-9 item responses on the resulting total score for adolescents with T1D was evaluated via correlations of each of the items with the total score if that item was not included in the total score (corrected item total correlation). The same analysis was conducted separately in the control group.

Aim 3 Analytic Approach

The goal of Aim 3 was to examine associations of demographic factors, healthcare utilization, and depressive symptoms with diabetes-related clinical outcomes (i.e., HbA1c and time in range) and self-management (i.e., number of daily insulin boluses and frequency of daily BG monitoring). Descriptive statistical summaries of the study variables for the sample of adolescents from the Eskind Pediatric Diabetes Clinic were generated and evaluated. Frequency

distributions were used to summarize the nominal and ordinal categorical variables, including the PHQ-9 item responses. All the continuous variables were skewed to some extent, with some extremely skewed. Thus, median (IQR) was used to appropriately summarize those distributions. Associations of factors and symptoms with the continuous outcome variables were conducted using Pearson correlations (unadjusted associations) and linear regression (adjusted associations). Skewed continuous distributions were transformed to normal as needed to meet the underlying normal distribution assumptions of Pearson correlations and linear regressions.

Bivariate (unadjusted) associations of the demographics, healthcare utilization, and PHQ-9 scores with HbA1c were generated using Pearson and point-biserial correlations. Adjusted associations were tested using a hierarchical linear regression model. In the initial step, the model included demographic (i.e., age, sex, race) and health care utilization variables (i.e., diabetes-related hospitalizations, clinic visits). Once those variables were controlled for, the additive (adjusted) effect of the PHQ-9 total scores on the HbA1c was tested in the next step. Post hoc analyses were conducted to determine whether item-level responses were associated with HbA1c levels. Glycemic control was categorized into lower HbA1c (< 7.0) and higher HbA1c (≥ 7.0) using ADA's (2021) recommendations for optimal glycemic control in adolescents with T1D. Furthermore, due to the sparse endorsement of depressive symptoms, each PHQ-9 item was dichotomized into two categories: 0 (not endorsed) and 1 (endorsed, responses of 1–3). Logistic regressions were then used to assess the association of each of the PHQ-9 item endorsement with the dichotomized HbA1c.

For CGM-users (n = 69), we used time in range as an indicator of glycemic control. Time in range refers to the percentage of time the BG values are 71–179 mg/dL. Time in range has been indicated as a strong indicator of glycemic control and risk for long-term complications

(ADA, 2021; Vigersky & McMahon, 2019). The goal of safe glucose control is to maximize the time in range while reducing time below and above range. The International Consensus Time in Range recommends a target of > 70% time in range for people younger than 25 years of age. (Battelino et al., 2019)

Sample Size

For Aims 1 and 2, adolescents from the two settings were matched by sex, race, and age (+ or − 3 months), resulted in a sample of $n = 477$ pairs. The sample size was not determined apriori. The control subjects were selected only if a completed PHQ-9 was available in the EHR and then matched with the sample of adolescents with T1D. For Aim 3, we used PHQ-9 survey data, demographic, health care utilization, and clinical variables from adolescents with T1D. The number of adolescents with completed PHQ-9 surpassed this final sample size. Once the inclusion and exclusion criteria were applied, $N = 1{,}403$ were included for analyses. From this sample, data from diabetes devices for a randomly selected subsample ($n = 500$) were extracted from the EHR. The size of this subsample was selected due to feasibility (time and cost) as all the device reports had to be manually coded and verified by the Vanderbilt Institute for Clinical and Translational Research crowdsourcing team. Of those cases selected, 432 contained data for key variables in the analyses resulting in 69 with reported data from CGM, 267 with data from BGM, and 93 from insulin pumps.

CHAPTER 4

Results

Analysis of Hypothesis and Aims

Sample Characteristics (Aims 1 and 2)

The median age of both cohorts was 13.0 (IQR = 13.0, 14.0), with 53.5% (n = 255 per cohort) identifying as male and 71.7% (n = 342 per cohort) identifying as White. Summaries of unmatched characteristics are presented in Table 3. Compared to the T1D cases, a statistically significantly higher percentage of adolescents in the control cohort identified as Hispanic and had public health insurance ($p < .001$). There was considerable confounding of ethnicity and type of insurance with 94% of those identifying as Hispanic having public insurance and 96% of those with private insurance identifying as non-Hispanic. Thus, in subsequent analyses that adjusted for these differences, only insurance type with the full sample was included.

Table 3

Unmatched Characteristics of Adolescents With and Without Type 1 Diabetes

	T1D		No T1D		
Characteristics	*N*	*n* (%)	*N*	*n* (%)	*p*
Ethnicity (Hispanic)	460	26 (5.7)[a]	454	203 (44.1)[a]	< .001
Insurance (private)	477	274 (57.4)	475	52 (10.9)[b]	< .001

Note. [a] Missing ethnicity from 17 control and 23 case subjects. [b] Missing insurance information from 2 control subjects.

Aim 1 Results

We hypothesized PHQ-9 total scores would be higher for the T1D cohort than for the non-T1D cohort. We also hypothesized the T1D cohort would have greater levels of endorsement of PHQ-9 depressive symptoms (items) resembling diabetes symptoms than the non- T1D cohort. Summaries of the PHQ-9 total scores and score categories are reported in Table 4.

