CHAPTER 33

PSYCHIATRIC AND PSYCHOSOCIAL ISSUES AMONG INDIVIDUALS LIVING WITH DIABETES

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SUMMARY

Research interest in psychiatric and psychosocial aspects of diabetes care has grown exponentially since *Diabetes in America, 2nd edition*. Epidemiologic data have accumulated to consistently demonstrate elevations in the prevalence of several psychiatric disorders, as well as subclinical elevations in emotional distress, among individuals living with diabetes. The literature is most developed for depression, where studies indicate between 1.2 and 1.6 times higher prevalence of major depressive disorder among adults diagnosed with type 2 diabetes compared to those without diabetes. Data suggest a bidirectional relationship: depression symptoms predict the onset of type 2 diabetes, and the diagnosis of type 2 diabetes is associated with increased depressive symptoms over time, with the first directional effect appearing to be more robust than the second. Evidence is less supportive of higher prevalence of depression in adults and youth with type 1 diabetes. Risk for depression is related to severity of illness, functional limitations, comorbidity, and treatment burden. Although relatively fewer studies are available, prevalence of anxiety disorders is also between 1.1 and 1.4 times greater among adults with diabetes. Eating disorders appear to be between 1.9 and 3.1 times more prevalent among adolescent females with type 1 diabetes than those without diabetes, although few studies are available. Serious mental illness (i.e., Schizophrenia) is associated with between 1.5 and 2.5 times increased risk for development of type 2 diabetes, most likely through exposure to psychotropic medications and shared environmental and behavioral risk factors.

The presence of psychiatric comorbidity, especially depression, which is often comorbid with other psychiatric conditions, has been consistently associated with medication non adherence, sub-optimal glycemic control, and development of diabetes-related complications. The mechanisms to explain these relationships remain poorly understood. Depression, anxiety, and eating disorders could affect health outcomes through biologic (e.g., hypothalamic-pituitary-adrenal axis dysregulation) and/or behavioral (e.g., treatment nonadherence) pathways. However, confounding is possible due to overlap with symptoms of diabetes and comorbid illness, along with shared relationships with socioeconomic and other background variables that may also explain noncausal association.

Emotional distress that does not reach thresholds for a psychiatric diagnosis also appears to be quite common in individuals living with diabetes. These psychosocial issues are more prevalent than true psychiatric conditions and are often more closely related to diabetes-related stressors and outcomes. Longitudinal and intervention studies, mostly focused on depression, do not generally support the expectation that improvement in psychiatric conditions or emotional distress *per se* would reliably lead to better glycemic control. However, too few high-quality studies are available for this evidence to be conclusive.

To have the strongest impact on advancing this field and guiding decisions about patient care, future studies need to be more rigorous in differentiating among psychiatric conditions, elevations in levels of emotional distress, and psychosocial difficulties specific to the burdens of diabetes and its treatment. These studies should also directly evaluate explanatory mechanisms that link these constructs to diabetes health outcomes. Comprehensive approaches to patient-centered care are needed to better understand how to maximize the benefits of intensive treatment for both psychosocial and health outcomes of diabetes care.

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INTRODUCTION

The following sections review evidence for the prevalence of psychiatric and psychosocial issues among adults and children with diabetes. Within each section, findings linking illness- and patient-level factors to variations in prevalence are reviewed, important measurement issues are discussed, and evidence linking psychiatric and psychosocial issues to diabetes health outcomes is considered. Evidence for causal pathways and treatment outcomes is reviewed, when available. The first section is the most detailed because much more research is available on major depressive disorder, depressive symptoms, and emotional distress, relative to other psychiatric and psychosocial issues. This is also the area of research that is most developed in regard to measurement issues, potential causal pathways, and treatment. Much of the information discussed in this section is relevant to issues discussed later in the chapter.

DEPRESSIVE DISORDERS, DEPRESSIVE SYMPTOMS, AND DIABETES-RELATED DISTRESS

OVERVIEW AND DEFINITIONS

Major depressive disorder (MDD) is a serious psychiatric condition that affects approximately 6.9% of U.S. adults over a 12-month period (1). MDD is characterized by symptomatic episodes of at least 2-weeks duration that include either marked loss of interest or pleasure and/or depressed mood, along with several other somatic, psychological, and cognitive symptoms—appetite disturbance or weight loss, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, feelings of guilt and worthlessness, diminished concentration, and recurrent suicidal ideation. MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) of the American Psychiatric Association (2), informs most research on depression in diabetes. Dysthymia is a less severe but more chronic presentation of depressive symptoms (duration of at least 2 years); it affects far fewer individuals, with a 12-month prevalence of 1.5% (3). Elevations in depressive symptoms, which are often measured by self-report scales that mix MDD symptoms with various symptoms of emotional distress, are a third construct reported in this literature. Elevated depressive symptoms do not necessarily indicate the presence of a psychiatric disorder and may be more reflective of emotional distress related to various life stressors (4). Finally, diabetes-related distress, which is conceptualized as emotional distress that relates specifically to the burden of living with diabetes and its management, emphasizes the situational context of diabetes to explain the occurrence of distress and is not a psychiatric condition (5,6). Though these are separate constructs, they share considerable conceptual and measurement overlap.

PREVALENCE AND COURSE

MDD is significantly more prevalent in patients with chronic illness (7), and available research has shown a consistent pattern of increased risk for depression in individuals with diabetes. For example, a widely cited meta-analysis of controlled (i.e., included a nondiabetic comparison group) and uncontrolled studies found that the prevalence of elevated depressive symptoms was twice as high in adults with type 1 or type 2 diabetes compared to adults without diabetes (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.8–2.2) (8). However, a subsequent meta-analysis of controlled studies in type 2 diabetes suggested a similar elevation in depression prevalence (OR 1.59, 95% CI 1.5–1.7), but the authors cautioned that diabetes groups differed from comparison groups on variables known to be associated with increased risk of depression. Furthermore, studies that used diagnostic interviews for depression, rather than self-report scales, suggest the prevalence of true MDD is more modestly increased in adults with type 1 or type 2 diabetes (9,10,11). Thus, attention to method of depression assessment is important in evaluating the evidence base.

International data collected between 2001 and 2004 from the World Health Organization's World Mental Health Surveys, which used the gold standard of assessment—a semi-structured clinical interview—to assess depression, suggest that the odds of MDD is 1.4 times (95% CI 1.2–1.6) greater among adults with diabetes compared to those who do not have diabetes. Dysthymia prevalence was not different between those with and without diabetes (12). The U.S. National Health Interview Survey (NHIS) 1999 also used diagnostic interviews for MDD in 30,801 adults: unadjusted 12-month prevalence was 9.3% versus 6.1% in those with (N=1,810) and without diabetes, respectively (13). As seen in Table 33.1, data from the Behavioral Risk Factor Surveillance System (BRFSS) 2006 survey of 18,814 adults with diabetes in the United States suggest an overall unadjusted point prevalence of MDD of 7.5% (8.3% age-adjusted) (14); however, an algorithm was applied to self-reported MDD symptoms to establish a symptom pattern that met the diagnostic criteria for a major depressive episode but only required 1-week duration, rather than 2 weeks as required by the *DSM-5* (2), likely yielding higher estimates than diagnostic interviews. Depression prevalence was twofold higher (14.4%) when based on meeting a validated and widely used screening cutoff score (Table 33.1) (14). For comparison, analysis of data from the overall BRFSS 2006 of 198,678 adults found unadjusted prevalence rates of 4.3% for probable major depressive episode and 8.6% for a positive screening result (15).

In a new analysis for *Diabetes in America, 3rd edition*, data from the National Health and Nutrition Examination Surveys (NHANES) 2005–2010 indicated significantly higher depression prevalence in those with diagnosed diabetes compared to those with normal glucose metabolism (Table 33.2). However, there were wide

differences in prevalence based on the method of defining depression, as 12.6% of adults with diagnosed diabetes had a positive screening result, yet only 5.9% reported symptom patterns consistent with major depressive episode. Somatic symptoms (e.g., poor sleep, appetite disturbance, low energy) were twice as prevalent among those diagnosed with diabetes than cognitive-affective symptoms (e.g., sadness, loss of interest, feeling like a failure) of depression; screening positive was more than twice as common as endorsing symptom patterns necessary for a diagnosis of MDD. Nevertheless, as shown in Table 33.2, prevalence was significantly higher in those with diagnosed diabetes compared to those with normal glucose metabolism, across all measures.

Further complicating data on the prevalence of depression in diabetes is the strong possibility that depression evaluations can be biased by emotional distress that is specific to the stress of diabetes and its management, conceptualized as diabetes-related distress (5,6). Although few epidemiologic studies have attempted to compare prevalence rates of depression and diabetes-related distress, data from a multinational study of 8,596 adults with type 1 or type 2 diabetes showed that

TABLE 33.1. Prevalence of Likely Major Depressive Episode Versus Positive Screen for Depression in Adults Age ≥18 Years With Diabetes, U.S., 2006

CHARACTERISTICS	N	PERCENT (STANDARD ERROR)	
		Likely Major Depressive Episode*	Positive Screen for Depression
Unadjusted	18,814	7.5 (0.4)	14.4 (0.6)
Age-adjusted	18,814	8.3 (0.5)	17.4 (1.1)
Age (years)			
18–29	230	3.2 (1.0)	12.7 (3.4)
30–39	848	13.7 (2.0)	27.4 (3.1)
40–49	2,251	11.6 (1.1)	21.4 (1.8)
50–59	4,634	10.0 (0.8)	17.3 (1.0)
60–69	5,387	5.5 (1.0)	11.2 (1.2)
70–79	3,939	4.0 (0.9)	8.3 (1.0)
≥80	1,525	2.0 (0.7)	5.8 (1.0)
Sex†			
Men	7,896	5.9 (0.7)	12.9 (1.3)
Women	10,918	11.1 (0.8)	22.4 (1.6)
Race/ethnicity†			
Non-Hispanic white	13,392	9.5 (0.7)	17.6 (1.3)
Non-Hispanic black	2,296	5.6 (1.0)	13.7 (1.6)
Hispanic	1,775	5.4 (0.8)	17.3 (3.0)
Asian	296	1.1 (0.6)	3.1 (1.3)
American Indian/Alaska Native	392	27.8 (4.7)	36.0 (4.9)
Other‡	663	13.2 (3.5)	27.7 (4.6)
Type of diabetes†§			
Type 1	810	6.3 (1.1)	20.4 (2.8)
Type 2, use of insulin	3,759	13.3 (1.8)	24.0 (2.3)
Type 2, no insulin	12,892	8.3 (0.7)	17.3 (1.6)

* Major depressive episode is defined as having at least five of eight Patient Health Questionnaire-8 (PHQ-8) symptoms, one of which must be "depressed mood" or "loss of interest or pleasure," for ≥7 days in the past 2 weeks.
† Adjusted for age.
‡ Includes native Hawaiian or Pacific Islander, multiracial, and other race/ethnicity.
§ Participants with missing data on age at diabetes onset and use of insulin were excluded.

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TABLE 33.2. Depression Among Adults Age ≥20 Years, by Diabetes Status, U.S., 2005–2010

	DIAGNOSED DIABETES (N=2,310)					UNDIAGNOSED DIABETES (N=717)	PREDIABETES (N=3,168)	NORMAL GLUCOSE (N=3,890)
		A1c						
	All	<7.0%	7.0%–<8.0%	8.0%–<9.0%	≥9.0%			
Prevalence (standard error)								
Major depressive episode*	5.9 (0.60)†	6.0 (0.81)	5.1 (1.40)	1.4 (0.69)[1]	7.2 (1.62)	4.5 (1.04)	2.9 (0.33)	2.5 (0.33)
Positive PHQ-9 screen‡	12.6 (0.94)†	11.9 (1.09)	8.9 (1.55)	15.4 (3.44)	15.4 (2.46)	8.8 (1.05)§	7.0 (0.64)	6.0 (0.51)
Mean (standard error)								
PHQ-9 total score	0.44 (0.02)†	0.44 (0.02)	0.38 (0.03)	0.46 (0.04)	0.49 (0.04)	0.34 (0.02)	0.31 (0.01)	0.30 (0.01)
PHQ-9 somatic-affective score‖	0.60 (0.02)†	0.59 (0.03)	0.51 (0.04)	0.69 (0.07)	0.67 (0.05)	0.49 (0.03)§	0.43 (0.02)	0.42 (0.01)
PHQ-9 cognitive-affective score¶	0.31 (0.01)†	0.31 (0.02)	0.27 (0.03)	0.29 (0.03)	0.35 (0.03)	0.23 (0.02)	0.22 (0.01)	0.21 (0.01)

Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or FPG ≥126 mg/dL; prediabetes is defined as A1c 5.7%–6.4% or FPG 100–125 mg/dL; normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; FPG, fasting plasma glucose; PHQ-9, Patient Health Questionnaire 9-item depression screen.
* Likely meets symptom criteria for major depressive episode based on PHQ-9 self-reported symptoms with duration over the prior 2 weeks of at least "more than half the days."
† p<0.001 compared to normal glucose
‡ Prevalence of PHQ-9 score ≥10
§ p<0.05 compared to normal glucose
‖ Somatic-affective score includes items on sleep, fatigability, appetite, and psychomotor agitations/retardation.
¶ Cognitive-affective score includes items on lack of interest, depressed mood, negative feeling about self, concentration problems, and suicidal ideation.
[1] Relative standard error >40%–50%

SOURCE: National Health and Nutrition Examination Surveys 2005–2010

across 17 countries, 13.8% of participants screened positive for depression (19% in the United States) and 44.6% had significant diabetes-related distress (28% in the United States) (16). Thus, MDD prevalence appears to be significantly elevated in diabetes, but subthreshold depressive symptoms and diabetes distress far exceed prevalence of MDD.

MDD is frequently conceptualized as having a relapsing-remitting course. Approximately 50%–85% of people who meet criteria for a major depressive episode will experience a second episode within their lifetime (17,18). A similar recurring course has been found in diabetes. For example, approximately 80% of a small sample of adults with MDD and type 2 diabetes who successfully responded to depression treatment experienced a relapse of MDD over 5 years, with nearly 60% experiencing recurrence within the first year (19). Prior history of MDD raises risk for subsequent episodes in individuals with diabetes. In an ethnically diverse sample of adults with type 2 diabetes, those who did not meet diagnostic criteria for MDD at baseline, but had a prior lifetime episode of MDD, were more than four times more likely to develop MDD over 18 months of follow-up compared to those who did not have prior episodes (20). Similarly, a prospective survey of patients with type 2 diabetes showed a strong relationship between baseline depressive symptoms and risk for screening positive 5 years later; those who screened positive at baseline were more than 11 times more likely to screen positive at year 5 (21).

Other data suggest that depressive symptoms and diabetes distress, and not MDD *per se*, may be particularly enduring. In a three-wave longitudinal study (baseline, 9 months, 18 months) of 508 adults with type 2 diabetes, approximately 11% met diagnostic criteria for MDD at baseline and 19.8% on at least one of three waves of follow-up. Of those who had MDD at one wave, 28% continued to meet criteria for MDD at the next assessment; 14% of those with MDD at two waves also met criteria at a third (11). Elevations in depressive symptoms were more common and much more persistent: 76% of those with elevated depressive symptoms at one time point reported elevations at another, and 77% of these also scored similarly at a third wave. Of those with high diabetes-related distress at one time point, 50% had high diabetes distress at the second time point, and 86% of these had high diabetes distress at the third wave (11).

Illness Factors Related to Prevalence

Although studies focusing on depression prevalence in type 1 diabetes are less common than in type 2 diabetes, evidence suggests that depression elevations in type 1 diabetes may be more modest. A systematic review of depression prevalence studies in adults with type 1 diabetes found insufficient evidence to conclude that depression was more prevalent than in well-matched controls (10). Data from the T1D Exchange, including 6,172 adults with type 1 diabetes from across the United States, showed that 4.6% met symptom criteria for major depressive episode based on self-report, and 10.3% reached the screening cutoff (Table 33.3) (22). Although the sample may not be representative of the population of adults with type 1 diabetes, population-based BRFSS data from 2006 also suggest that prevalence of depression is lower in adults with type 1 diabetes than in those with type 2 diabetes. This difference is particularly marked when comparing to type 2 diabetes patients on insulin, who likely have greater disease and treatment burdens associated with more advanced illness, than to type 2 patients not taking insulin (Table 33.1) (14). Other studies show that more intensive treatment (i.e., prescription of insulin) is associated with increased risk of depression and diabetes distress in adults with type 2 diabetes compared to those taking oral medications or whose diabetes is managed with lifestyle changes (12,14,23,24).

The primary comparisons for youth with type 1 diabetes have been to youth without diabetes or normative data. Several studies suggest prevalence of depression that is two to three times that of the general population (25,26,27). However, meta-analysis of the wider literature indicates that differences are often amplified by disparities in comparison group characteristics. Results show that the magnitude of this difference appears to be smaller in more recent studies, perhaps suggesting a link between newer treatment approaches and improved well-being (28). More recent efforts to screen for depression and distress in pediatric diabetes clinics suggest that between 10% and 20% of youth with type 1 diabetes reach screening cutpoints (29), similar to what would be expected in the general population. In sum, there are mixed results on prevalence, with more recent data trending toward few differences between youth with and without type 1 diabetes. Very few high-quality studies are available.

The few studies that have examined youth with type 2 diabetes, or differences between type 1 and type 2 diabetes, suggest that those with type 2 diabetes have more emotional distress (30). Measurement limitations are present as these studies largely focus on self-report measures and likely capture general psychological distress instead of depression or diabetes-specific distress. Nevertheless, there appear to be elevated risks for distress and possible depression for youth with type 2 diabetes. A longitudinal investigation (31) from the SEARCH for Diabetes in Youth Study (32) examined the first 6 years of diabetes for 1,307 youth with either type 1 or type 2 diabetes. Scores on depression and quality-of-life measures (that include emotional subscales) were significantly higher for youth with type 2 diabetes versus those with type 1 diabetes at all time points. Although it is difficult to estimate the number of youth with type 2 diabetes and depression based on available studies, they appear to be at increased risk.

The diagnosis and treatment of diabetes appear to be important to understanding risk for depression and emotional distress, perhaps representing a more powerful impact on depression risk than

TABLE 33.3. Factors Related to Prevalence of Likely Major Depressive Episode Versus Positive Screen for Depression in Adult Participants of the T1D Exchange

		PROBABLE MAJOR DEPRESSION: PHQ-8 ≥10		PROBABLE MAJOR DEPRESSION: PER ALGORITHM	
	ALL (*N*=6,172)	Depressed (*n*=638)	Not Depressed (*n*=5,534)	Depressed (*n*=283)	Not Depressed (*n*=5,889)
Age (years)*					
Median (25th–75th percentile)	34.0 (21.0–51.0)	35.0 (22.0–50.0)	34.0 (21.0–51.0)	36.0 (22.0–48.0)	34.0 (21.0–51.0)
18 to <26 (*n* [%])	2,196 (36)	216 (34)	1,980 (36)	91 (32)	2,105 (36)
26 to <50 (*n* [%])	2,314 (37)	253 (40)	2,061 (37)	128 (45)	2,186 (37)
50 to <65 (*n* [%])	1,204 (20)	141 (22)	1,063 (19)	56 (20)	1,148 (19)
≥65 (*n* [%])	458 (7)	28 (4)	430 (8)	8 (3)	450 (8)
P value		0.98		0.95	
Sex, female (*n* [%])†	3,380 (55)	395 (62)	2,985 (54)	175 (62)	3,205 (54)
P value		<0.001		0.01	
Race/ethnicity (*n* [%])†					
White non-Hispanic	5,491 (89)	465 (82)	4,964 (90)	233 (82)	5,258 (89)
Black non-Hispanic	174 (3)	22 (3)	152 (3)	10 (4)	164 (3)
Hispanic or Latino	316 (5)	57 (9)	259 (5)	24 (8)	292 (5)
Other race/ethnicity	191 (3)	32 (5)	159 (3)	16 (6)	175 (3)
P value		<0.001		0.002	
Duration of T1D (years)*					
Median (25th–75th percentile)	16.0 (9.0–28.0)	18.0 (10.0–29.0)	16.0 (9.0–28.0)	19.0 (11.0–28.0)	16.0 (9.0–28.0)
<20 (*n* [%])	3,621 (59)	345 (54)	3,276 (59)	148 (52)	3,473 (59)
20 to <40 (*n* [%])	1,887 (31)	216 (34)	1,671 (30)	103 (36)	1,785 (30)
≥40 (*n* [%])	664 (11)	77 (12)	587 (11)	32 (11)	631 (11)
P value		0.009		0.03	
BMI (*n* [%])*‡					
Under-/normal weight	2,059 (43)	201 (41)	1,858 (43)	81 (37)	1,978 (43)
Overweight	1,659 (35)	140 (29)	1,519 (35)	71 (32)	1,588 (35)
Obese	1,078 (22)	150 (31)	928 (22)	67 (31)	1,011 (22)
P value		0.01		0.02	
Household income (*n* [%])*					
<$35,000	962 (20)	207 (40)	755 (18)	87 (39)	875 (19)
$35,000–<$75,000	1,449 (30)	144 (28)	1,305 (30)	74 (33)	1,375 (30)
≥$75,000	2,392 (50)	164 (32)	2,228 (52)	61 (27)	2,331 (51)
P value		<0.001		<0.001	
Insurance status (*n* [%])†					
Private insurance	4,636 (80)	403 (68)	4,233 (81)	178 (67)	4,458 (81)
Other insurance	1,046 (18)	169 (29)	877 (17)	78 (30)	968 (18)
No insurance	109 (2)	20 (3)	89 (2)	8 (3)	101 (2)
P value		<0.001		<0.001	
Education level (*n* [%])*					
High school diploma/GED or less	2,879 (47)	345 (55)	2,534 (46)	155 (55)	2,724 (47)
Associate's or bachelor's degree	2,171 (35)	208 (33)	1,963 (36)	97 (35)	2,074 (36)
Master's, professional, or doctorate degree	1,066 (17)	77 (12)	989 (18)	28 (10)	1,038 (18)
P value		<0.001		<0.001	
Marital status (*n* [%])†					
Living alone	3,117 (51)	363 (57)	2,754 (50)	163 (58)	2,954 (50)
Married/living together	3,017 (49)	270 (43)	2,747 (50)	120 (42)	2,897 (50)
P value		<0.001		0.02	
Employment status (*n* [%])†					
Student	1,371 (22)	113 (18)	1,258 (23)	46 (16)	1,325 (23)
Working full-/part-time	3,362 (55)	285 (45)	3,077 (56)	121 (43)	3,241 (56)
Not working	1,386 (23)	236 (37)	1,150 (21)	115 (41)	1,271 (22)
P value		<0.001		<0.001	
Complications (*n* [%])†§					
None	2,754 (65)	203 (47)	2,551 (68)	83 (43)	2,671 (66)
≥1	1,461 (35)	233 (53)	1,228 (32)	110 (57)	1,351 (34)
P value		<0.001		<0.001	

BMI, body mass index; GED, general educational development; PHQ-8, Patient Health Questionnaire 8-item depression screen; T1D, type 1 diabetes.

* *P* value from Wilcoxon rank-sum test. Ordinal income and education variables were analyzed.

† *P* value from χ^2 test

‡ For participants <20 years of age, BMI <5th percentile is considered underweight, 5th to <85th percentile normal weight, 85th to <95th percentile overweight, and ≥95th percentile obese. For participants >20 years of age, BMI <18.5 is considered underweight, 18.5 to <25 normal weight, 25 to <30 overweight, and ≥30 obese.

§ Cardiovascular complications, neuropathy, retinopathy, and renal disease

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problems with glucose regulation *per se*. For example, depression appears to be elevated only among those with diagnosed type 2 diabetes; undiagnosed diabetes and impaired glucose metabolism are not associated with increased prevalence of depression. Mezuk *et al*. (33) classified adults in the NHANES 2005–2007 according to fasting glucose levels as having normal glucose (<100 mg/dL [<5.55 mmol/L]), undiagnosed prediabetes (100–125.9 mg/dL), clinically identified prediabetes (100–125.9 mg/dL, plus clinician diagnosis), undiagnosed type 2 diabetes (>126 mg/dL [>6.99 mmol/L]), and clinically identified type 2 diabetes (>126 mg/dL, plus clinician diagnosis or use of antidiabetic medications). Clinically identified diabetes was associated with an approximately fourfold greater odds of having probable major depression in adjusted models compared to those with normal glucose metabolism (Table 33.4). No significant elevation of depression was observed in those with undiagnosed diabetes. The same pattern was found for antidepressant use (33).

Findings from a *Diabetes in America* analysis using NHANES 2005–2010 data were consistent: differences in depression were most pronounced when comparing those previously diagnosed with diabetes to those with normal glucose levels (all p<0.001). Although those with undiagnosed diabetes (glycosylated hemoglobin [A1c] ≥6.5% [≥48 mmol/mol] or fasting plasma glucose [FPG] ≥126 mg/dL) were significantly more likely to screen positive for depression than those with normal glucose metabolism (A1c <5.7% [<39 mmol/mol] and FPG <100 mg/dL) and had higher total scores on the screening instrument, this difference was not observed for the major depressive episode algorithm and appeared to be primarily accounted for by increased levels of somatic symptoms, rather than differences in cognitive-affective symptoms of depression. No measure of depression was significantly elevated among those with prediabetes (A1c 5.7%–6.4% [39–46 mmol/mol] or FPG 100–125 mg/dL [5.55–6.94 mmol/L]) (Table 33.2). Symptom-level analyses showed only one significant elevation among those with undiagnosed diabetes: "feeling tired or having little energy"; those with prediabetes reported feeling down, depressed, or hopeless more frequently than those with no diabetes. The significance of these differences could be viewed as marginal in light of multiple comparisons. In contrast, every symptom of MDD was rated with significantly (p<0.001) greater severity among those with diagnosed diabetes compared to those with normal glucose metabolism (Table 33.5).

Overall, meta-analysis of the available literature (13 studies) supports the consistency of these observations. Adults with undiagnosed diabetes were no more likely to be depressed than those with normal (OR 0.94, 95% CI 0.71–1.25) or impaired glucose metabolism (OR 1.16, 95% CI 0.88–1.54); they were, however, significantly less likely to be depressed than those with diagnosed diabetes (OR 0.57, 95% CI 0.45–0.74). Adults with impaired glucose metabolism were also significantly less likely to be depressed (OR 0.59, 95%

TABLE 33.4. Association Between Depression Syndrome and Clinically Identified and Undiagnosed Diabetes

CHARACTERISTICS	ODDS RATIO (95% CONFIDENCE INTERVAL)			
	Model 1	Model 2	Model 3	Model 4
Diabetes status (ref. normal glucose)				
Undiagnosed diabetes	1.06 (0.59–1.89)*	1.35 (0.73–2.49)	1.28 (0.69–2.39)	1.35 (0.75–9.34)
Clinically identified prediabetes/diabetes	3.22 (1.80–5.75)	4.14 (2.11–8.12)*	3.91 (1.98–7.72)*	4.26 (0.83–9.07)*
Age		0.97 (0.95–0.99)*	0.97 (0.95–0.99)*	0.97 (0.83–1.00)
Gender (ref. men)		2.03 (1.20–3.43)*	2.09 (1.24–3.50)*	2.25 (0.83–3.78)*
Race/ethnicity (ref. non-Hispanic white)				
Non-Hispanic black		0.79 (0.42–1.49)	0.79 (0.42–1.49)	0.74 (0.83–1.42)
Hispanic		0.47 (0.25–0.90)*	0.51 (0.26–1.01)	0.41 (0.83–0.90)*
Low education		1.48 (0.71–3.09)	1.41 (0.67–2.97)	1.36 (0.83–2.77)
High PIR†		0.35 (0.17–0.71)*	0.36 (0.18–0.71)*	0.45 (0.83–0.94)
Count of poor health behaviors (ref. none)				
One			1.31 (0.68–2.52)	1.28 (0.83–2.42)
Two			1.60 (0.79–3.25)	1.43 (0.83–2.90)
Three or four			1.67 (0.72–3.88)	1.39 (0.83–3.34)
Count of trying to engage in health promotion behaviors (ref. none)				
One				1.08 (0.83–2.29)
Two				2.28 (0.83–4.58)*
Three				0.72 (0.83–1.61)
Health insurance (ref. none)				0.42 (0.83–0.78)*
Total *n*	3,183	3,183	3,183	3,183

Estimates are adjusted for all covariates in the model. Models: Model 1, unadjusted; Model 2, adjusted for demographic characteristics; Model 3, additional adjustment for poor health behaviors (smoking, excessive alcohol use, and poor eating habits); Model 4, additional adjustment for adherence to health promotion behaviors (increasing physical activity, controlling weight, and managing diet) and health insurance.