Table 4

PHQ-9 Total Scores and PHQ-9 Score Categories for Adolescents With and Without T1D

	T1D *N* = 477	Non-T1D *N* = 477		
	Median (IQR)	Median (IQR)	Unadjusted *p* value	Adjusted *p* value
PHQ-9 Total	2.0 (0.0, 5.0)	2.0 (0.0, 5.0)	.076	.003 [a]
PHQ-9 Score category (range)	n (%)	n (%)	Unadjusted *p* value	Adjusted *p* value
			.513	.377[a]
Minimal (0–4)	329 (69.0)	353 (74.0)		
Mild (5–9)	98 (20.5)	86 (18.0)		
Moderate (10–14)	39 (8.2)	31 (6.5)		
Moderately severe (15–19)	6 (1.3)	4 (0.8)		
Severe (≥ 20)	5 (1.0)	3 (0.6)		

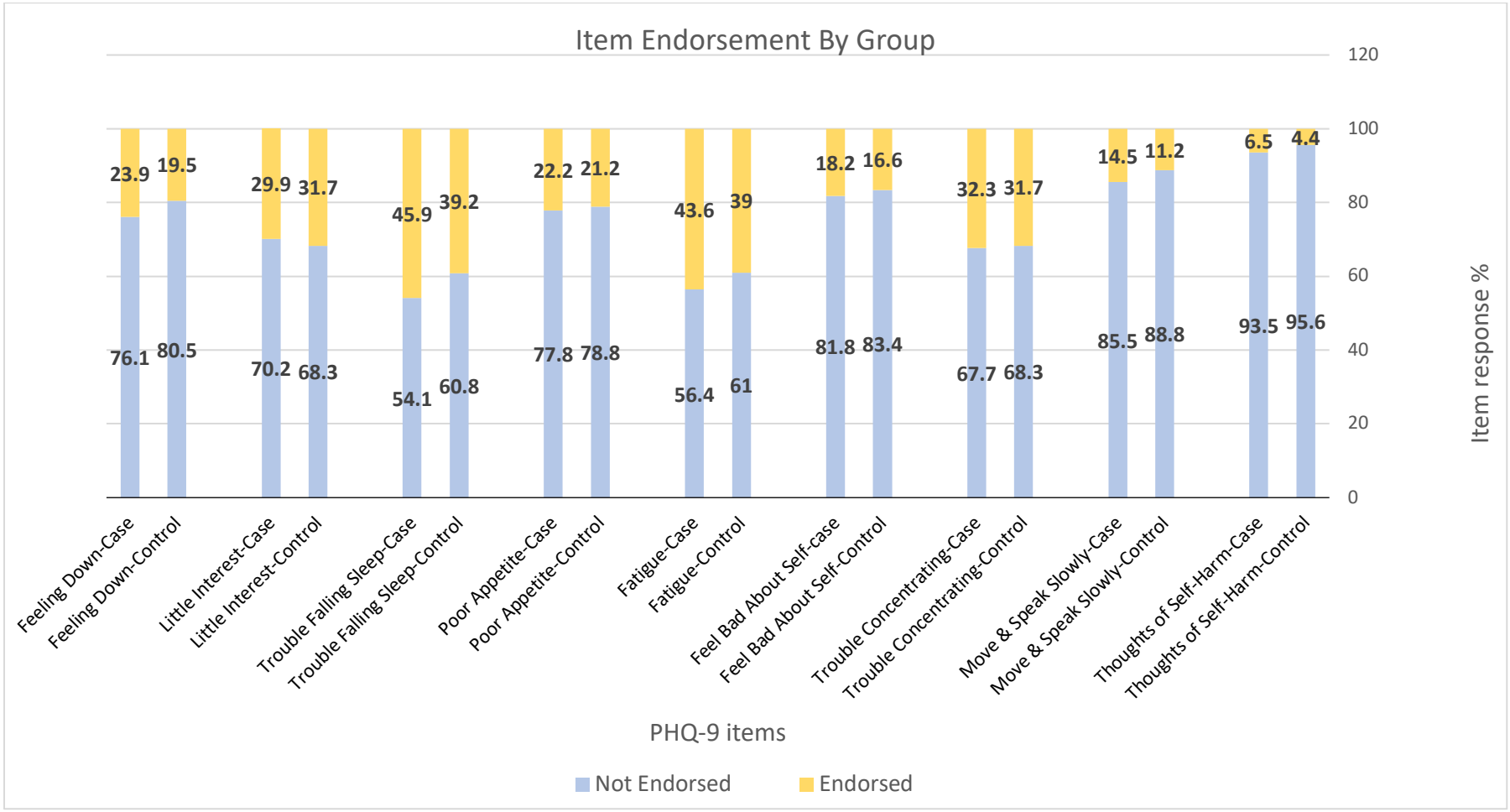
Note. [a] Adjusted for insurance type.

The PHQ-9 is a 4-point Likert scale (0–3) with the total score range of 0–27. As shown in Table 4, the PHQ-9 total score for all adolescents was very low for both groups (median = 2.0) with 25% having a score higher than 5. Close to 8% of adolescents without T1D and 10.5% of those with T1D had a PHQ-9 total score above the cutoff of 10 (moderate to severe depressive categories). Although the unadjusted difference between groups was not statistically significant

(p = .076), after adjusting for the differences in insurance types, the findings indicated adolescents with T1D had significantly higher PHQ-9 total scores (p = .003). Figure 3 presents a visual depiction of the item response patterns for case and control cohorts.

Figure 3

Distribution of Item Response Patterns by Case and Control Groups



Summaries and comparisons of the item level response patterns for the cases and controls are shown in Table 5. Results are shown both for unadjusted analyses and those adjusted for insurance type. As summarized, most of the slightly increased PHQ-9 total scores for the adolescents with T1D can be explained by increased endorsement of trouble falling asleep and fatigue. A higher percentage of the adolescents in the T1D group endorsed some level of difficulty falling asleep (45.9%) compared to adolescents in the control group (39.2%, $p = .036$). This effect strengthened some after controlling for type of insurance with the likelihood of endorsement being 1.72 times greater for those with T1D than those in the control group (95% CI: 1.26–2.34). Although the increased endorsement of fatigue was not statistically significant (T1D: 43.6%, Control: 39.0%, $p = .148$), after controlling for insurance type, that difference became statistically significant (OR: 1.35, 95% CI: 1.01–1.81; $p = .039$). Furthermore, after adjusting for insurance type, the difference between the distributions of the PHQ-9 fatigue item became significantly different with the direction of higher rates of endorsement by those in the T1D group (OR: 1.35, 95% CI: 1.01–1.81]; $p = .039$). See Table 5 for a description of the PHQ-9 items endorsed by each group.