* p<0.05

† Household poverty-to-income ratio (PIR)

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TABLE 33.5. Mean Value of Severity of PHQ-9 Symptoms Among Adults Age ≥20 Years, by Diabetes Status, U.S., 2005–2010

SYMPTOMS	MEAN (STANDARD ERROR)			
	Diagnosed Diabetes (N=2,330)	Undiagnosed Diabetes (N=723)	Prediabetes (N=3,181)	Normal Glucose (N=3,898)
Have little interest in doing things	0.44 (0.024)*	0.34 (0.034)	0.30 (0.014)	0.27 (0.012)
Feeling down, depressed, or hopeless	0.43 (0.022)*	0.33 (0.056)	0.31 (0.015)†	0.27 (0.013)
Trouble sleeping or sleeping too much	0.76 (0.032)*	0.65 (0.051)	0.59 (0.024)	0.57 (0.019)
Feeling tired or having little energy	0.97 (0.032)*	0.81 (0.045)†	0.69 (0.024)	0.69 (0.014)
Poor appetite or overeating	0.47 (0.026)*	0.35 (0.030)	0.33 (0.017)	0.32 (0.012)
Feeling bad about yourself	0.32 (0.019)*	0.20 (0.031)	0.22 (0.010)	0.22 (0.011)
Trouble concentrating on things	0.31 (0.021)*	0.23 (0.030)	0.22 (0.014)	0.22 (0.012)
Moving or speaking slowly or too fast	0.22 (0.021)*	0.15 (0.026)	0.13 (0.012)	0.12 (0.007)
Thought you would be better off dead	0.08 (0.009)*	0.05 (0.009)	0.04 (0.006)	0.04 (0.004)

Diagnosed diabetes is based on self-report. Undiagnosed diabetes is defined as A1c ≥6.5% or FPG ≥126 mg/dL; prediabetes is defined as A1c 5.7%–6.4% or FPG 100–125 mg/dL; normal glucose is defined as A1c <5.7% and FPG <100 mg/dL. Range of values for mean is 0–3 (0=not at all, 1=several days, 2=more than half the days, 3=nearly every day in the past 2 weeks). Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; FPG, fasting plasma glucose; PHQ-9, Patient Health Questionnaire 9-item depression screen.

* p<0.001 compared to normal glucose

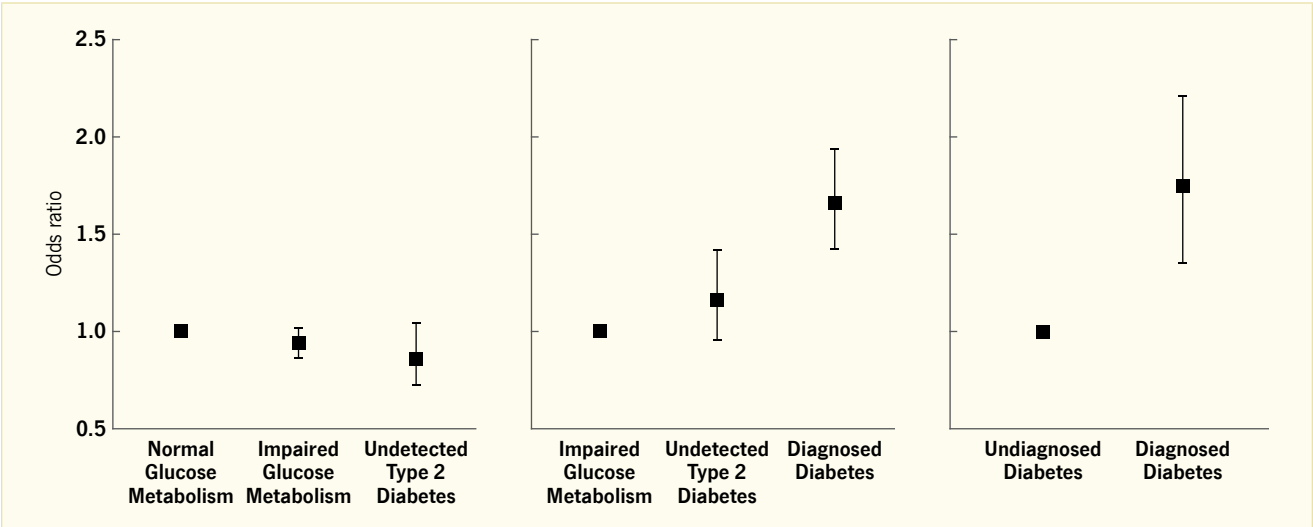
† p<0.01 compared to normal glucose

SOURCE: National Health and Nutrition Examination Surveys 2005–2010

CI 0.48–0.73) than those with previously diagnosed diabetes but did not differ from those with normal glucose levels (OR 0.96, 95% CI 0.85–1.08) (Figure 33.1) (34,35). Thus, the diagnosis and treatment of diabetes seem to be more closely tied to risk for depression than dysregulation in glucose metabolism *per se*.

The presence of comorbid illness is associated with depression in diabetes. In one study, elevated depression symptoms were 2.5 times more common among adults with type 2 diabetes and at least one additional comorbid chronic illness (i.e., arthritis, cardiovascular disease, stroke, cancer, lung disease) compared to those without chronic disease. Prevalence of depression was elevated to a similar degree when comparing those with diabetes and comorbid illness to those with diabetes but no comorbid illness; the latter group was no more likely to be depressed than those with no chronic illness. Further analyses suggested an important role for functional limitations in explaining depression symptom variation (36). A survey of over 30,000 individuals found that functional disability was significantly more frequent among individuals with both diabetes (type 1 or type 2) and MDD than those with only one of the conditions (37). NHIS data showed that the prevalence of MDD in adults with diabetes was significantly increased by the presence of two or more comorbid chronic illnesses, particularly coronary artery disease, chronic arthritis, and stroke (33,38).

FIGURE 33.1. Effect of Impaired Glucose Metabolism, Undetected Diabetes, and Diagnosed Type 2 Diabetes on Odds of Depression in Adults



Data represent point estimates and 95% confidence intervals of odds ratios for depression, based on a meta-analysis by the European Depression in Diabetes Research Consortium.

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The presence of diabetes complications is associated with elevated depression symptoms in adults with type 2 diabetes (39) and type 1 diabetes (40). Severity of complications may also increase risk for depression symptoms over time. For example, severity of diabetic peripheral neuropathy, along with physical symptoms and functional impairments secondary to neuropathy, are associated with increased symptoms of depression, both cross-sectionally (41) and over 18 months (42) in adults with type 1 or type 2 diabetes. NHIS data showed that the 12-month prevalence of MDD, diagnosed by structured clinical interview, was considerably higher among those with major complications of diabetes compared to those who did not have complications (Table 33.6) (13). Perceived worsening of health status over the prior year was also an independent predictor of risk for MDD (Table 33.6) (13). In the T1D Exchange, self-reported depression symptoms over the prior 2 weeks were more common among adults with longer diabetes duration, higher body mass index (BMI), who had experienced diabetes complications, prior severe hypoglycemia, diabetic ketoacidosis (DKA), and poor glycemic control (Table 33.3) (22). These findings highlight the likely important role of health, somatic complaints, and functional impairments in explaining increased prevalence of depression in diabetes.

Patient Factors Related to Prevalence

Data from the BRFSS 2006 show that prevalence of self-reported depressive symptoms in adults with diabetes was low at age 18–29 years, increased at age 30–39 years, and decreased steadily after age 40 years (Table 33.1) (14). National data show that diagnosed diabetes is most robustly associated with increased symptoms of depression among younger adults and is not significantly associated with increased depression among those age >75 years (43). A negative linear trend for depressive symptoms and diabetes-related distress with increasing age was also found in a sample of adults with type 2 diabetes (44). Among adults with type 2 diabetes who did not meet criteria

TABLE 33.6. Factors Associated With Prevalence of Major Depressive Disorder in Adults Age ≥18 Years With Diabetes, U.S., 1999

CHARACTERISTICS	ADJUSTED ODDS RATIO (95% CI)
Race/ethnicity	
White (reference)	
Black	0.7 (0.3–1.3)
Hispanic/other	1.7 (0.9–3.2)
Age (years)	
18–34	3.3 (1.2–8.8)*
35–49	5.0 (2.4–9.9)*
50–64	2.8 (1.4–5.5)*
≥65 (reference)	
Sex	
Women	1.7 (1.1–2.8)*
Men (reference)	
Education	
<High school	0.5 (0.3–0.9)*
≥High school (reference)	
Poverty ratio (% of federal poverty level)	
<124%	2.7 (1.1–6.7)*
124%–199%	2.3 (0.9–5.2)
200%–399%	1.5 (0.7–3.1)
≥400% (reference)	
Employment	
Employed	0.8 (0.4–1.5)
Not employed (reference)	
Marital status	
Married	0.8 (0.5–1.3)
Not married (reference)	
Health status	
Better	1.6 (0.8–3.1)
Worse	5.9 (3.2–10.9)*
Same (reference)	
Obesity status (BMI, kg/m^2)	
<18.5	0.5 (0.1–4.0)
18.5–24.9	0.5 (0.1–4.0)
25.0–29.9	0.6 (0.1–4.2)
≥30.0 (reference)	
Smoking status	
Smoker	1.9 (1.1–3.4)*
Nonsmoker (reference)	
Years since diagnosis	
<5	1.3 (0.7–2.4)
5–9	0.9 (0.4–1.7)
≥10 (reference)	
Medication use	
Diet alone	0.9 (0.5–1.7)
Insulin or oral agents (reference)	
Major complications	
Yes	1.5 (0.9–2.5)
No (reference)	

BMI, body mass index; CI, confidence interval.

* Statistically significant at $p<0.05$. Dependent variable: major depressive disorder—yes versus no. Independent variables: age, sex, race/ethnicity, education, income, employment, marital status, health status, BMI, smoking, duration of diabetes, presence or absence of major complications, and type of treatment for diabetes.

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for MDD at baseline, younger age was significantly associated with increased risk of developing MDD over time in another study (20). A similar negative relationship between adult age and self-reported depressive symptoms has been observed in the general population (15).

Women are generally at increased risk for depression relative to men, and this pattern is also observed in patients with diabetes (Tables 33.1, 33.3, and 33.6) (8,9,12,13,14,22,45). This is consistent with the general population (15). Depression may also be more common among pregnant women with diabetes relative to pregnant women without diabetes. A retrospective cohort study of over 11,000 predominantly low-income women found that depression during or after pregnancy was reported by 15% of women with prepregnancy or gestational diabetes and 8.5% of those without diabetes (46).

BRFSS 2006 data showed substantial variation by race/ethnicity in the prevalence of likely major depressive episode. Compared with non-Hispanic whites (9.5%), non-Hispanic blacks (5.6%), Hispanics (5.4%), and Asians (1.1%) each had significantly lower rates of likely major depressive episode, whereas American Indians/Alaska Natives (27.8%) had a much higher rate than any other group (Table 33.1) (14). Other studies have shown that racial minorities with diabetes report depressive symptoms at rates above those found in whites (47,48). Hispanics have been found more likely to report higher levels of depressive symptoms compared with non-Hispanic whites and blacks (45,46,47,48,49). U.S. data from the Diabetes Attitudes, Wishes, and Needs Second Study (DAWN2) of over 1,000 adults with diabetes showed that ethnic minorities tended to have better indicators of general emotional well-being but had significantly higher levels of diabetes distress than non-Hispanic whites (49). Whereas national data from the NHIS 1999 did not show an independent relationship between race/ethnicity and prevalence of MDD, individuals living at <124% of the federal poverty level had significantly increased prevalence (Table 33.6) (13). Data from the T1D Exchange suggest that Hispanics, those without private health insurance, those with a lower household income and a lower education level, and those who are living alone are all at increased risk for depressive symptoms (Table 33.3) (22).

MEASUREMENT ISSUES

Accurate assessment of depression in diabetes is challenging, and this has limited progress in the literature. An important consideration in evaluating evidence linking diabetes and psychiatric conditions is that somatic symptoms and emotional experiences, often included in measures used to assess psychopathology, are common aspects of living with a chronic illness. Confounding of MDD symptoms and somatic symptoms known to be associated with diabetes, such as fatigue, appetite disturbance, and disrupted sleep, complicates the diagnosis of MDD in patients with diabetes and may lead to misdiagnosis (50).

Findings from a population-based, representative study of German adults underscore the problem of overlap between somatic symptoms associated with both depression and poorly controlled diabetes. Among approximately 15,000 participants, prevalence of diabetes increased linearly with increasing depression-screening score. However, when these scores were analyzed based on somatic versus cognitive-affective symptom components, a significant difference between those with and without diabetes was found only for somatic symptoms. An item-level analysis showed that significant differences were limited to symptoms of fatigue, appetite disturbance, and psychomotor changes (51). In a new analysis of data from NHANES 2005–2010 for *Diabetes in America*, a MDD symptom-level analysis showed a much more consistent pattern of significance for all MDD symptoms when comparing those with clinically identified diabetes to those with normal glucose metabolism (Table 33.5). Multiple factors, such as greater severity of functional limitations and perceptions of illness burden, may contribute to the differences between these samples, and further research into symptom patterns is warranted. A meta-analysis of prospective studies on cognitive-affective versus somatic symptoms as predictors of cardiovascular outcomes in patients with heart disease underscores the importance of this distinction. In minimally adjusted analyses, both dimensions were significantly associated with an increased hazard for worsening prognosis. However, in fully adjusted analyses, somatic symptoms remained significantly associated with worse prognosis (hazard ratio [HR] 1.19, 95% CI 1.10–1.29), but cognitive-affective symptoms did not (HR 1.04, 95% CI 0.97–1.12) (52). The authors are not aware of similar analyses in diabetes.

Fisher and colleagues have published several studies suggesting that diabetes-related distress—emotional distress that arises from the difficulties of living with and managing diabetes—may be more closely related to problems with diabetes treatment adherence and worse diabetes control than clinical depression *per se* (53,54,55). However, others have suggested that either depressive symptoms primarily (56) or both depressive symptoms and diabetes-related distress (57) have independent relationships to diabetes self-management. Furthermore, even during structured clinical interviews for depression, adults with type 1 and type 2 diabetes often explain their symptoms as being caused by diabetes or its treatment (58,59). Thus, there appears to be substantial overlap between depressive symptoms and diabetes-related distress.

For the above reasons, it is important to recognize that self-report screening measures for MDD will result in frequent false positives. For example, a review of 234 studies using depression-screening instruments in adults with type 1 or type 2 diabetes found that prevalence estimates varied widely within and across instruments, and positive predictive values ranged from 23% to 56% (60). One study using a widely used self-report questionnaire to screen for depression in adults with type 2 diabetes showed that

approximately 70% of those who screened positive did not meet criteria for MDD or dysthymia based on a semi-structured interview (53). In a study of 368 adults with type 1 diabetes (61), depression screening questionnaires were scored by more and less conservative cutoffs for caseness. These results were then compared to depression diagnosis, based on structured interview. Similar to results from the *Diabetes in America* analysis of NHANES 2005–2010 data (Table 33.2), the prevalence of a positive screening result was 11.4%, but self-reported symptom patterns consistent with major depressive episode were much lower, at 4.6%. The prevalence of MDD diagnosed by structured interview was lower still, at 3.5%. Depending on the screening criterion, 52%–71% of positive screening cases were false positives (61). Regardless of method of classification, more than 90% of those identified as depression cases also reported elevated diabetes distress.

Thus, a positive screening result cannot be equated with meeting criteria for a psychiatric disorder and may share considerable overlap with diabetes-related distress. Reliance on screening measures to identify cases of depression likely contributes to conflicting findings in the literature. The ambiguities relating to depression screening in diabetes raise challenges for the implementation of self-report-based screening programs in clinical practice. Further assessment will be needed to correctly distinguish between true positives and false positives.

ASSOCIATION WITH DIABETES TREATMENT OUTCOMES

Meta-analysis has previously demonstrated consistent relationships between depression and poor glycemic control in type 1 and type 2 diabetes (Table 33.7) (62). However, most subsequent studies that examined changes in depression and glycemic control over time failed to find significant relationships (Table 33.8) (54,57,63,64,65). Thus, there is reason for caution in assuming a particular direction of causal influence for the frequently observed association between depression and poor glycemic control in diabetes. In a new analysis for *Diabetes in America*, data from NHANES 2005–2010 suggest that depression prevalence was generally highest among those with A1c ≥9.0% (≥75 mmol/mol); prevalence was generally lowest for those with A1c 7.0%–8.0% (53–64 mmol/mol) (Table 33.2). Research suggests that diabetes-related emotional distress, and not depression *per se*, may be more closely associated with glycemic control over time (54,57).

A meta-analysis showed consistent relations between depression severity and diabetes complications, although available studies were cross-sectional (Table 33.9) (66). Subsequent longitudinal studies have consistently found depression to predict the onset of complications, including diabetic retinopathy, nephropathy, neuropathy, macrovascular disease, sexual dysfunction, and foot ulcers (Table 33.10) (67,68,69,70,71,72). Review of findings in this table suggests that a variety of depression measures have been shown to be associated with complication incidence, even measures that capture elevations in depressive symptoms that are unlikely to indicate presence of psychopathology. Depression is also associated with greater functional impairment (37,73,74,75) and increased likelihood of dementia (76). Meta-analysis demonstrates that depressive symptoms are associated with increased risk of mortality, primarily among adults with type 2 diabetes (Table 33.11) (77). Although these data cannot speak to causality, the consistency of findings linking depressive symptoms to poor diabetes health outcomes suggests that elevations should be seen as a marker of increased health risk.

CAUSAL ISSUES AND EXPLANATORY MECHANISMS

The relationship between depression and type 2 diabetes may be bidirectional (23,78,79,80). Meta-analysis of 13 prospective studies showed that elevations in depressive symptoms were associated with a 60% increased risk of developing type 2 diabetes (79), an increase of comparable magnitude to

TABLE 33.7. Meta-Analysis of Association Between Depression and Hyperglycemia in Adults With Diabetes

GROUPING OF STUDIES	*k*	WEIGHTED *p* AND *z*	WEIGHTED *r* (95% CI)	UNWEIGHTED *r* (95% CI)	TESTS OF HOMOGENEITY
All	30	*p*=0.00001 *z*=5.44	0.16 (0.13–0.20) (*k*=28)	0.20 (0.16–0.24) (*k*=28)	Heterogeneous
Cross-sectional	26	*p*=0.00001 *z*=5.43	0.17 (0.13–0.21) (*k*=24)	0.19 (0.16–0.23) (*k*=24)	Homogeneous
Depression per self-report scales	21	*p*<0.00001 *z*=4.52	0.15 (0.11–0.19) (*k*=19)	0.16 (0.12–0.19) (*k*=19)	Homogeneous
Depression per diagnostic criteria	6	*p*<0.00002 *z*=3.51	0.28 (0.20–0.36) (*k*=6)	0.30 (0.22–0.38) (*k*=6)	Homogeneous
Type 1 diabetes sample	11	*p*=0.00002 *z*=3.7	0.19 (0.12–0.25) (*k*=9)	0.21 (0.15–0.28) (*k*=9)	Homogeneous
Type 2 diabetes sample	7	*p*=0.005 *z*=2.76	0.16 (0.09–0.22) (*k*=7)	0.16 (0.09–0.22) (*k*=7)	Homogeneous
Mixed type 1 and type 2 diabetes sample	9	*p*=0.00001 *z*=3.56	0.17 (0.11–0.23) (*k*=9)	0.22 (0.16–0.28) (*k*=9)	Heterogeneous

CI, confidence interval; *k*, number of studies.

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TABLE 33.8. Depression and Glycemic Control: Longitudinal, Change-Based Studies

YEARS (REF.)	SUBJECTS: Type of Diabetes (N)	SUBJECTS: Sex (M/F)	DEPRESSION ASSESSMENT	STATISTICAL ANALYSES	P VALUE
NR (63)	Type 2 (253)	50/203	PHQ-9	Regression analysis: baseline PHQ-9 predicts 6-month A1c, with baseline A1c controlled.	0.361
				Regression analysis: baseline A1c predicts 6-month PHQ-9	0.558
NR (54)	Type 2 (506)	218/288	CIDI and CES-D	Multilinear modeling: prospective analyses and time-covarying models	
				MDD diagnosis (CIDI):	
				Prospective analyses: baseline CIDI predicting linear change in A1c over 18 months	0.55
				Time-covarying model: changes in depression and A1c over 18 months	0.20*
				Depressive symptoms (CES-D):	
				Prospective analyses: baseline CES-D predicting linear change in A1c over 18 months	0.89
				Time-covarying model: changes in depression and A1c over 18 months	0.18*
2001–2004 (64)	Type 1 and type 2 mixed (28/62)	19/71	BDI and HAM-D	Regression analyses examining effects of CBT-based depression treatment on A1c	
				Depressive symptoms (BDI):	
				Regression analysis: effects of changes in BDI over time on A1c	0.68
				MDD diagnosis (HAM-D):	
				Regression analysis: effects of changes in HAM-D over time on A1c	0.59
1997–2006 (65)	Type 2 (11,525)	11,179/346	ICD-9 diagnosis (patient notes)	General linear mixed-model regression analysis: time-varying depression diagnosis predicts higher A1c over time.	0.008
				General linear mixed model regression analysis: depression-by-time interaction predicting differences in change in A1c over time.	0.443
NR (57)	Type 2 (253)	126/127	PHQ-9	Regression analysis: baseline PHQ-9 predicts 6-month A1c	0.267†

A1c, glycosylated hemoglobin; BDI, Beck Depression Inventory; CBT, cognitive-behavioral therapy; CES-D, Center for Epidemiologic Studies-Depression Scale; CIDI, Composite International Diagnostic Interview; HAM-D, Hamilton Psychiatric Rating Scale for Depression; ICD-9, International Classification of Diseases, Ninth Revision; MDD, major depressive disorder; NR, not reported; PHQ-9, Patient Health Questionnaire 9-item depression screen.
* Patient sex, race, age, education, and time since diabetes diagnosis were included in the model.
† Adjusted for age, sex, and regimen and both before and after adjusting for each other.

SOURCE: References are listed within the table.

TABLE 33.9. Meta-Analysis of Association Between Depression and Diabetic Complications in Adults With Diabetes

STUDY AGGREGATIONS	*k*	COMBINED WEIGHTED *p* AND *z*	WEIGHTED *r* (95% CI)	UNWEIGHTED *r* (95% CI)	TESTS OF HOMOGENEITY
All studies/all complications combined	27	$p<0.00001$ $z=5.94$	0.25 (0.22–0.28) (*k*=22)*	0.31 (0.24–0.37) (*k*=22)	Heterogeneous
Presence versus absence of any complications	3	$p=0.004$ $z=2.59$	0.25 (0.16–0.35) (*k*=3)	0.30 (0.09–0.51) (*k*=3)	Heterogeneous
Number of complications	6	$p=0.05$ $z=1.67$	0.29 (0.22–0.37) (*k*=4)	0.30 (0.19–0.40) (*k*=4)	Heterogeneous
All complications					
Type 1 diabetes samples	11	$p<0.00001$ $z=4.68$	0.21 (0.17–0.25) (*k*=8)	0.25 (0.14–0.35) (*k*=8)	Heterogeneous
Type 2 diabetes samples	6	$p=0.01$ $z=2.27$	0.27 (0.17–0.37) (*k*=4)	0.30 (0.23–0.36) (*k*=4)	Homogeneous
Type 1 and type 2 diabetes mixed samples	11	$p=0.0006$ $z=3.29$	0.30 (0.25–0.34) (*k*=10)	0.36 (0.25–0.46) (*k*=10)	Heterogeneous

CI, confidence interval; *k*, number of studies.
* Some studies did not provide enough information to calculate effect size *r*. These studies were omitted from effect size *r* analysis.

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TABLE 33.10. Depression and Incidence of Diabetic Complications: Longitudinal Studies

YEARS (REF.)	SUBJECTS: Type of Diabetes (N)	SUBJECTS: Sex (M/F)	DEPRESSION ASSESSMENT	COMPLICATION ASSESSMENT METHOD	STATISTICAL ANALYSES	P VALUE
1993–1994 (67)	Type 2 (2,830)	1,173/1,657	CES-D, CIDI	Patient self-report	Survival analysis: Diabetes and lifetime MDD or dysthymia (based on CIDI), diabetes and minor depression (CES-D ≥16), diabetes and minimal depression (CES-D 1–15), compared to no diabetes and no depression predicting outcomes over a 7-year follow-up.	
					Macrovascular complications: HR (95% CI)	
					Lifetime depression: 2.64 (1.73–4.04)	<0.05*
					Minor depression: 2.40 (1.71–3.36)	<0.05*
					Minimal depression: 3.56 (1.21–2.00)	<0.05*
					Microvascular complications: HR (95% CI)	
					Lifetime depression: 11.32 (8.76–15.43)	<0.05*
					Minor depression: 8.63 (5.40–13.79)	<0.05*
					Minimal depression: 2.43 (1.90–3.14)	<0.05*
2001–2003 (68)	Type 1 and type 2 mixed (333)	235/98	HADS	Self-report and/or physical exam for foot ulcer	Survival analysis: Continuous measure of baseline self-reported depressive symptom severity predicting time to foot ulceration over an 18-month follow-up.	
					HADS Z-score: HR (95% CI)	
					First foot ulcer: 1.68 (1.20–2.35)	<0.01†
					Recurrent foot ulcer: 0.88 (0.61–1.27)	NS‡
2000–2007 (69)	Type 2 (3,723)	1,941/1,782	PHQ-9	Medical record review	Proportional hazards models: Examined likely major depressive episode (*DSM* algorithm for major depressive episode applied to PHQ-9) and as minor depression (at least one core MDD symptom for a total of 2–4 symptoms) as predictors of complications of diabetes over a 5-year follow-up.	
					Likely major depressive episode: HR (95% CI)	
					Microvascular: 1.36 (1.05–1.75)	<0.05§
					Macrovascular: 1.24 (1.00–1.54)	<0.05§
					Minor depression: HR (95% CI)	
					Microvascular: 1.31 (0.98–1.74)	NS§
					Macrovascular: 1.00 (0.79–1.27)	NS§
2000–2007 (70)	Type 2 (3,474)	1,807/1,667	PHQ-9	Medical record review	Survival analysis: Examined likely major depressive episode (*DSM* algorithm for major depressive episode applied to PHQ-9) and as minor depression (at least one core MDD symptom for a total of 2–4 symptoms) as predictors of first diabetic foot ulcer over a 5-year follow-up.	
					Likely major depressive episode: HR (95% CI)	
					First foot ulcer: 2.00 (1.24–3.25)	<0.05‖
					Minor depression: HR (95% CI)	
					First foot ulcer: 1.37 (0.77–2.44)	NS‖
1982–2002 (71)	Type 1 (483)	195/288	BDI	Medical exam, blood assays	Logistic Regression analysis: Participants who scored >14 on the BDI at baseline and 6-year follow-up compared to those who scored below the cutoff at both time points on odds of incidence of any proteinuria over 6-year follow-up.	
					Positive on both depression screens: OR (95% CI)	
					Proteinuria: 3.01 (1.14–7.99)	<0.05¶
1982–2002 (72)	Type 1 (483)	195/288	BDI	Ocular exam, stereoscopic fundus photographs, grading scale	Logistic Regression analysis: Participants who scored >14 on the BDI at baseline and 6-year follow-up compared to those who scored below the cutoff at both time points on odds of progression of retinopathy and diagnosis of PDR over 6-year follow-up.	
					Positive on both depression screens: OR (95% CI)	
					Progression of retinopathy: 2.44 (1.01–5.88)	<0.05#
					Progression to PDR: 3.19 (1.30–7.87)	<0.05**

A1c, glycosylated hemoglobin; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies-Depression Scale; CIDI, Composite International Diagnostic Interview; *DSM, Diagnostic and Statistical Manual of Mental Disorders*; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; MDD, major depressive disorder; NDS, Neuropathy Disability Score; NS, nonsignificant; OR, odds ratio; PDR, proliferative diabetic retinopathy; PHQ-9, Patient Health Questionnaire 9-item depression scale.

* Adjusted for sociodemographic characteristics.

† Adjusted for retinopathy, vibration perception threshold score, and foot self-care, based on significant univariate relations.

‡ Unadjusted, based on lack of significant univariate relations.

§ Adjusted for any prior microvascular/macrovascular event, sociodemographic characteristics, clinical characteristics (e.g., diabetes duration, treatment intensity), body mass index, smoking, limited physical activity, and A1c.

‖ Adjusted for sociodemographic characteristics, clinical characteristics (e.g., diabetes duration, treatment intensity), number of diabetes complications, foot self-care, and A1c.

¶ Adjusted for albumin excretion ratio, systemic hypertension, A1c, cholesterol, and socioeconomic status.

Adjusted for A1c.

** Adjusted for A1c, diabetes duration, and systemic hypertension.

SOURCE: References are listed within the table.

other known risk factors for developing diabetes, such as smoking (81). Data from the English Longitudinal Study of Ageing, including 4,238 community-dwelling adults age ≥50 years, provide interesting clues about the directions of the relationship between diagnosis of type 2 diabetes and depression. In age-adjusted models, elevated levels of depressive symptoms significantly predicted undiagnosed (OR 1.91, 95% CI 1.03–3.57) and diagnosed (OR 3.03, 95% CI 1.66–5.54) diabetes over 6 years of follow-up; the latter association remained significant after covariate adjustment. Diagnosed diabetes was associated with future elevated depressive symptoms among participants age 52–64 years (OR 2.17, 95% CI 1.33–3.56), but not among those age ≥65 years (OR 0.96, 95% CI 0.59–1.57), over 4 years of follow-up (82). Thus, the evidence is consistent in showing that depression can be a significant risk marker for future type 2 diabetes. The diagnosis of type 2 diabetes is associated with risk for future depression, but not after age 65 years, when chronic illness is more common and diagnosis and treatment may be less disruptive to important areas of functioning. Data on youth with type 1 diabetes show that diabetes usually precedes depression, likely reflecting the typical pattern of depressive symptoms becoming more frequent during adolescence and young adulthood than in childhood (26,27,83). There is little reason to expect that depression would play a causal factor in the development of type 1 diabetes.