Table 5

PHQ-9 Item Endorsement by Group

PHQ-9 Item	T1D *N* = 477 *n* (%)	No T1D *N* = 477 *n* (%)	Unadjusted *p*	Adjusted [a] *OR* (95% CI)	*p*
Feeling down depressed			.097	1.28 (0.89–1.84)	.173
Not at all	363 (76.1)	384 (80.5)			
Several days or more	114 (23.9)	93 (19.5)			
Little interest pleasure			.522	1.15 (0.8–1.58)	.40
Not at all	335 (70.2)	326 (68.3)			
Several days or more	142 (29.8)	151 (31.7)			
Trouble falling asleep			.035	1.72 (1.26–2.34)	< .001
Not at all	258 (54.1)	290 (60.8)			
Several days or more	219 (45.9)	187 (39.2)			
Poor appetite			.692	1.17 (0.8–1.69)	.373
Not at all	371 (77.8)	376 (78.8)			
Several days or more	106 (22.2)	101 (21.2)			
Feeling tired			.139	1.35 (1.01–1.81)	.039
Not at all	269 (56.4)	291 (61.0)			
Several days or more	208 (43.6)	186 (39.0)			
Feeling bad about self			.487	1.07 (0.72–1.60)	.729
Not at all	390 (81.8)	398 (83.4)			
Several days or more	87 (18.2)	79 (16.6)			
Trouble concentrating			.835	1.17 (0.8–1.61)	.311
Not at all	323 (67.7)	326 (68.3)			
Several days or more	154 (32.3)	151 (31.7)			
Moving or speaking slowly			.175	1.44 (0.94–2.26)	.091
Not at all	408 (85.5)	422 (88.5)			
Several days or more	69 (14.5)	55 (11.5)			
Thoughts of self-harm			.156	1.67 (0.88–3.16)	.114
Not at all	446 (93.5)	456 (95.6)			
Several days or more	31 (6.5)	21 (4.4)			

Note. [a] Adjusted for insurance type

Aim 2 Results

We hypothesized items assessing symptoms of depression that could also be symptoms of diabetes would be more highly correlated with the total scores on the PHQ-9 as compared to

those correlations for adolescents without T1D. As shown in Table 6, all items on the PHQ-9 correlated with the total score in both case and control groups with r = .47–.61 and r = .44–.64 for the T1D and non-T1D groups, respectively. The lowest correlations were observed for the item "thoughts of self-harm" in both groups, along with the item "moving slowly" in the control group. As shown in Table 5, these were the cells with the lowest endorsement prevalence of endorsement.

Table 6

Item–Total Correlation and Cronbach's α for the PHQ-9 in Adolescents With and Without T1D

	T1D (N = 477)		No T1D (N = 477)	
Reliability (Cronbach's α)	.828		.824	
Item	r [a]	α [b]	r [a]	α [b]
Down and depressed	.615	.803	.631	.795
Little interest or pleasure	.528	.811	.503	.809
Trouble falling asleep	.594	.807	.578	.804
Poor appetite	.500	.814	.516	.807
Fatigue	.578	.805	.636	.792
Feeling bad about self	.577	.807	.560	.803
Trouble concentrating	.556	.809	.540	.806
Moving or talking slowly	.521	.815	.444	.815
Thoughts of self-harm	.466	.823	.452	.820

Note. [a] r represents corrected item–total correlation. [b] Indicates internal consistency of remaining items if the selected item is deleted from the total score.

Aim 3 Results

Aim 3 hypothesized there would be a positive association of increased diabetes-related hospitalization with HbA1c and a negative association with time in range. We also hypothesized

a negative association of PHQ-9 total with self-management indicators (frequency of SMBG and daily insulin boluses).

Demographic and clinical characteristics for the full sample of 1,403 adolescents with T1D and random subsample of those same adolescents who also had at least one type of device data (n = 432) are summarized in Table 7. The demographic and clinical characteristics of the subsample were similar to the full sample. Median age of the full sample was 14.0 (IQR = 13.0, 16.0) and the median age of the subsample was 15.0 (IQR = 13.0, 15.0). Approximately half of the full and subsamples were male, and approximately 80% were White. More than half of the adolescents in the full and subsample had private health insurance coverage. Approximately 14% had more than one hospitalization in the past 12 months with a median of three clinic visits during the same timeframe. Finally, HbA1c values were also very similar with medians of 8.7 and 8.8 (see Table 7).

Table 7

*Characteristics of Full Sample (*N *= 1,403) and Subsample With Device Data (*n *= 432)*

Demographics	Full sample (*N* = 1,403)	Subsample (*n* = 432)
Age at screening, years (Median, IQR)	14.0 (13.0, 16.0)	15.0 (13.0, 16.0)
	n (%)	*n* (%)
Sex: Male	732 (52.2)	214 (49.5)
Race: White	1,137 (81.0)	352 (81.5)
Ethnicity: Hispanic *	63 (4.6)	16 (3.8)
Insurance: Private	834 (59.4)	271 (62.7)
Clinical characteristics	*n* (%)	*n* (%)
Diabetes-related hospitalizations (0–1)	1,209 (86.2)	367 (85.0)
Diabetes-related hospitalizations (≥ 2)	194 (13.8)	65 (15.0)
At least one Emergency Department visit (not admitted) (%)	113 (8.1)	31 (7.2)
	Median (IQR)	Median (IQR)
Clinic visits (past 12 mo.)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
HbA1c	8.7 (7.5, 10.4)	8.8 (7.6, 10.4)

Note. * Full sample: *N* = 1,362, Subsample: *n* = 423.

Depressive Symptoms

The PHQ-9 total scores in both the full and subsamples of adolescents was 2.0 (full: IQR = 0.0, 5.0; subsample: IQR = 0.0, 5.8). Given the possible range of 0–27, most of the PHQ-9 total scores were low, with fewer than 25% having scores > 6. In fact, approximately 90% of the adolescents' PHQ-9 scores fell in the minimal to mild categories of depressive symptom severity (0–9; see Table 8). The most frequently endorsed depressive symptoms were trouble falling asleep and fatigue (~43%), trouble concentrating, and little interest or pleasure in doing things (both ~28%). Only 6.3% of adolescents in the full sample and 6.0% in the subsample endorsed having thoughts of self-harm. Given this study was focused on depression screening and not

provider responses and referrals to mental health providers, we did not search the diabetes clinic provider notes for how endorsement of thoughts of self-harm was handled.