Several large studies have linked antidepressant use to increased risk for the development of type 2 diabetes over time, even after controlling for depressive symptom severity and other potential confounding factors (84,85,86). A systematic review found evidence for an association between antidepressant use and increased risk of type 2 diabetes, but results were mixed and study quality was variable (87). Spurious association is quite plausible if individuals with diabetes who report depressive symptoms, which include somatic complaints, can be assumed to be more likely to seek medical care, thus increasing their likelihood of antidepressant prescription and diabetes diagnosis (33). This possibility is further supported by findings from the British Whitehall II longitudinal study, which showed that antidepressant use among 5,978 civil servants free of diabetes at baseline was associated with significantly increased incidence of diagnosed (OR 3.10, 95% CI 1.66–5.78), but not undiagnosed diabetes (OR 0.88, 95% CI 0.45–1.72). There was essentially no difference between users and non-users of antidepressants in glucose changes (88).

TABLE 33.11. Meta-Analysis of Association Between Depression and Mortality in Adults With Diabetes

	N OF STUDIES	WITHIN GROUP	
		Pooled HRs	95% CI
Meta-analysis			
Random effects	10	1.50	1.35–1.66
Fixed effects	10	1.48	1.36–1.60
Meta-regression			
Study site			
U.S.	7	1.50	1.39–1.62
Non-U.S.	3	1.36	1.39–1.62
Study populations			
Community-based	6	1.46	1.27–1.69
Hospitals or clinics	4	1.66	1.38–1.63
Populations			
Mixed age	7	1.47	1.33–1.62
Older adults	3	1.56	1.24–1.96
Gender			
Majority female	7	1.47	1.34–1.61
Majority male	3	1.55	1.15–2.09
Quality scores			
Less than or equal to 13.5	5	1.48	1.32–1.64
Greater than 13.5	5	1.42	1.26–1.58
Mean follow-up years			
Shorter than or equal to 6.5 years	5	1.45	1.29–1.62
Longer than 6.5 years	5	1.45	1.29–1.60
Number of observations			
Less than or equal to 5,000	7	1.42	1.26–1.59
Greater than 5,000	3	1.47	1.32–1.62

CI, confidence interval; HR, hazard ratio.

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The consistent associations between emotional distress and worse diabetes health outcomes have led to a search for potential causal mechanisms. Poor health behaviors and treatment adherence represent a plausible mechanism. For example, meta-analysis of 47 independent samples, including over 17,000 adults with type 1 or type 2 diabetes, found depressive symptom elevations to be associated with poorer diabetes treatment adherence and various aspects of self-management (Table 33.12) (89). In a longitudinal investigation of the association between depressive symptoms and glycemic control in adults with type 2 diabetes, health behaviors accounted for 13% of the association (90). Among adolescents with type 1 diabetes, positive correlation between depressive symptoms and hyperglycemia was partially mediated by less frequent blood glucose monitoring (91).

Biologic pathways through which depression may impact type 2 diabetes and its complications include hormonal abnormalities, alterations in glucose transport function, and increased immuno-inflammatory activation (92,93,94). For example, some studies suggest that depression is associated with enhanced

TABLE 33.12. Meta-Analysis of Relation Between Depression and Diabetes Treatment Nonadherence in Adults, Children, and Adolescents With Type 1 or Type 2 Diabetes, Aggregated by Type of Self-Care

TYPE OF SELF-CARE	*n*	*z* (*P*)	WEIGHTED *r* (95% CI)	HETEROGENEITY Q (df) AND I^2	FAIL-SAFE *n* (*r* = 0.05)
Overall analysis	47	9.81 (<0.001)	0.21 (0.17–0.25)	217.66 (46); *P*<0.001; I^2=78.87	149
Appointment keeping	4	21.58 (<0.001)	0.31 (0.29–0.34)	1.79 (3); *P*=0.617; I^2=0.00	22
Composite measures	18	9.66 (<0.001)	0.29 (0.23–0.34)	38.60 (17); *P*=0.002; I^2=55.96	88
Diet	18	7.60 (<0.001)	0.18 (0.13–0.22)	33.67 (17); *P*=0.009; I^2=49.51	37
Medication	18	5.15 (<0.001)	0.14 (0.09–0.20)	49.73 (16); *P*<0.001; I^2=65.82	24
Exercise	13	7.89 (<0.001)	0.14 (0.10–0.17)	14.43 (12); *P*=0.274; I^2=16.86	22
Glucose monitoring	15	3.50 (<0.001)	0.10 (0.04–0.16)	31.00 (14); *P*=0.006; I^2=54.82	4
Foot care	2	0.88 (0.380)	0.07 (-0.08–0.21)	4.27 (1); *P*=0.039; I^2=76.59	NA

CI, confidence interval; NA, not applicable.

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neuroendocrine activity, especially hypercortisolism, a risk factor for type 2 diabetes (95,96). Enhanced activity of the hypothalamic-pituitary-adrenal (HPA) axis with subclinical hypercortisolism has been observed in patients with type 2 diabetes and is associated with the presence and severity of diabetic complications (97,98,99). Given the association between HPA axis activity and glucose intolerance (100), subclinical hypercortisolism is another plausible mechanism linking distress to worse metabolic control. A population-based study showed that higher daily cortisol exposure was associated with higher interleukin (IL)-6, suggesting that cortisol rhythm is associated with a pro-inflammatory state (101). A pro-inflammatory effect of depressive symptoms has been observed in adults with type 2 diabetes (102). At this point, it is not clear from the available correlational evidence whether these plausible biologic pathways represent causal mechanisms (35).

Some research suggests that the effect of type 1 diabetes on brain structure, function, and neural chemistry leads not only to altered cognition, but also to changes in regions of the brain that regulate affect. Changes in cortical brain structure, as evaluated by voxel-based morphometry and cortical thickness analysis, have been linked to higher A1c, increased depressive symptoms, and alterations in cognitive function (103,104). Moreover, higher levels of the neurotransmitter glutamate have been associated with more depressive symptoms and altered memory function (105). Glutamate is an excitatory neurotransmitter, which in excess has been found to be potentially harmful to neuronal structures. Acute and chronic elevations in blood glucose and, thus, brain glucose could lead to fluctuation in neuronal glutamate levels. Eventually, there may be reciprocal relationships as worsening symptoms negatively impact diabetes from a management perspective and, potentially, from a biologic perspective (106). Though plausible, there is currently insufficient evidence for this full pathway.

Although the above explanatory mechanisms are often discussed in the literature, they are rarely directly tested, and no study has comprehensively evaluated pathways for the link between depression or emotional distress and glycemic control. Furthermore, well-designed intervention studies that have been successful in reducing depressive symptom severity and diabetes distress have had no impact on self-management, treatment adherence, and/or A1c, raising questions about the causal nature of these relationships (107,108,109; see the following section *Treatment and Intervention*). Moreover, evidence suggests that somatic symptoms that overlap with MDD symptom criteria may differ from cognitive-affective symptoms. Depression has been conceptualized along the lines of these distinct symptom profiles in cardiovascular disease research, where a cognitive-affective depression subtype is thought to be marked by psychosocial vulnerability (e.g., poor coping, neurotic personality, emotional reactivity) and a somatic-affective subtype is characterized by vascular disease—atherosclerosis, inflammation markers, sickness behavior, and dysregulation of HPA processes (15,110). Causal mechanisms linking these symptom presentations to poor diabetes outcomes may be distinct.

Correlational data linking depression and poor diabetes outcomes should be interpreted alongside a general lack of evidence for a link between depression and either undiagnosed diabetes or impaired glucose metabolism. It is currently unclear whether depression is significantly elevated in type 1 diabetes. Depression appears to mostly be associated with diagnosed type 2 diabetes and is more common among patients with complications and comorbidity. Type 2 diabetes seems to increase risk for depression only when it is diagnosed during middle adulthood, rather than in older age, when experience with chronic illness is more common and, perhaps, when management is less disruptive to important life roles. Depressive symptoms also significantly predict the diagnosis of type 2 diabetes, perhaps through overlap with somatic symptoms of illness, sedentary lifestyle, or through increased contact with health care providers. Depressive symptoms also overlap with emotional distress that is specific to facing the existential threat and coping with the challenges of managing

diabetes. Depression could plausibly affect outcomes of diabetes care, through poor self-management or biologic pathways, but evidence is not conclusive. Complications and worsening health associated with diabetes and comorbid illness could have a reverse causal role in increasing depression. Noncausal association is also possible through shared relationships with factors that may be more common in both depression and diabetes: disparities in health care access and quality, sedentary lifestyle, lower socioeconomic status, unemployment, multiple comorbidities, lower quality of life, and the experience of chronic stress (35,47). Such noncausal associations would nevertheless support the need for coordination of care, given the close links among emotional distress and illness and treatment characteristics and diabetes health outcomes.

TREATMENT AND INTERVENTION

Numerous treatment studies for depression in adults with diabetes have been conducted (111,112). These interventions have included psychological treatments, such as cognitive-behavioral therapy (CBT), pharmacological treatments, and combined approaches. Although overall these interventions have shown success in reducing the severity of depression, effects on glycemic control and treatment adherence have been less consistent. Two meta-analyses of this literature have concluded that psychotherapeutic, pharmacological, and combined approaches generally have consistently significant effects on depression amelioration in adults with diabetes (113,114). One early trial of CBT for depression reported a significant effect on glycemic control in adults with type 2 diabetes; but glucose self-monitoring significantly decreased in the intervention group (115). Subsequent studies' effects on glycemic control have been modest and highly variable, although antidepressant trials (n=5) of selective serotonin reuptake inhibitors have generally found significant improvements in glycemic control, with little heterogeneity in effect sizes (standardized mean difference -0.38, 95% CI -0.64 to -0.12) (114). However, three of these trials produced glycemic benefits without a significant impact on depression severity (116,117,118), one had a significant impact on depression without an impact on glycemic control (119), and only one had a significant impact on both (120), leaving in doubt the question of whether glycemic improvements were due to change in depression *per se*.

It is important to note the limitations of the trials included in these meta-analyses before drawing general conclusions. Of the 18 trials included in the most recent meta-analysis (114), 15 had 60 or fewer total participants; one trial with 120 participants included patients with depression and/or anxiety (121). Several trials in adults with type 2 diabetes with relatively larger sample sizes (n=329–417) have tested collaborative care interventions comprised of pharmacological and psychological treatment components; these have all failed to demonstrate a significant impact on glycemic control, despite significant improvement in depression (122,123,124). Other relatively larger trials testing a variety of behavioral or pharmacological interventions for depression in adults with diabetes have also failed to demonstrate impacts on glycemic control, despite showing significant improvements in depression symptom severity (125,126,127). Many of these trials used screening measures to identify cases for treatment. Evidence reviewed above suggests that most enrolled participants would be false positives for MDD.

Data from available depression treatment trials in diabetes suggest that the treatment of depression may be necessary, but not sufficient, to improve glycemic control or self-management in adults with diabetes (109,122,123,124). To impact depressive symptoms and medical outcomes, a more holistic, integrative approach may be needed (108,128,129). One intervention that successfully impacted depression severity, medication adherence, and glycemic control in a small trial of adults with type 2 diabetes and MDD achieved these effects via integration of CBT for depression with review of glucose meter downloads and electronically recorded medication adherence over time. Thus, it is difficult to ascribe glycemic benefits to depression treatment alone. In fact, depression reductions were lost at follow-up with continued maintenance of self-management and glycemic control benefits (130).

Diabetes distress was directly targeted in a trial of 392 adults with type 2 diabetes. Results suggested that diabetes distress decreased over time, with a general lack of differential effects for behavioral interventions of varying degrees of intensity. *Post hoc* analyses suggested that participants who at baseline were high in distress related to their treatment regimen, a specific aspect of diabetes distress, were more likely to benefit from intervention when assigned to receive a behavioral intervention focused on problem-solving skills. Diet, physical activity, medication adherence, and A1c were not differentially affected by intervention assignment (107). Another relatively strong trial randomized 214 mostly poorly controlled adults with type 2 diabetes with elevated depressive symptoms to an active control group receiving diabetes education or to a CBT intervention, which focused on amelioration of diabetes-related distress as a key topic. At 12-months post-intervention, those assigned to receive CBT had a significantly greater reduction of depressive symptoms and diabetes distress, as well as a 37% reduced incidence of likely major depressive episode. General wellbeing, diabetes self-care behaviors, acceptance of diabetes, and A1c did not differ between groups. Furthermore, no differences were found in indicators of subclinical inflammation (IL-1RA, high-sensitivity C-reactive protein, IL-6, or total adiponectin) (131). Like most well-designed depression treatment trials, these studies suggest that behavioral interventions can be helpful in ameliorating depressive symptoms and diabetes-related distress but do not indicate that these changes reliably translate into significant benefits for A1c or that they result in changes in purported mechanisms linking emotional distress to poor

health outcomes in diabetes (i.e., diabetes self-management or inflammation).

Few data are available on the best treatment options for youth with diabetes. Several reports suggest CBT can be beneficial (132,133); however, much work remains to be done in this area. The Treatment of Adolescent Depression Study was the largest trial to date of options for the treatment of MDD in adolescents (134). While none of the adolescents had diabetes, results suggested that treatment combining antidepressant medication (fluoxetine) with CBT is more effective than either in isolation or placebo for short-term treatment of MDD in adolescents.

ANXIETY DISORDERS, SYMPTOMS OF ANXIETY, FEAR OF HYPOGLYCEMIA, FEAR OF SELF-INJECTION

OVERVIEW AND DEFINITIONS

Various anxiety disorders are defined by the *DSM-5* (2). These generally involve excessive fear or worry and symptoms of recurring intrusive thoughts or concerns, excessive avoidance behavior aimed at overly feared situations, and physical symptoms of hyperarousal. The prevalence of any anxiety disorder may be as high as 18.1%, including approximately 40 million U.S. adults (135). Generalized anxiety disorder (GAD) involves intense and difficult-to-control worry about various issues in life and fears of unrealistic, worst-case scenarios. Symptoms of restlessness, fatigue, concentration difficulties, irritability, muscle tension, and sleep disturbance are also part of the diagnostic presentation. Twelve-month prevalence of GAD among adults is estimated at 3.1% (136). Panic Disorder affects approximately 2.7% of the U.S. population at least once within a 12-month period and is characterized by unexpected attacks of anxiety that peak in intensity relatively quickly and involve various symptoms of sympathetic nervous system arousal (137). Post-traumatic stress disorder (PTSD) can develop after exposure to a life-threatening or terrifying event involving potential for or actual occurrence of serious harm. Individuals with PTSD experience frightening thoughts and memories of the event, may experience sleep problems, feel detached, or be easily startled, sometimes experiencing chronic hyperarousal. Approximately 3.5% of U.S. adults experience PTSD over a 12-month period (138). About 8.7% of U.S. adults meet criteria for a specific phobia, a marked and persistent fear and avoidance of a specific object or situation, over a 12-month period (139).