Table 8

*PHQ-9 Total Scores and PHQ-9 Score Categories for Full Sample (*N *= 1,403) and Random Subsample (*n *= 432)*

PHQ-9	Full sample	Subsample
Total score: Median (IQR)	2.0 (0.0, 5.0)	2.0 (0.0, 5.8)
Total score category (score ranges)	*n* (%)	*n* (%)
Minimal (0–4), *n* (%)	1,006 (71.7)	299 (69.2)
Mild (5–9), *n* (%)	260 (18.5)	86 (19.9)
Moderate (10–14), *n* (%)	99 (7.1)	35 (8.1)
Moderately severe (15–19), *n* (%)	27 (1.9)	7 (1.6)
Severe (≥ 20), *n* (%)	11 (0.8)	5 (1.2)

As shown in Table 9, there were several statistically significant correlations among demographic and health care utilization variables. In this sample of adolescents with T1D, compared to adolescents identifying as White, a higher percentage of adolescents of color had public insurance (60% vs. 36%, $p \leq .001$) and fewer clinic visits in the past 12 months (median = 2 vs. 3, $p = .003$). Furthermore, a higher percentage of adolescents with public insurance had more than one hospitalization in the past 12 months than did those with private insurance (20% vs. 10%, $p \leq .001$).

Table 9

Intercorrelations Among Demographic and Health Care Utilization

	Age	Sex	Black/ other race	Insurance type	Clinic visits	Hospitalization
Age	—	≤ −.01 (.898)	.05 (.043)	−.07 (.009)	−.16 (< .001)	−.05 (.060)
Female sex		—	.05 (.060)	.03 (.197)	−.04 (.187)	−.07 (.009)
Non-White Race			—	.19 [a] (< .001)	−.09 [b] (.003)	.05 (.044)
Public insurance				—	−.07 (.013)	.14 (< .001)
# Clinic visits					—	.07 (.006)
≥ 2 Hospitalizations						—

Note. Values in cells: Continuous variables, *r* (*p* value); nominal variables, Cramer's *V* (*p*-value); race, *R* (*p*-value); age and number of clinic visits were transformed to normal using square root.

Correlations of the demographic and health care utilization variables with the PHQ-9 total scores are shown in Table 10. As noted, except for age and number of clinic visits, all the correlations were statistically significant. Females had higher PHQ-9 scores than males ($p < .001$), adolescents with public insurance had higher PHQ-9 scores compared to those with private insurance ($p < .001$), and those who identified as a race/races other than White had higher PHQ-9 total scores than those identifying as White ($p = .005$). In terms of health care utilization, adolescents with two or more diabetes-related hospitalizations had higher PHQ-9 total scores compared to those with no or only one hospitalization in the past year ($p = .004$).

Table 10

Bivariate Correlations of Demographic and Health Care Utilization With PHQ-9 Scores

Demographic and health care utilization	PHQ-9 total
Age	–.02 (.457) *
Female sex vs. male	.13 (< .001) **
Non-White race	.08 (.005) *
Public insurance vs. private	.17 (< .001) **
# Clinic visits	.01 (.737) *
≥ 2 Hospitalizations vs. 0–1	.08 (.004) **

Note. Values in the cells: *r* (*p* value); race values are *R* (*p* value); * Pearson correlations; ** Point-biserial correlation; PHQ-9 total scores were transformed using log; age and number of clinic visits were transformed using square root.

Associations of Depressive Symptoms with Glycemic Control and Self-Management

HbA1c. Correlations (unadjusted associations) of the demographic and health care utilization variables and the PHQ-9 total scores with HbA1c are shown in Table 11, along with the adjusted associations. Among demographic and health care utilization variables, the strongest and statistically significant associations were observed for participant insurance type, race group, and health care utilization. Adolescents with public insurance had higher HbA1c values compared to those with private insurance, those identifying as Black or other non-White races had higher HbA1c values than those identifying as White, and those with higher health care utilization had higher HbA1c values (all $p < .001$).

Table 11

*Associations of Demographic and Health Care Utilization, PHQ-9 Total With HbA1c (*N = *1,403)*

Variables	Unadjusted		Adjusted	
	β	*p*	*β*	*p*
			$R = .28^a$, $p < .001$	
PHQ-9 (total score)	.05	.052	.03	.307
Demographics				
Age	–.02	.519	–.03	.345
Female sex	–.05	.064	–.05	.037
Black/other race	.12	< .001	.07	.005
Public insurance	.14	< .001	.09	< .001
Health Care Utilization				
# Clinic visits (past 12 months)	–.16	< .001	–.16	< .001
≥ 2 Hospitalizations (past 12 months)	.18	< .001	.16	< .001

Note. β: regression coefficient; *R:* Multiple correlation; *[a] Adjusted $R^2 = .08$*

Neither the bivariate (unadjusted) association nor the association after controlling for demographic and health care utilization variables (adjusted) of PHQ-9 total scores with HbA1c were statistically significant (p > .05; see Table 11). The regression model that included demographic and health care utilization variables accounted for 8% of the variability in HbA1c ($R = .28$, adjusted $R^2 = .08$, $p < .001$). After controlling for those variables, the total PHQ-9 scores contributed less than 1% added explanatory effect on HbA1c ($p = .307$).

As in Aim 1, we examined the associations of each of the PHQ-9 depressive symptom endorsements with glycemic control as defined by lower HbA1c (< 7.0) and higher HbA1c (≥ 7.0). In the full sample ($N = 1,403$) 16.1% ($n = 226$) adolescents had HbA1c < 7.0 and 83.9% ($n = 1,177$) had HbA1c ≥ 7.0. Summaries of PHQ-9 item endorsement in each of the HbA1c groups are presented in Table 12, and tests of the differences in those percentages are shown in Table 13 (unadjusted column). Statistically significant differences in the prevalence of endorsement

between the two HbA1c groups were observed for both Item 4: poor appetite (p = .003) and Item 7: trouble concentrating (36.3% vs. 27.2%, p = .006). As indicated by the percentages, a lower proportion of the adolescents in the higher HbA1c group endorsed those items than did adolescents in the lower HbA1c group (poor appetite: 20.6% vs. 29.6%, respectively, trouble concentrating: 27.2% vs. 36.3%).