Along with these psychiatric disorders, diabetes-specific constructs related to anxiety have been examined in the literature. Some children and adults with diabetes can experience intense fear and worry about hypoglycemia or insulin self-injections that could meet criteria for a phobia diagnosis. Many more patients will experience anxiety over these issues that falls short of a diagnosis but that may nevertheless interfere with self-management and cause distress.

PREVALENCE

Whereas there appears to be a higher prevalence of anxiety disorders in adults with diabetes than in the general population, prevalence estimates are not well established, and anxiety has received much less research attention than depression. The available estimates vary considerably, most probably due to differences in measurement methods and sampling. The BRFSS 2006 survey found the age-adjusted prevalence of lifetime diagnosis of an anxiety disorder was 19.5% in adults with self-reported, diagnosed diabetes and 10.9% in those without diabetes; people with diagnosed diabetes had a 20% higher lifetime odds than those without diabetes after adjusting for covariates (Table 33.13) (140). However, results from this survey should be considered with caution in light of the use of a single item to assess participant-reported lifetime diagnosis of an anxiety disorder by health care professionals. Diabetes was also assessed by participant report of a diagnosis by a clinical care provider.

Patients with diabetes were 50% more likely to have Panic Disorder and 30% more likely to have PTSD or social phobia than those without diabetes in the BRFSS 2006 (140). Fisher *et al*. found 85% higher rates of Panic Disorder and 123% higher rates of GAD, relative to national estimates, using structured clinical interviews (11). International data, based on structured clinical interviews to assess specific anxiety disorders and participant self-report to assess diagnosis of diabetes by a health care provider or diabetes treatment, suggest that the prevalence of GAD (OR 1.6, 95% CI 1.3–2.0), Panic Disorder (OR 1.5, 95% CI 1.1–1.9), social phobia (OR 1.3, 95% CI 1.0–1.6), and PTSD (OR 1.3, 95% CI 1.0–1.8) are all significantly increased among individuals diagnosed with diabetes (12).

PTSD symptoms have been associated with risk for developing type 2 diabetes, independent of depression, other mental illness, and demographic covariates (141). Adults with PTSD symptoms have been found to be more likely to have suboptimal glycemic control compared to those without PTSD symptoms (141,142). PTSD has been associated with increased risk of diabetes, negative health outcomes, higher reporting of somatic symptoms, and lower health-related quality of life (143,144). Furthermore, PTSD has been repeatedly shown to be a risk factor for the metabolic syndrome in vulnerable populations, including combat veterans and poor urban populations (145,146,147).

A meta-analysis of 12 mostly international studies (two were from the United States) of more than 12,600 adults reporting on the relationship between anxiety disorders or symptoms of anxiety and diabetes concluded that the odds of anxiety disorders were 1.20-fold (95% CI 1.10–1.31) greater and odds of elevated anxiety symptoms were 1.48-fold (95% CI 1.02–1.93) greater for adults with diabetes compared to those without diabetes (Figure 33.2) (148). However, the

TABLE 33.13. Prevalence of Lifetime Diagnosis of Anxiety Disorder, U.S., 2006

		PREVALENCE (%)*				PREVALENCE RATIO (DIABETES VS. NO DIABETES)			
		Diabetes		No Diabetes		Unadjusted		Adjusted†	
	N	%	SE	%	SE	PR	95% CI	PR	95% CI
Total	201,575	19.5	1.3	10.9	0.2	1.39	1.29–1.50	1.20	1.12–1.30
Sex									
Men	79,317	15.2	1.9	7.8	0.2	1.37	1.19–1.56	1.24	1.08–1.41
Women	122,258	24.6	1.7	14.0	0.2	1.44	1.32–1.58	1.19	1.08–1.30
Race/ethnicity‡									
Non-Hispanic white	157,091	20.0	1.6	12.0	0.2	1.28	1.17–1.39	1.10	1.01–1.20
Non-Hispanic black	16,371	11.9	1.5	8.1	0.4	1.64	1.33–2.04	1.36	1.11–1.67
Hispanic	15,544	20.4	3.4	9.5	0.5	1.95	1.50–2.53	1.69	1.33–2.15
Asian	3,500	1.1	0.7	3.2	0.6	0.30	0.11–0.81	0.31	0.11–0.85
American Indian/Alaska Native	2,940	40.2	6.7	18.3	1.8	1.6	1.1–2.4	1.2	0.8–1.7
Other	6,129	30.8	4.9	14.7	1.2	1.1	1.8–1.5	1.0	0.7–1.3
Age (years)§									
18–29	19,783	24.8	4.8	11.5	0.4	2.17	1.47–3.20	1.70	1.19–2.43
30–39	29,666	22.7	2.9	11.5	0.3	1.98	1.52–2.56	1.28	1.00–1.64
40–49	38,935	21.5	1.8	11.7	0.3	1.83	1.55–2.17	1.32	1.12–1.57
50–59	43,487	18.2	1.0	12.4	0.3	1.47	1.31–1.65	1.09	0.98–1.21
60–69	33,776	14.6	1.4	9.8	0.3	1.49	1.23–1.81	1.28	1.07–1.52
70–79	23,801	8.5	1.7	7.4	0.4	1.15	0.95–1.40	1.12	0.93–1.36
≥80	12,127	5.0	0.7	6.1	0.4	0.83	0.61–1.12	0.85	0.63–1.14
Lifetime diagnosis of depression‖									
Yes	36,632	54.5	2.4	45.8	0.6	1.09	1.02–1.16	1.02	0.95–1.09
No	164,414	5.6	0.9	4.6	0.1	1.10	0.91–1.33	1.09	0.91–1.32
PHQ-8 depression¶									
Major	7,935	56.7	3.5	45.9	1.3	1.10	0.97–1.25	0.96	0.85–1.08
Minor	8,958	31.9	4.3	21.6	1.0	1.11	0.90–1.36	1.02	0.85–1.24
No	169,585	14.0	1.4	8.7	0.1	1.26	1.12–1.40	1.23	1.10–1.37

CI, confidence interval; PR, prevalence ratio; SE, standard error.

* Prevalence rates of total and subgroups stratified by gender and race/ethnicity were age-standardized according to the U.S. population in the year 2000.

† Adjusted for gender, race/ethnicity, age, educational levels, marital status, employment status, current smoking, leisure-time physical activity, and body mass index.

‡ The "Other" race/ethnicity category includes native Hawaiians or Pacific Islanders, multiracial, and other unspecified race/ethnicity. p<0.01 for the interaction between diabetes and race/ethnicity on anxiety disorders

§ p=0.04 for the interaction between diabetes and age on anxiety disorders

‖ Lifetime diagnosis of depression was assessed by the question "Has a doctor or other healthcare provider EVER told you that you have a depressive disorder (including depression, major depression, dysthymia, or minor depression)?".

¶ PHQ, Patient Health Questionnaire: the PHQ-8 was used to establish a provisional diagnosis of major and minor depression according to *Diagnostic and Statistical Manual of Mental Disorders-IV* diagnostic criteria.

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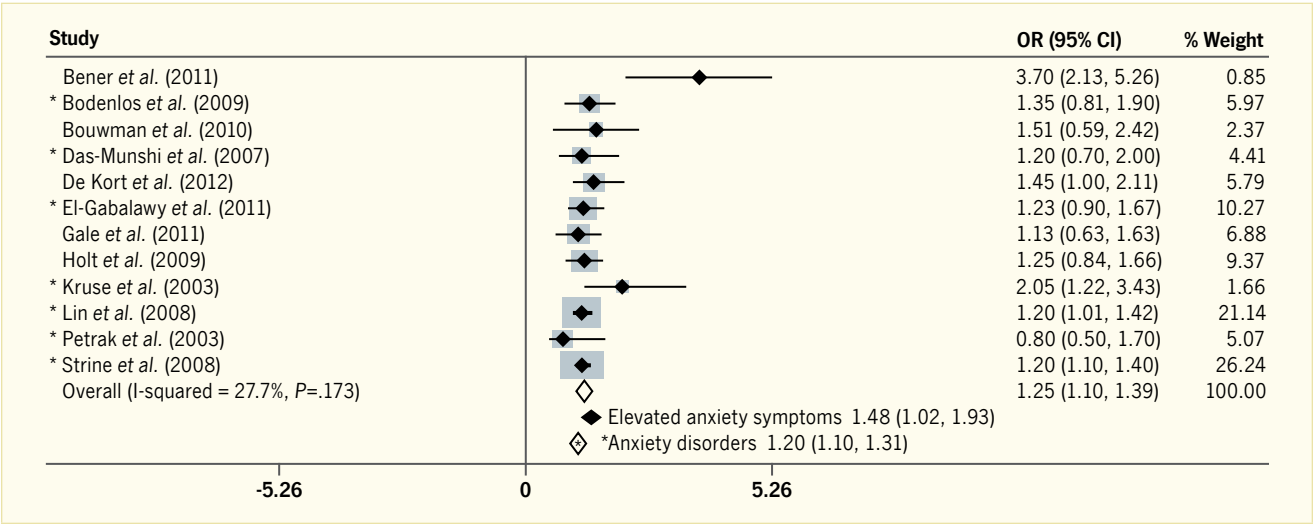
FIGURE 33.2. Meta-Analysis for Association of Diabetes With Anxiety Disorders and Elevated Anxiety Symptoms



Gray boxes indicate the weight of each study's contribution to the estimation of the overall effect. The pooled odds ratios for elevated anxiety symptoms and anxiety disorders are given individually at the bottom of the graph. CI, confidence interval; OR, odds ratio.

* Indicates studies where anxiety disorders were assessed. Unmarked studies evaluated elevated anxiety symptoms.

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review noted weaknesses of the literature, including varying and sometimes inadequate assessment methods for anxiety, failure to differentiate between type 1 and type 2 diabetes (most studies did not specify type), and inconsistent and often incomplete control for confounders (148). Thus, it appears likely that risk for anxiety is increased among adults living with diabetes, but better quality studies are needed to advance the understanding of this risk.

Data on the prevalence of anxiety disorders in youth with diabetes are not available. However, surveys that capture symptoms of GAD (e.g., State-Trait Anxiety Inventory for Children) suggest that 17% have clinically elevated levels of anxiety symptoms (149). More attention to anxiety in children and adolescents with diabetes is warranted.

Illness and Patient Factors Related to Prevalence

Relative to the data available for depression, far less attention has been paid to the identification of risk factors for anxiety in individuals with diabetes. Nevertheless, diabetes may provide an important context for the evaluation of symptoms of anxiety in patients. Specific presentations of anxiety and fear that do not meet criteria for a psychiatric diagnosis may have important relationships to diabetes care. For example, one study found that approximately 9% of insulin-treated diabetes patients report self-injecting-related anxiety symptoms (150). Another study of type 1 and 2 diabetes patients found that 28% reported elevated injection anxiety scores on a self-report questionnaire, with half avoiding injections as a result (151). While the exact prevalence is unknown, fear of hypoglycemia is another common concern in patients taking insulin (152,153,154). Patients may try to avoid hypoglycemia and may prefer to keep blood glucose at high levels to avoid the risk of low blood sugars (154). Fear of hypoglycemia is often preceded by hypoglycemic experiences (154,155,156) and can reach levels of intensity that have led some investigators to draw parallels to PTSD. One study found that 25% of its sample of type 1 diabetes patients met criteria for PTSD related to hypoglycemia because of avoidance and intrusive thoughts related to hypoglycemia (157). Patients may also present with subclinical symptoms of anxiety related to hypoglycemia that may not represent a clinical disorder but may still negatively impact diabetes self-management (157,158).

Epidemiologic data collected from adults suggest that diabetes is significantly more likely to be associated with lifetime diagnosis of an anxiety disorder in younger people (age 18–29 years) and in racial/ethnic minorities than their counterparts (Table 33.13) (140). Younger age was also found to be a significant risk factor for meeting diagnostic criteria for GAD, Panic Disorder, and comorbid MDD/GAD in adults with type 2 diabetes; female sex was associated with increased risk of Panic Disorder (11).

MEASUREMENT ISSUES

Similar to the issues discussed at length in the section on depression, the task of accurate assessment of problems with anxiety is complicated by the somatic burden of poorly controlled diabetes and overlap with emotional distress that is nonpathologic in the context of diabetes-related stressors (e.g., worry about complications, fear of hypoglycemia). On the other hand, problems with anxiety may be undertreated or misdiagnosed because they may resemble physiologic changes associated with hypoglycemic episodes, for example (152,159,160). Both patients and clinicians may have difficulty distinguishing between hypoglycemia and anxiety symptoms, such as dizziness, shakiness, lack of coordination, and heart palpitations. These issues have mostly not been addressed in the available literature on anxiety disorders and diabetes. In addition, anxiety disorders often co-occur with other psychiatric disorders—the comorbidity between anxiety and depression, for example, appears to be higher in people with diabetes than in the general population (11). Given their symptom overlap, it is perhaps not surprising that MDD and GAD co-occur more often than they occur in isolation.

ASSOCIATION WITH DIABETES TREATMENT OUTCOMES

Findings on the relationship between anxiety and diabetes have been mixed: among adults with type 2 diabetes, anxiety has been associated with the somatic burden of diabetes (e.g., fatigue, appetite, autonomic arousal) and lifetime hypoglycemia, but inconsistently with A1c, among individuals with and without diagnosed diabetes (161,162,163). Symptoms of anxiety appear to be associated with problems with disease management, worse clinical outcomes, and decreased functioning and quality of life. Meta-analysis of 11 studies found that overall the relationship between anxiety and hyperglycemia was not significant ($p=0.19$); but for the few studies ($k=3$) that used diagnostic interviews to assess anxiety, the effect ($r=0.25$, 95% CI 0.10–0.38, $p=0.003$) was significant (164). Other evidence showed that insulin-treated adult diabetes patients with severe fear of self-injecting or self-testing had higher levels of diabetes-related distress, poorer general wellbeing, and poorer treatment adherence than those who did not have such fears (150). In a sample of over 4,000 patients with diabetes, panic episodes were associated with worse diabetes control, diabetes complications and symptoms, greater disability, and lower self-rated health and functioning, even after controlling for the effects of comorbid depression (165). Adults with type 2 diabetes and GAD are more likely to have complications of diabetes; those with comorbid illness are at increased risk of meeting criteria for GAD, Panic Disorder, and comorbid MDD/GAD (11).