Table 12

*PHQ-9 Item Endorsement by HbA1c groups (*N*=1,403)*

PHQ-9 items	HbA1c < 7.0	HbA1c ≥ 7.0
	n (%)	*n* (%)
Feeling down and depressed		
Not at all	176 (77.9)	888 (75.4)
Several days or more	50 (22.1)	289 (24.6)
Little interest or pleasure		
Not at all	156 (69.0)	865 (73.5)
Several days or more	70 (31.0)	312 (26.5)
Trouble falling asleep		
Not at all	134 (59.3)	657 (55.8)
Several days or more	92 (40.7)	520 (44.2)
Poor appetite		
Not at all	159 (70.4)	935 (79.4)
Several days or more	67 (29.6)	242 (20.6)
Fatigue		
Not at all	123 (54.4)	676 (57.4)
Several days or more	103 (45.6)	501 (42.6)
Feeling bad about self		
Not at all	177 (78.3)	937 (79.6)
Several days or more	49 (21.7)	240 (20.4)
Trouble concentrating		
Not at all	144 (63.7)	857 (72.8)
Several days or more	82 (36.3)	320 (27.2)
Moving or talking slowly		
Not at all	198 (87.6)	1034 (87.9)
Several days or more	28 (12.4)	143 (12.1)
Thoughts of self-harm		
Not at all	209 (92.5)	1105 (93.9)
Several days or more	17 (7.5)	72 (6.1)

Table 13

*Adjusted and Unadjusted Associations of PHQ-9 Items With HbA1c (*N = *1,403)*

PHQ-9 items	Unadjusted		Adjusted [a]	
	OR (95% CI)	*p*	*OR* (95% CI)	*p*
Feeling down and depressed	1.15 (0.81–1.62)	.435	1.63 (1.02–2.60)	.040
Not at all				
Several days or more				
Little interest or pleasure	0.81 (0.58–1.10)	.168	0.83 (0.57–1.22)	.338
Not at all				
Several days or more				
Trouble falling asleep	1.15 (0.86–1.54)	.335	1.56 (1.09–2.23)	.015
Not at all				
Several days or more				
Poor appetite	0.61 (0.44–0.85)	.003	0.57 (0.39–0.83)	.003
Not at all				
Several days or more				
Fatigue	0.89 (0.66–1.18)	.403	0.95 (0.66–1.37)	.786
Not at all				
Several days or more				
Feeling bad about self	0.93 (0.65–1.31)	.660	0.91 (0.57–1.44)	.678
Not at all				
Several days or more				
Trouble concentrating	0.66 (0.48–0.89)	.006	0.61 (0.42–0.87)	.006
Not at all				
Several days or more				
Moving or talking slowly	0.98 (0.63–1.51)	.920	1.23 (0.75–2.01)	.407
Not at all				
Several days or more				
Thoughts of self-harm	0.80 (0.46–1.39)	.428	0.84 (0.43–1.61)	.594
Not at all				
Several days or more				

Note. [a] Overall model: χ^2 (9, 1,403) = 26.05, p = .002

Results of the multivariate analyses of the PHQ-9 item endorsements with the likelihood of being in the higher HbA1c group are also shown in Table 13. The overall model that included all 9 items was statistically significant, χ^2 (9, 1,403) = 26.05, p = .002. Both items, poor appetite (*OR* = 0.57, 95% CI = 0.39–0.83, p = .003) and trouble concentrating (*OR* = 0.61, 95% CI =

0.42–0.87, p = .006) remained statistically significant and in the same direction (higher prevalence in lower HbA1c group) as observed in the bivariate analyses. Yet in the multivariate analysis, Item 1: "Feeling down and depressed" and Item 3: "Trouble Falling Asleep," both became statistically significant indicating adolescents in the higher HbA1c group endorsed those items with a higher prevalence than those in the lower HbA1c group (Feeling down: *OR* = 1.63, 95% CI = 1.02–2.60, p = .040; Falling asleep: *OR* = 1.56, 95% CI = 1.09–2.23, p = .006).

Time in Range. In addition to HbA1c, a second indicator of glycemic control included in this study was the percentage of time in range for the subsample of adolescents with CGM (n = 69). The small sample size did not allow for replication of most of the analyses conducted with HbA1c as the glycemic control indicator. In the sample, the percentage time the CGM was in use was a median: 85.7% (IQR = 63.5, 97.0) of time. In that time of use, median percentage time in range was 46.0 (IQR= 30.5, 63.0), and median percentage of time below range was 2.0 (IQR = 1.0, 5.0). This finding indicates, although these adolescents were actively using the CGM most of the day, their BG levels were in the target ranges approximately half of that time. None of the correlations of these indicators with the PHQ-9 total scores were statistically significant (percent active: r_s = –.18, p = .170; % in-range: r_s = –.13, p = .275; % below target: r_s = .04, p = .771).

Self-Management

Self-management was assessed using data from the random subsample of adolescents using BG meters and/or insulin pumps. Specifically, frequency of daily SMBG readings was used from BG meter data, and number of daily insulin boluses was used from insulin pump data. Data from 267 BG meters were available indicating adolescents using those meters had a median 2.5 SMBG readings per day (IQR: 1.3, 3.6, min = 0, max = 8). Higher numbers of BG meter readings were associated with lower depressive symptom scores. A median 4.2 daily insulin

boluses were found for the 93 insulin pumps in the subsample of adolescents with device data (IQR: 2.9, 5.9). The correlation of number of daily insulin boluses with PHQ-9 total scores was not statistically significant ($r = -.05$; $p = .629$).

CHAPTER 5

Summary of Findings, Implications, and Directions for Future Research

The purpose of this study was to compare depressive symptom presentation in adolescents with and without T1D, and to build on prior work examining depressive symptoms in relation to diabetes outcomes. To identify systematic endorsement of depressive symptoms that may be associated with diabetes, we compared PHQ-9 scores and patterns of item endorsement in adolescents with T1D with a matched control group from a general adolescent sample. This study also evaluated the relationships between demographic, health care utilization variables, and depressive symptoms with glycemic control and self-management. This chapter will summarize key findings from and limitations of the study. Lastly, implications and recommendations for future research will be discussed.