CAUSAL ISSUES AND EXPLANATORY MECHANISMS

The development of anxiety symptoms in patients with diabetes may arise from a number of underlying causes. Although research on the biobehavioral

mechanisms between anxiety and diabetes is generally lacking, plausible mechanisms linking anxiety and diabetes include reactions to the stress associated with the self-management of diabetes and underlying biologic changes that may be associated with both anxiety and glycemic control. Models that have been proposed to account for neuroendocrine pathways between depression and diabetes also have relevance for anxiety (92). Comorbid anxiety may play an important role in the HPA axis dysregulation seen in patients with depression (166). Elevated cortisol inhibits insulin function (167), and cortisol levels appear to be dysregulated in patients with anxiety disorders (168).

Diabetes patients may experience short-term, episodic stress related to self-care activities or more long-term, chronic stress related to living with a chronic illness, which may eventually develop into anxiety symptoms or a chronic anxiety disorder (169). The stress of dealing with diabetes may impact patients' psychosocial functioning and quality of life, which may also increase the risk for developing anxiety symptoms (170). Certain aspects of the diabetes self-care regimen, such as frequent self-testing of blood glucose and insulin injections, may lead to the development or exacerbation of anxiety symptoms, such as phobias, intrusive worry, and avoidance (153,155,156,171). Patients who experience diabetes-related distress may experience anxiety and avoidance related to their self-care, which may cause them to be less adherent to their treatment regimen, which may in turn affect their blood glucose control or cause complications—thus, leading to even greater levels of anxiety. Finally, psychiatric illness, such as anxiety disorders, often co-occurs with tobacco and other substance use, highlighting a potential pathway between anxiety and worse diabetes outcomes (172). There is little evidence for the mechanisms underlying the associations between anxiety and diabetes, and questions remain as to the directionality and causal nature of these relationships.

TREATMENT AND INTERVENTION

Psycho-educational interventions, including group-based interventions, have been found to be helpful in reducing stress, anxiety, and negative emotions, improving coping, and improving diabetes control (173,174,175,176). A review of 10 studies evaluating the efficacy of stress management interventions in adults with type 2 diabetes (176) noted several promising avenues of clinical intervention. Patients who completed a program consisting of five group-based sessions involving training in progressive muscle relaxation, guided imagery, and instruction in behavioral and cognitive skills to recognize and reduce stress showed improvement in glycemic control over 12 months relative to control patients. Surprisingly, no differences in stress or anxiety were observed (177). Individually delivered, biofeedback-assisted relaxation training was found to reduce symptoms of anxiety and depression, decrease muscle tension, and improve diabetes control in a small trial of 30 patients with type 2 diabetes (178). A group-based, six-session program that included relaxation training, cognitive restructuring, and training in problem-solving skills was associated with improvements in anxiety symptoms and stress and demonstrated some evidence of a small effect on glycemic control in a small sample of 19 adults with type 2 diabetes (179). Relative to research on depression treatment in diabetes, the treatment of anxiety has received inadequate attention.

EATING DISORDERS, UNHEALTHY EATING BEHAVIOR AND ATTITUDES, INSULIN OMISSION FOR WEIGHT LOSS

OVERVIEW AND DEFINITIONS

Eating disorders are characterized by extreme reductions of food intake, overeating, and/or feelings of significant distress or concern about body weight or shape. Anorexia nervosa is characterized by an obsessive pursuit of thinness, a distortion of body image, and intense fear of gaining weight. Restriction of food intake to achieve weight loss can lead to emaciation. Though often severe, prevalence rates of anorexia are relatively low—approximately 0.6% of the U.S. adult population report a lifetime prevalence (180). Bulimia nervosa is marked by recurrent episodes of eating unusually large quantities of food with a perceived lack of control over eating during these bingeing episodes. Compensation includes purging (e.g., vomiting), excessive exercise, and/or fasting. Intense dissatisfaction and distress about body size and shape accompany these behaviors. Lifetime prevalence of bulimia is also 0.6% among U.S. adults (181). Binge eating disorder (BED) is characterized by bingeing episodes that are not followed by purging, excessive exercise, or fasting. Guilt, shame, and/or distress accompany binge eating, and most individuals experience overweight or obesity as a result of excessive caloric intake. Lifetime prevalence of BED is estimated at 2.8% of the U.S. adult population, with 1.2% meeting criteria within the prior 12 months (182). All of these eating disorders are far more prevalent among women than among men. Subclinical presentations including some of these disordered eating behaviors or attitudes are more common and can complicate diabetes management.

PREVALENCE

Disordered eating appears to be more prevalent in individuals with diabetes than those without, with the majority of the literature focused on the comorbidity in adolescent female populations with type 1 diabetes (183). One of the largest case-control studies of adolescent females age 12–19 years showed that the presence of any eating disorder was 2.4 times more common among those with type 1 diabetes compared to nondiabetic controls (Table 33.14) (184).

A systematic review of controlled studies of females with diabetes compared to nondiabetic controls

TABLE 33.14. Frequency of Diagnosed and Subthreshold Eating Disorders Among Adolescent Females Age 12–19 Years With Type 1 Diabetes and Matched Controls

EATING DISORDER	NUMBER (%)		ODDS RATIO (95% CI)	P VALUE*
	Type 1 Diabetes (n=356)	Controls (n=1,098)		
DSM-IV disorder	36 (10)	49 (4)	2.4 (1.5–3.7)	<0.00
Anorexia nervosa	0	0		
Bulimia nervosa	5 (1)	5 (0.5)	3.1 (0.9–10.8)	0.07
Not otherwise specified	31 (9)	44 (4)	2.3 (1.4–3.7)	<0.001
Subthreshold disorders	49 (14)	84 (8)	1.9 (1.3–2.8)	<0.001

CI, confidence interval; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition.*
* For χ^2 tests

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found that the prevalence of anorexia nervosa was not significantly increased, but prevalence of bulimia nervosa was significantly greater among those with diabetes (1.73%) than among controls (0.06%) (185). The presence of anorexia nervosa or bulimia in adults with type 2 diabetes appears to be minimal and not significantly different from those without diabetes (186,187).

Among people with type 2 diabetes, estimates of the prevalence of BED vary considerably, ranging from 1.4% to 25.6% (183,186,187,188,189,190,191). One study of 3,000 primary care patients found that individuals with diabetes were 2.4 times more likely to have BED than those without diabetes (192). Due to the small sample sizes of most studies and the variability of methods used to assess binge eating, questions remain about the heterogeneity and generalizability of these estimates.

Night-Eating Syndrome, characterized by greater than 25% of caloric intake occurring after the evening meal and/or waking up at least three times per week to eat at night (193), had a 9.7% prevalence among a sample of adults with diabetes (194) compared to an estimated prevalence of approximately 1.5% in community samples (195) and 9%–14% in obesity treatment clinic samples (196,197).

Omitting or reducing insulin to induce glycosuria and weight loss is a form of calorie purging and has significant health consequences in diabetes. Whereas relatively little attention has been paid to reasons for intentional insulin nonadherence, concerns about weight gain represent one possible contributor (198). Insulin omission appears to be more common among patients with type 1 diabetes and eating disorders than those without eating disorders (199,200).

Maladaptive eating behaviors, such as occasional binge eating, extreme dietary restraint, or excessive exercise, appear to be more common in preteen and early teenage girls with type 1 diabetes (201,202). These subclinical presentations are 1.9 times more likely in this group (95% CI 1.3–2.8) (Table 33.14) (184) and are associated with poorer glycemic control in some, but not all, studies (189,201,203). Other studies suggest higher risk of retinopathy and nephropathy (204,205) compared to individuals with diabetes who do not exhibit these eating behaviors. In addition, maladaptive eating attitudes, such as excessive concern with eating, weight, and body shape, have been shown to significantly correlate with poorer glycemic control (189). These studies suggest that diabetes control can be affected by poor body image issues and eating behaviors, even in patients without a diagnosable eating disorder.

MEASUREMENT ISSUES

Diabetes management often includes focus on the quality and quantity of food eaten. This may complicate the evaluation of abnormal eating behaviors and attitudes used to diagnose eating disorders and may contribute to the development of eating disorders in at-risk individuals (206,207). Weight gain associated with insulin administration can also contribute to concerns regarding weight and body image; women with type 1 diabetes enrolled in the Diabetes Control and Complications Trial expressed concern about insulin-associated weight gain (208). Longitudinal research with a small sample of adolescents with type 1 diabetes suggests concern over weight and body shape and dietary restraint increase from adolescence to young adulthood, especially among females; insulin underuse was more likely among females than males (209). Possible diabetes-related signs of an underlying eating disorder include unexplained episodes of DKA, frequent episodes of hypoglycemia, or easy control in inpatient settings of glucose levels that were previously difficult to manage out of the hospital (210,211).

ASSOCIATION WITH DIABETES TREATMENT OUTCOMES

Negative health outcomes are associated with eating and weight-related disorders in patients with diabetes. Patients who restrict their insulin have poorer metabolic control (212,213) and higher rates of nephropathy (200,214,215), retinopathy (200,207,214,215), other microvascular complications, and DKA (184,200,203). Moreover, insulin omission was shown to increase the relative risk of mortality by more than three times in a study of adult women with type 1 diabetes (216). The same investigators later showed that fear of weight gain was a significant contributor to new cases of insulin restriction in this cohort (217).

The relationship between BED and worse diabetes outcomes is less clear. A report of youth with type 2 diabetes found that those with both clinical and subclinical

levels of binge eating, as assessed by self-report, had significantly higher rates of extreme obesity, abdominal obesity, depressive symptoms, and impaired quality of life (218). Further research may be needed, given the few studies examining BED in diabetes. Morse *et al*. (194) found that patients with either type 1 or type 2 diabetes and Night-Eating Syndrome were more likely to be less adherent with diet, exercise, and glucose monitoring. They were also more likely to be obese, to have worse diabetes control, and to have more diabetes complications.

CAUSAL ISSUES AND EXPLANATORY MECHANISMS

There are various plausible explanations for the relationship between eating disorders and diabetes. Several studies have shown that family dysfunction predicts the development of maladaptive eating behaviors in females with and without type 1 diabetes (219,220). Daneman *et al*. (207) found that eating disturbances were associated with self-reported family functioning, and more severe eating problems were linked to greater levels of family dysfunction in girls with type 1 diabetes. Other research has found this relationship to be moderated by body image dissatisfaction. Those with eating disturbances reported significantly more negative comments from peers and family about their diet and parents that were not responsive to their needs, leading to greater feelings of anger and hopelessness toward their parents. Family environment and maternal weight and shape concerns were also related with eating disturbances in young women with type 1 diabetes (221).

Daneman *et al*. postulated that individual, family, and societal factors interact with diabetes-specific vulnerabilities and lead to core features of eating disorders, such as body dissatisfaction, drive for thinness, and dietary restraint. These features then lead to disordered eating behaviors, resulting in negative diabetes health outcomes (207). The extent to which these etiologic factors may be relevant for adults with type 2 diabetes is not clear.

TREATMENT AND INTERVENTION

To date, no rigorous treatment studies have been conducted to evaluate treatment of eating disorders in type 1 diabetes. Although many studies have investigated the efficacy of weight loss programs in people with type 2 diabetes, few interventions for treating eating disorders or maladaptive eating behaviors and attitudes that would fall short of a psychiatric diagnosis in people with diabetes have been investigated. Additionally, of the limited published psychotherapy intervention studies addressing disordered eating in patients with diabetes, most lack methodologic rigor (206,222). One trial investigated the efficacy of CBT compared to nonprescriptive therapy, a supportive approach with no specific theoretical or empirical support in eating disorders (meant to control for nonspecific factors of therapy), for binge eating in 24 women with diabetes. CBT and the supportive approach were similarly effective, though CBT appeared to provide more sustained change, as there were significantly fewer relapses in the CBT-treated group. Across treatments, decreases in bingeing were associated with improved diabetes control (223). Although this investigation shows preliminary support for the successful treatment of BED in diabetes, further research is needed.

OTHER IMPORTANT MENTAL HEALTH ISSUES

SERIOUS MENTAL ILLNESS

Schizophrenia, a chronic and severe disorder characterized by deficits in thought processes, perceptions, and emotional responsiveness, affects approximately 1.1% of U.S. adults over a 12-month period (224). Bipolar Disorder, an often-disabling mood disorder marked by dramatic shifts in mood, activity, and energy, has a 12-month prevalence of 2.6% (225).

Prevalence of Diabetes in Individuals With Serious Mental Illness

Estimates from a range of national and international epidemiologic studies have shown the prevalence of diabetes in patients with Schizophrenia to be 1.5–2.5 times greater than that found in the general population, with the difference particularly striking among younger patients (226,227,228,229). The true prevalence of diabetes among individuals with serious mental illness may be grossly underestimated due to the silent nature of diabetes and the myriad of other, more immediately pressing medical, economic, and social problems faced by people with psychotic disorders (227,230,231,232). Studies have also shown that the prevalence of type 2 diabetes is increased among patients with Bipolar Disorder (233,234,235). An examination of a sample of more than 4,000 Veterans Health Administration patients with Bipolar Disorder found the prevalence of diabetes to be >17% (234). Patients with Bipolar Disorder and diabetes are older, more chronically ill, present with rapid shifts in mood, and have an overall lower level of global functioning than patients with Bipolar Disorder and no diabetes; they also had higher rates of long-term disability and were more likely to have higher BMIs (236).

Measurement, Treatment, and Causal Mechanisms

Up to 60%–70% of cases of type 2 diabetes in individuals with serious and persistent mental illness go undiagnosed (237). Thus, screening for diabetes and diabetes risk factors is important in these patients, even when diabetes is not identified as part of the medical history. Attention to diabetes risk factors is particularly important in patients treated with atypical antipsychotic medications (238,239,240). As lithium treatment poses risk for reduction in thyroid function and weight gain, these patients should also be evaluated for type 2 diabetes risk (241).

Piette *et al*. (242) assessed treatment adherence in individuals with comorbid Schizophrenia, diabetes, and hypertension and found that adherence was better for oral medications for diabetes and hypertension than for antipsychotic medications. Individuals with Schizophrenia often have difficulties with treatment adherence for Schizophrenia (227,231,242); thus, treatment adherence to psychotropic medications should be carefully assessed, as control of the psychotic disorder will likely be a necessary condition for addressing diabetes risk.