Aim 1

The first aim of this study was to examine the severity of depressive symptoms and the symptom endorsement patterns in a case cohort of adolescents with T1D and an age-, sex-, and race-matched control cohort of adolescents without T1D. Routine depression screening provided a large sample for analysis. Matching the case and control adolescents reduced possible confounding on factors related to age, sex, and race. However, the two cohorts were statistically significantly different in the two unmatched demographic characteristics of ethnicity and insurance type ($p < .001$). The control cohort had 44.1% of adolescents identifying as Hispanic compared to 5.7% of those in the case cohort. The control cohort also had a significantly higher percentage of adolescents with public insurance (89% vs. 43%). Ethnicity was not found to have

a significant relationship with PHQ-9 scores and thus ethnicity was not controlled for in our analyses. It is possible matching for race may have reduced the influence of ethnicity as a confounder. However, the type of health insurance did have a statistically significant association with PHQ-9, and thus we adjusted for health insurance type in the analyses.

Overall level of depressive symptoms in the samples of adolescents with and without T1D was low, with a median score of 2.0 out of a possible range of 0–27 for total PHQ-9. This average score is consistent with previous studies in adolescents with T1D (Mulvaney et al., 2019; Vassilopoulos et al., 2020). Studies of adolescents with T1D have reported varying prevalence rates of depression from 5%–30 % (Buchberger et al., 2016; Corathers et al., 2013; Fisher et al., 2016; Vassilopoulos et al., 2020); thus, our prevalence falls within the range of previously reported rates for T1D. Given a PHQ-9 cutoff of ≥ 10 indicates a positive screen (moderate to severe depressive symptoms), our results indicated 10.5% of the T1D cohort and 7.9% of the non-T1D cohort endorsed moderate to severe depressive symptoms. This finding is consistent with other studies that have indicated greater likelihood of depressive symptoms in adolescents with T1D than those without T1D (Buchberger et al., 2016; Grey et al., 2002; Silverstein et al., 2015). Although the prevalence of moderate to severe depressive symptoms is greater in this T1D cohort, it is not two to three times higher than those without T1D as reported in previous studies. Given the significantly higher percentage of adolescents without T1D with public insurance, this finding may have been influenced by insurance type. A recent report on adults with T1D suggests insurance type and other socioeconomic variables may contribute to glycemic control (Kelly et al., 2022).

This study showed symptom presentation was largely similar in the sample of adolescents with T1D as compared to the general pediatric sample of adolescents without T1D. However,

comparison of the item response patterns between the case and control cohorts indicated the likelihood of adolescents with T1D endorsing trouble falling asleep was greater than that of adolescents without T1D. This difference was statistically significant in both the unadjusted (p = .035) and adjusted (p < .001) models. In addition, in the adjusted model, the likelihood of fatigue being endorsed was also greater in those with T1D than without T1D (p = .039).

These findings are consistent with previous research on the relationships of sleep and fatigue in young adults with T1D (Bächle et al., 2015) and other chronic conditions (Crane et al., 2010; Knight, Vickery, et al., 2015). Higher reports of trouble falling asleep aligns with the initial research question that sought to determine whether the endorsement of some depressive symptoms may represent physical or emotional manifestations of diabetes. Given the retrospective nature of this study, there is no qualitative data to help explain the nature of these sleep difficulties and how fatigue is experienced in adolescents with T1D. Adolescents with T1D who endorse these somatic symptoms may be doing so as a result of burdens of managing diabetes, if, for example, worries about diabetes management are contributing to difficulties falling asleep. Adolescents with T1D may also delay bedtime to manage low or high BG levels. The PHQ-9 does not allow for an adolescent to describe reasons for sleep disturbances or fatigue.

Aim 2

The second aim of this study was to evaluate the relative contribution of each depressive symptom on the PHQ-9 and the total PHQ-9 score for adolescents with and without T1D. The item-level comparison did not reveal any significant differences in item to total correlations in the case and control cohorts. The PHQ-9 had good reliability in both cohorts (Cronbach's α = .83 and .82 in the T1D and non-T1D cohorts, respectively). These findings suggest the PHQ-9 is

consistent as a depression screening measure for a general population of adolescents and those with T1D.

Aim 3

The final aim of this study was to examine associations of demographic factors, healthcare utilization and PHQ-9 items with diabetes outcomes. We assessed glycemic control using HbA1c and CGM time in range, and self-management indicators were number of daily BG checks and number of daily insulin boluses. The large sample of adolescents with T1D had no missing PHQ-9 data and few missing HbA1c levels. Thus, few adolescents had to be excluded because of missing data. A randomly selected smaller sample of subjects with device data provided the CGM time in range and self-management indicators.

The full sample of adolescents with T1D and the subsample for which CGM reports were available had similar PHQ-9 scores with almost 90% of the PHQ-9 total scores representing minimal to mild depressive symptoms, but approximately 6% endorsing suicidal ideation. These findings are similar to those of previous studies (Iturralde et al., 2017; Mulvaney et al., 2019; Vassilopoulos et al., 2020; Wolfgram et al., 2020). Bivariate correlations indicated female sex, identifying as any race other than White, having public insurance, and having two or more diabetes-related hospitalizations were significantly associated with higher PHQ-9 total scores. This finding is consistent with previous research by Picozzi and DeLuca (2019). Additionally, longer duration of diabetes, older age at diagnosis, and higher HbA1c were identified as other factors associated with more depressive symptoms (Picozzi & DeLuca, 2019). For this study, duration of diabetes and age at diagnosis were not available fields in the EHR and were not included in these analyses. Therefore, we cannot establish whether there are associations of these variables to diabetes outcomes.

Previous studies have indicated large variability in the relationship between depressive symptoms and HbA1c. Some studies have reported greater depressive symptoms were associated with higher HbA1c (Garey et al., 2021; Mulvaney et al., 2019; Picozzi & DeLuca, 2019). Others did not indicate a significant direct relationship, but instead, variability in frequency of BGM (adherence) and fear of hypoglycemia were found to mediate the effect of depression on HbA1c in previous studies (Jurgen et al., 2020; McGrady et al., 2009).

The majority (83.9%) of the adolescents did not meet the ADA recommendation for HbA1c < 7.0%. This study identified the association between PHQ-9 total scores and HbA1c was not statistically significant (p = .052). However, there was a significant difference in depressive symptom endorsement in those meeting ADA recommendations for HbA1c and those who did not (p = .002) when adjusting for demographic and healthcare utilization, indicating those with HbA1c > 7.0% endorsed depressive symptoms at higher rates. This study found those who identified as female, were a person of color, had public insurance and had two or more hospitalizations had significantly higher PHQ-9 scores which is consistent with previous research. These results suggest that insurance type as a social determinant of health may contribute to a meaningful difference in HbA1c. Feeling down and depressed and trouble falling asleep were more likely to be endorsed by those in the higher HbA1c groups, while poor appetite and trouble concentrating were more likely endorsed by those with lower HbA1c. This finding was especially surprising because studies in T1D report trouble concentrating being a symptom of both hypo and hyper glycemia (Northam, 2020; Schwartz et al., 2014). While disordered eating in the T1D population has been studied and found to be associated with worst glycemic control and increases in depressive symptoms, (Bächle et al., 2016; Luyckx et al., 2019), appetite changes have not been critically evaluated in this population. These findings emphasize the need

for further investigation of the endorsement of depressive symptoms in adolescents with T1D. For the subsample of adolescents with device data, number of daily BG checks had a statistically significant inverse relationship with PHQ-9 total indicating more SMBG was associated with lower depressive symptoms. This finding is consistent with previous studies (Hilliard et al., 2013; Jurgen et al., 2020; McGrady et al., 2009).

The results of this study support the hypothesis that a positive association exists between PHQ-9 total scores and increased diabetes-related hospitalization and the following demographic variables: female sex, public insurance coverage, and races other than White. For those adolescents with BG meter data (n = 267), the results support the hypothesis that depressive symptoms were negatively associated with frequency of daily SMBG indicating more frequent SMBG was associated with lower depressive symptoms. However, there was not a significant association between PHQ-9 total scores and number of daily insulin boluses (p = .709).

Strengths and Limitations

This was the first study to compare depressive symptom presentation in adolescents with T1D with an age-, sex-, and race-matched sample of adolescents without T1D. Despite the tight age matching of plus and minus 3 months, along with matching for sex and race, our sample size was large (N = 477 matched pairs). The control subjects for Aims 1 and 2 came from a clinic affiliated with the same medical center. Strengths of Aim 3 included: (a) large sample of 1,403 adolescents with T1D, (b) assessment of health care utilization that included both inpatient and outpatient care, (c) use of device reports extracted from the EHR, (d) use of CGM time in range as a glycemic control indicator for those with CGM reports, and (e) use of insulin pump and BG meter reports for indicators of self-management.

Although there were several strengths of the research, there are limitations. First, an important diabetes-related variable we were not able to collect was the duration of diabetes as at the time of this study, as this data field was not available in the EHR. Second, our T1D study population came from a single diabetes clinic with a majority having private health coverage, which may limit generalizability of the findings. Not all adolescents with T1D receive care by an endocrinologist and/or a multidisciplinary team of providers including mental health providers. Therefore, the experience of adolescents from the Eskind Pediatric Diabetes Clinic may not be generalized to those who live in underserved rural settings without a specialized care team. Third, the retrospective design does not allow exploration of situational context of depressive symptom endorsement, which could provide a deeper understanding of factors that influenced adolescents' emotional state at the time of the PHQ-9 completion and rationale for response patterns. The depression screening assessed how the adolescent was feeling in relation to the previous two weeks, and it was not clear if they were explicitly thinking of diabetes when responding to the survey questions or not. Lastly, although matched by age, sex, and race, the case and control samples were significantly different in ethnicity and type of insurance coverage.

The randomly selected subsample of adolescents with T1D had very few CGM users which might have reduced our power to detect relationships to CGM variables. The dates of the first PHQ-9 completion for this group of CGM users was mostly from the earlier dates of PHQ-9 collection in the Eskind Diabetes Clinic (2016–2018). Even though the full sample was available from 2016 to 2020, the random selection conducted in SPSS resulted in this subsample. Unfortunately, this study was limited by the cost and time needed to extract and manually code device reports from the EHR. Therefore, from the sample of 1403 adolescents only 432 were included in the examination of associations of depressive symptoms and self-management using

data available from devices. The current sample of CGM reports were too small to be able to identify a meaningful relationship between demographic and health care utilization and depression symptoms with time in range.

Clinical and Research Implications

Our findings for Aim 1 indicated two PHQ-9 items more frequently endorsed by adolescents with T1D than those without T1D. Trouble falling asleep, and fatigue were PHQ-9 items identified, possibly related to diabetes. This finding highlights the need to examine whether those depressive symptoms may be overestimated in adolescents with T1D. Given the findings from Aim 2 did not indicate any difference in item to total correlation for the case and control subjects, statistical methods reported in other studies such as item response theory (Nguyen et al., 2014) or multiple indicators multiple causes models (Bozzay et al., 2017) may be considered as an alternative measurement framework to determine whether PHQ-9 items function differently between groups. Item response theory specifically focuses on the relationship of each item in an instrument to the construct it is meant to measure (Nguyen et al., 2014), and multiple indicators multiple causes modeling is a type of structural equation modeling that allows for examination of a latent variable (e.g., depression) on outcomes. These measurement techniques may be able to identify item variance indicating items behaving differently in different groups referred to differential item functioning.

This study calls attention to the need to further explore factors related to diabetes symptoms and burdens of diabetes management that may influence depressive symptom endorsement. Clinical implications of these findings indicate the need to explore factors underlying depressive symptom endorsement that may or may not be related to diabetes. Potential recommendations include: (a) exploring the reason for symptom endorsement during

clinic visits with follow-up questions for the adolescent with T1D tailored to items endorsed on the PHQ-9 to elucidate the rationale for symptom endorsement and any issues with diabetes management that may influence the adolescent's response, (b) as mentioned in the introduction, a variety of instruments are used for depression screening; standardizing depression screening instruments used across all diabetes clinics will allow for better insight into prevalence rates and depressive symptom presentation, (c) reviewing diabetes device data during clinic visits is the standard of care. Clinicians should be more intentional about asking if self-management (e.g., BG meters, insulin pumps) and glucose variability and time in range (CGM) are specifically related to depressive symptoms or a result of challenges with managing diabetes, and (d) evaluating diabetes distress in addition to depression to provide a deeper understanding of the burden of diabetes.