Antipsychotic medications, particularly newer atypical antipsychotics, have been associated with metabolic disturbance and higher risk of diabetes (230,232). This is particularly important given the dramatic increase in the prescription of atypical antipsychotics, including among individuals without Schizophrenia. A comparison of Medical Expenditure Survey data from 1996–1997 and 2005–2006 found a 17% increase in the prescription of antipsychotic medications for affective disorders (243). Some atypical antipsychotics, as well as conventional antipsychotics, have been associated with higher rates of diabetes and metabolic dysregulation both independently and through certain medication side effects, such as weight gain, insulin resistance, decreased physical activity, and the metabolic syndrome (227,232,244,245, 246,247,248,249,250,251). However, the association between Schizophrenia and diabetes appears to extend beyond medication regimen, which could be explained by physiological abnormalities co-occurring with Schizophrenia, socioeconomic and other environmental correlates of Schizophrenia, or a combination of these factors (250,252). Still, there is reason for concern about diabetes risk resulting from antipsychotic medications, particularly when other treatment options exist. A retrospective cohort study compared children and young adults who had initiated antipsychotic drugs to matched controls who had initiated other types of non-antipsychotic, psychotropic drugs. Those with diabetes at baseline were excluded, as were those with a diagnosis of Schizophrenia or other conditions for which antipsychotics are the only generally recognized therapy. Use of antipsychotics was associated with a threefold increased risk for type 2 diabetes over the follow-up period (HR 3.03, 95% CI 1.73–5.32), with strong evidence of increased risk with increased cumulative dose exposure. No increased risk of type 1 diabetes was found in antipsychotic medication users (HR 1.13, 95% CI 0.43–3.00) (253).

Mood stabilizers, such as lithium and anticonvulsants, are often the first line of pharmacological treatment for Bipolar Disorder, and treated individuals frequently experience weight gain (254). Numerous studies have found associations between lithium treatment and weight gain, but how lithium precipitates weight gain remains unclear (255). Valproic acid (Depakote) can increase levels of testosterone in women and increase the likelihood of developing polycystic ovary syndrome, which can result in obesity, as well as endocrine disruption (256).

Poor diet, physical inactivity, smoking, and poor treatment adherence—independent risk factors for type 2 diabetes and its complications—are also more common among individuals with Schizophrenia (228,242,244,247,257,258,259,260,261, 262,263). Individuals with Schizophrenia may have impaired glucose metabolism even before they develop Schizophrenia, and historical surveys of the comorbidity literature show an association between Schizophrenia and diabetes before the use of neuroleptics and antipsychotics became common treatments for Schizophrenia (226,247,250,264). Individuals with Schizophrenia have more than three times the intra-abdominal fat as matched healthy controls and are also at higher risk for developing features of the metabolic syndrome—both risk factors for insulin resistance and diabetes (265).

The 2009 Schizophrenia Patient Outcomes Research Team (PORT) recommendations for weight loss interventions for individuals with Schizophrenia include comprehensive weight loss efforts persisting for at least 3 months, and the recommendations caution that weight loss is likely to be modest (266). McKibbin *et al*. conducted a randomized controlled trial to examine the feasibility and efficacy of their Diabetes Awareness and Rehabilitation Training (DART) group lifestyle intervention for adults age >40 years with comorbid Schizophrenia and diabetes (267). The DART intervention is a 24-week manualized intervention based on social learning theory that addresses comprehensive diabetes self-care and utilizes behavioral techniques to assess and reinforce achievable lifestyle goals. Patients in the DART group lost an average of 5 pounds, whereas those in the control group gained a mean of 6 pounds; significant effects were also found for reductions in triglycerides, improvements in diabetes knowledge, diabetes self-efficacy, and self-reported physical activity, but not for FPG or A1c (267). Research on individuals with Bipolar Disorder has found similar results: attendance at programs that involve social support, regular weigh-ins, as well as educational components, can lead to weight loss and the prevention of weight gain (237,268). Metformin has also been used to facilitate weight loss among individuals on antipsychotic treatment and improve weight loss outcomes on its own, as well as for individuals engaged in healthy lifestyle interventions. Focusing on treatment adherence to metformin in these patients could result in multiple health benefits (268,269).

Regarding smoking cessation, the most recent PORT guidelines recommend bupropion therapy for 10–12 weeks (266) as a first-line treatment. As bupropion may also result in weight loss, decrease depression, and improve glucose control in type 2 diabetes, multiple benefits may be derived from this treatment for patients (270).

SUBSTANCE-RELATED DISORDERS AND SUBSTANCE USE

Substance use disorders are quite prevalent in the U.S. population—more than 22 million people (8.9% of the population) age ≥12 years met diagnostic criteria for substance dependence or abuse in 2008 (271). Whereas substance abuse or alcohol abuse are not more common in individuals living with diabetes than in the general population, substance and/or alcohol use disorders complicate diabetes care, increase the risk of complications, and increase health care costs (272). Substance use disorders are commonly comorbid with other psychological problems and may accompany many of the clinical presentations reviewed above. Among a population drawn from the Veterans Health Administration, disparities in diabetes care were found to be more pronounced when patients had a substance use disorder, increasing in a dose-response effect with additional comorbid mental health diagnoses (273).

Cigarette smoking is the leading cause of preventable death in the United States, and in 2008, 20.6% of adults were current smokers (274). Individuals with depression (Table 33.6) (13) and other mood disorders smoke at higher rates than the general population (172,232,275,276), and smoking is associated with insulin resistance, reduced insulin secretion responses, increased central adiposity, and the development of type 2 diabetes (81,277), as also described in Chapter 13 *Risk Factors for Type 2 Diabetes*. Weight gain often occurs during and after smoking cessation attempts. Smokers, especially frequent smokers, tend to have heavier weight than light smokers or nonsmokers and tend to have greater central adiposity than nonsmokers (81,278,279). Smoking has been associated with increased risk of insulin resistance (279). More frequent smoking has also been associated with increased risk for developing type 2 diabetes, lower consumption of fruit and vegetables, greater physical inactivity, and heavier alcohol consumption, as well as more frequent relapses from attempts to quit smoking (279).

THE SOCIO-CULTURAL CONTEXT FOR PSYCHOSOCIAL ISSUES IN DIABETES

Although a comprehensive review is beyond the scope of this chapter, it is important to acknowledge the role of social factors, structural barriers, and lack of access to adequate care that may increase risk for significant psychiatric and psychosocial issues. Those at lower levels of socioeconomic status are consistently found to be more likely to suffer from psychiatric disorders and significant emotional distress than those at higher levels of socioeconomic status (280,281,282). Evidence clearly shows that socially disadvantaged individuals are at increased risk for the development of type 2 diabetes, as described in Chapter 13; those with diabetes often have poorer control and are at increased risk for complications (283,284). Costs are a common patient-reported barrier to self-management (285) and have been associated with reduced treatment adherence (286) and preventive care (287). Socioeconomically disadvantaged individuals may not have access to technological developments meant to improve diabetes care. For example, socially disadvantaged children with type 1 diabetes are far less likely to be on insulin pump therapy than individuals at higher socioeconomic status levels (288). Thus, social determinants of health outside the scope of medical practice have robust effects on diabetes treatment outcomes and may contribute to an increased psychosocial burden of diabetes among socially disadvantaged individuals.

Ethnic minorities achieve relatively poor diabetes treatment outcomes; they also experience more emotional distress and report lower quality of life than whites (284). Ethnic minorities with type 2 diabetes may be more likely to worry about drug side-effects and medication dependency; they may also be more reluctant to accept treatment intensification when clinically indicated (289). A survey of 14,357 adults with diabetes found that 16% of low-income adults experienced severe hypoglycemia in the prior year compared with 8.8% of high-income adults. Similar differences were found between those with low (11.9%) and high (8.9%) levels of education (290). These disparities may contribute to increased risk of psychosocial distress and psychiatric disorder in individuals treated for diabetes. Because it is difficult to control for these often crudely measured social factors in epidemiologic studies, these factors may underlie at least a portion of the relationships among psychiatric disorders, psychosocial distress, and poor outcomes in diabetes care.

GENERAL CONCLUSIONS AND IMPLICATIONS FOR PUBLIC HEALTH

The data reviewed in this chapter suggest that psychiatric disorders have close relations to diabetes and its management. Emotional distress and psychosocial issues that do not rise to levels of severity or functional impairment to warrant a psychiatric diagnosis are even more common among individuals living with diabetes. That these issues are at least as closely related to negative health outcomes suggests that research focused on psychiatric issues will provide only a partial understanding of explanatory mechanisms. The implications of this distinction between subthreshold presentations of emotional distress and psychiatric disorders have received the most attention in depression research, but they are relevant to other issues reviewed here, as well. Overall, evidence suggests little difference between subthreshold and diagnosable presentations of depression in relation to health outcomes, such as mortality (291). Although major diagnostic

systems for depression use a categorical approach, a dimensional approach has been proposed, with increasing severity ranging across a continuum from nonspecific depressive symptoms—which are nonpathological, often specific to a situational context, and transient—to subthreshold depression and major depression (291,292,293). Defining these boundaries has been difficult. Thus, many of the measurement issues noted in this chapter relate to fundamental challenges in the conceptualization and measurement of psychiatric disorders for which no biologic tests are available, questions of etiology remain unanswered, and for which diagnosis relies on expert opinion.

Despite these measurement challenges, evidence reviewed suggests a consistent association among depression, incident type 2 diabetes, and poor health outcomes in those diagnosed with diabetes. The presence of elevated symptoms of depression and/or emotional distress is consistently associated with risk for the development of type 2 diabetes and for poor health outcomes, including complications and all-cause mortality, in both type 1 and type 2 diabetes. Thus, elevated depressive symptoms and/or emotional distress are appropriately viewed as risk markers in diabetes and should be a focus of continued investigation.

To advance this area of research, better measurement practices that distinguish between presence of disorder and other presentations of emotional distress are necessary. Investigators should appreciate that categorical approaches using screening cutoffs on self-report questionnaires will result in imprecision and reduced power for statistical analyses; continuous approaches to symptom severity are likely to be more appropriate for hypothesis testing of relations between depression and diabetes outcomes (294). Further work to distinguish among various symptom presentations of depression (e.g., somatic vs. cognitive-affective) may prove fruitful in understanding these relationships. Greater sensitivity to the context of diabetes as a chronic stressor that may contribute to depression and emotional distress, as well as to problems of measurement overlap between symptoms of depression and diabetes and related illnesses, could clarify inconsistencies in the literature (5,6). In order to avoid false positives in clinical practice and misclassification of research participants, structured clinical interviews should be used more frequently to definitively establish the presence of a psychiatric disorder.

Although less developed, the literature on other psychiatric comorbidities and related psychosocial issues is largely consistent with the literature on depression. Anxiety disorders appear to be more prevalent among those with diabetes than those who do not have diabetes. Symptoms of anxiety also appear to be associated with worse diabetes treatment outcomes, raising the same subthreshold issue as discussed above. Fear of self-injection and hypoglycemia share symptoms with anxiety disorders but are generally not indicative of psychiatric illness; they may nevertheless complicate treatment. Eating disorders and, more commonly, unhealthy behavioral patterns and attitudes about eating and body shape are likely more prevalent among individuals living with diabetes. Aspects of diabetes management—focus on dietary intake and weight, as well as treatment-related weight gain—may contribute to unhealthy eating behavior and attitudes, perhaps particularly among adolescent girls with type 1 diabetes. Finally, serious psychiatric conditions, including Bipolar Disorders and Schizophrenia, are likely related to diabetes through common biologic and social risk factors. However, psychotropic medications for these psychiatric conditions may also directly increase risk for type 2 diabetes. As significant depression is inherent to some of these disorders (e.g., Bipolar Disorders and Schizophrenia) and often present as comorbid MDD with others (e.g., anxiety and eating disorders, substance abuse), research will need to be sensitive to overlap among these conditions in order to gain better clarity about the nature of these relationships.

Despite the limitations of most correlational research reviewed here in addressing questions of directionality and causality, evidence from the small number of available treatment trials of pharmacological and psychotherapeutic interventions does shed some light on these questions. These trials, mostly limited to the treatment of depression in adults with type 2 diabetes, generally show that psychopharmacological and psychotherapeutic treatments can be effectively applied in individuals with diabetes, with consistent evidence of improvement in symptom severity, although better evidence is needed for children and adolescents. Though findings are sometimes characterized as being supportive of effects on glycemic control, it is difficult to ascribe these benefits, which are inconsistently observed in often low-quality trials, to depression amelioration *per se*. Depression could plausibly have a causal impact on diabetes self-management or other biologic pathways that could explain links with negative health outcomes, but available trials have generally failed to demonstrate these effects, despite impacts on depression-related outcomes. Methodologic limitations of existing studies may mask these effects, but it is possible that depression, as well as other psychiatric and psychosocial issues discussed in this chapter, is not a major cause of diabetes self-management and treatment outcomes. Alternatively, depression and emotional distress may often represent consequences of multiple chronic stressors related to diabetes risk and treatment: the diagnosis and lifelong management of diabetes, threat or experience of diabetes complications, experience of treatment side-effects, comorbid illness, functional impairment, and other socioeconomic and environmental stressors. Future work should go beyond dichotomous models that compare the presence versus the absence of diabetes and examine the cumulative effects of illness and treatment burdens on risk of psychiatric disorders and emotional distress over time.

Improving the recognition and treatment of psychiatric conditions and better managing emotional distress among individuals living with diabetes would have a significant impact on public health, independent of any resulting benefits for diabetes-related outcomes. Scientific interest in explanatory pathways for links with diabetes should not overshadow the direct impact of these problems on patient functioning and quality of life. Research reviewed here is sufficiently suggestive to support continued study, with stronger designs, of pathways linking these problems to diabetes risk and diabetes treatment outcomes. Such studies may elucidate explanatory pathways and inform improvements in the management of diabetes and related psychiatric and psychosocial issues. These pathways are likely to be complex and bidirectional, requiring more comprehensive evaluation than has been common in the existing literature.

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
BED . . . . . .binge eating disorder
BMI . . . . . .body mass index
BRFSS . . . . . .Behavioral Risk Factor Surveillance System
CBT . . . . . .cognitive-behavioral therapy
CI . . . . . .confidence interval
DART . . . . . .Diabetes Awareness and Rehabilitation Training
DKA . . . . . .diabetic ketoacidosis
DSM-5 . . . . . .*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
FPG . . . . . .fasting plasma glucose
GAD . . . . . .generalized anxiety disorder
HPA . . . . . .hypothalamic-pituitary-adrenal
HR . . . . . .hazard ratio
IL . . . . . .interleukin
MDD . . . . . .major depressive disorder
NHANES . . . . .National Health and Nutrition Examination Survey
NHIS . . . . . .National Health Interview Survey
OR . . . . . .odds ratio
PORT . . . . . .Schizophrenia Patient Outcomes Research Team
PTSD . . . . . .Post-Traumatic Stress Disorder

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

DUALITY OF INTEREST

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