Future research can include a mixed-methods study. Semistructured interviews with a random sample of adolescents in the Eskind Pediatric Diabetes Clinic, for whom we have PHQ-9 surveys, may provide a deeper understanding of rationale for depressive symptom endorsement and distinguish alternative causes that led to symptom endorsement. Interview questions could focus on depressive items highly endorsed by adolescents with T1D that resemble diabetes symptoms.

Having a chronic illness causes a level of acute and chronic stress that has been reported both in adolescents with T1D and in those with IBD (Stapersma et al., 2018). Like IBD, adolescents with T1D experience acute complications, such as DKA and episodes of hypoglycemia and hyperglycemia. In their systematic review, Stapersma et al. (2018) found during times of active illness, adolescents with IBD reported increased depressive symptoms. Screening for depressive symptoms in T1D may also be influenced by the timing of PHQ-9

completion; prevalence and symptom endorsement patterns may vary for an adolescent who is experiencing an acute complication, such as a recent DKA episode. A recent longitudinal study that followed adolescents with and without T1D over 14 years starting at age 12, found depressive symptoms worsened in those with T1D from adolescence to emerging adulthood while, depressive symptoms decreased over this same timeframe in those without T1D (Helgeson et al., 2022). Furthermore, other psychosocial variables such as parental and peer relationships (support and conflict) were examined identifying supportive relationships with parents and friends reduced depressive symptoms at the close of the study. Although, there is limited longitudinal research that focuses on changes in depressive symptom presentation during times of transition, the small sample size in this study was homogeneous with high attrition over the 14 years. Therefore, a longitudinal study of depression screening with a larger more heterogeneous sample could be valuable in exploring situational factors at play related to living with T1D. These factors may be acute illness, disruptions in family structure, changes in insulin regimen, or initiation or discontinuation of a diabetes device. This study excluded adolescents with T2D. While previous studies have indicated higher depression rates with T2D (Hood et al., 2014; Monaghan et al., 2021; Silverstein et al., 2015), others have suggested specific factors, such as diabetes duration and having relatives with T2D, are associated with an increased prevalence of depression with T2D (Wong et al., 2020). Findings identifying different underlying pathways of depression between T1D and T2D warrant further exploration of depression in adolescents with T2D.

The Eskind Pediatric Diabetes Clinic providers estimate 60–80% of adolescents use CGMs currently, and our findings related to time in range need to be replicated with a more representative sample. However, the sample of CGM users in this study was small. Future

studies are recommended to explore further the interaction of depressive symptoms with T1D self-management and glycemic control, taking advantage of device data available in the EHR.

This study had one of the largest samples of adolescents with T1D and age-, sex-, and race-matched adolescents without T1D with completed PHQ-9 instruments. Insights gained from this study reveal the need for further exploration of underlying pathways of depressive symptom presentation in adolescents with T1D. Fatigue, sleep disturbances, trouble concentrating, and poor appetite are of particular interest given our findings. Qualitative research will further enhance our understanding of the underlying reasons for endorsement of these symptoms.

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APPENDIX A

Data Dictionary

Variable	Format and values	Notes and next steps
Date ranges T1D cohort data: 2016–2020 Non-T1D cohort data: 2018–2020	12 months—In relation to the screen	
Study ID	Subjects receive subject IDs with site code followed by consecutive four-digit ID (10001, 10002). Site Codes Eskind Pediatric Diabetes Clinic: 1 Pediatrics Clinic: 2	
Diagnosis	T1D for Eskind Pediatric Diabetes Clinic	
Age at screening	In months	
Race	Asian Black White Alaskan/Indian Pacific Islander Other Declined Missing/unknown	
Ethnicity	If available: Hispanic (1) Non-Hispanic (0)	
Gender	Male (0) Female (1)	
Insurance status	Code: 1 = private; 2 = public; 3 = missing Up to 1 year prior, use most recent	
Insulin regimen	Codes: 1: Pump 2: MDI 3: NPH, 4: Long acting 5: None	
CGM usage	At the time of PHQ, if not then the most recent update. Coded as (0/1)	
Other mood Dx (not depression)	0/1	

Variable	Format and values	Notes and next steps
Anxiety Dx	0/1	
Behavioral Dx	0/1	e.g., ADD/ADHD
Recent A1c value	If not taken on screening date, search up to 6 months before the screening	
A1c time diff	Difference between PHQ screen and recent previous A1c in days	
% hyperglycemia	Define >180 Based on reports from devices	CGM users only
% in range	See high/lows; time-in-range (70–180)	CGM users only
% hypoglycemia	Define < 70	CGM users only
Average Number of BG checks/day	Within/for last 90 days before screen if possible	BG Meter only
The date range for BG data	Start and end dates	
DKA Events	Sum of previous 12 months. May be defined variably; Use ICD code if possible	
Number of diabetes clinic visits	Sum of previous 12 months	
Hospitalizations for hyperglycemia (Not DKA)	Sum of previous 12 months. ICD if possible	
Hospitalizations for hypoglycemia	Sum of previous 12 months. ICD if possible	
Total diabetes-related hospitalizations	Sum of previous 12 months	
Depression Dx	0/1; (self-report or) ICD code	
Indication of treatment for depression	Code (0/1); Within 12 months prior to dep screen	
Treatment method psychotherapy	0/1	
Treatment method medications	0/1	
Action: ED	0/1 Emergency department	
First PHQ date		Use only the first documented scree
PHQ Item 1		
PHQ Item 2		
PHQ item 3		
PHQ item 4		
PHQ item 5		

Variable	Format and values	Notes and next steps
PHQ item 6		
PHQ item 7		
PHQ item 8		
PHQ item 9		
Total score		

APPENDIX B

Patient Health Questionnaire-9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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