



# NIDDK International Conference Report on Diabetes and Depression: Current Understanding and Future Directions

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**Comorbid diabetes and depression are a major clinical challenge as the outcomes of each condition are worsened by the other. This article is based on the presentations and discussions during an international meeting on diabetes and depression convened by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with the National Institute of Mental Health and the Dialogue on Diabetes and Depression. While the psychological burden of diabetes may contribute to depression in some cases, this explanation does not sufficiently explain the relationship between these two conditions. Shared biological and behavioral mechanisms, such as hypothalamic-pituitary-adrenal axis activation, inflammation, autonomic dysfunction, sleep disturbance, inactive lifestyle, poor dietary habits, and environmental and cultural risk factors, are important to consider in understanding the link between depression and diabetes. Both individual psychological and pharmacological depression treatments are effective in people with diabetes, but the current range of treatment options is limited and has shown mixed effects on glycemic outcomes. More research is needed to understand what factors contribute to individual differences in vulnerability, treatment response, and resilience to depression and metabolic disorders across the life course and how best to provide care for people with comorbid diabetes and depression in different health care settings. Training programs are needed to create a cross-disciplinary workforce that can work in different models of care for comorbid conditions.**

Comorbid diabetes and depression represent a major clinical challenge as the outcomes of each condition are worsened by the presence of the other (1). In October 2012, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in collaboration with the National Institute of Mental Health and the Dialogue on Diabetes and Depression (2), convened a meeting of experts from 15 countries for two primary purposes. First, there was an opportunity to present and summarize the current state of the science on the association between depression and diabetes in the areas of basic, clinical, behavioral, and public health research. The second aim was to identify and highlight gaps in current scientific knowledge to inform the direction of future research and training (3).

This article is not a review article but rather summarizes the evidence-based presentations and discussions during the meeting and synthesizes the scientific content and future research recommendations. Although no conference could include

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everyone who conducts research relevant to diabetes and depression at the global level, this conference was unique in its design in presenting research on findings related to diabetes and depression spanning bench science to population science. This article describes the major themes drawn from the diversity of these presentations and perspectives. The structure of the article follows the format of the conference presentations, which were divided into three main areas: 1) the mechanisms and pathogenesis underlying the depression–diabetes association, 2) treatment of diabetes and depression, and 3) prevention and public health consideration of the two disorders. At the end of each section, we have described the critical gaps and key opportunities to improve our understanding of the prevalence, impact, mechanism, treatment, and public health considerations of the depression–diabetes association. Greater detail of these research recommendations can be found in Tables 1–3.

The authors were elected by the larger conference planning committee immediately following the conference to report on the presentations and recommendations of the speakers. All speakers were given the opportunity to review and comment on the report before approving its final content.

### METHODOLOGICAL CONSIDERATIONS IN DEFINING DEPRESSION

Investigations of the psychosocial correlates and diabetes and depression treatment trials form the foundation of our existing knowledge base for the prevalence and impact of these comorbid conditions. Although the core symptoms of depression are essentially the same across cultures, the presentation may vary because of patients' and their immediate reference group's perception of whether they are depressed; this perception will affect help-seeking behavior and the attribution of causation and issues such as stigma may differ across cultures (4).

Furthermore, the term "depression" covers a range of problems that span minor, occasional negative mood states to incapacitating and treatment-resistant disorders. The definition of "depression" varies markedly across studies ranging from high levels of self-reported depressive symptoms to diabetes-related distress to formal psychiatric diagnoses,

such as major depressive disorder, dysthymia, or adjustment disorder with depressed mood. Variability of measurement and use of terminology have contributed to heterogeneity and inconsistency in the reported results of prevalence and treatment outcomes. In this report, we have specified the definition of depression where indicated by speakers (e.g., depressive symptoms, diagnosed depression, diabetes-related distress). Where the definition of depression was heterogeneous or unspecified, we use the italicized term *depression* to denote a range of assessment techniques or definitions used during the presentations of the relevant literature.

### PREVALENCE AND INCIDENCE OF DIABETES AND DEPRESSION

The prevalence of comorbid *depression* varies considerably by method of depression assessment. For example, prevalence rates for elevated depressive symptoms range from 12–27% across studies of people with type 1 and type 2 diabetes, while rates of depressive disorders, as assessed by psychiatric interview protocols, range from 8–15% in adults with type 1 and type 2 diabetes (5,6). There are few studies of the prevalence of depressive disorders in pediatric populations, but these suggest that the rates of *depression*, anxiety, and distress are also elevated in children and young adults with type 1 diabetes compared with the general population with prevalence rates ranging from 10–26% (7). Similar rates of *depression* are also seen in adolescents with type 2 diabetes or in populations with both type 1 and type 2 diabetes (8.6–14.8%) (8). Rates of diabetes-related distress have been shown to be higher (54%) than rates of psychiatrically diagnosed depression (9).

#### Impact of Comorbid Depression and Diabetes

In adults, there is only a weak relationship between *depression* and glycemic control (10). By contrast, there is a stronger association between comorbid depressive symptoms and a range of diabetes complications (11), although this was not observed in the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (12). Increased health care costs (13), worsened functional disability (14), and early mortality are seen in adults with comorbid diabetes and *depression*

compared with either condition alone (15). Higher mortality among those with diabetes and *depression* is attributable to a variety of medical causes rather than primarily cardiovascular disease as previously assumed (15,16) and is not wholly explained by traditional risk factors (17). In children and adolescents, depressive symptoms are associated with poorer glycemic control (7) and predict rehospitalization and retinopathy in children with type 1 diabetes (18,19).

#### Research Recommendations:

##### Phenomenology

Much greater clarity and specificity are needed to describe and measure depressive symptoms, diabetes-related distress, and specific disorders in the depressive spectrum. Prospective longitudinal studies of depression spectrum (e.g., major depressive disorder, dysthymia, etc.) and other psychiatric diagnoses, such as bipolar disorders or psychotic disorders, are needed in separate populations of people with type 1 and type 2 diabetes to characterize inception predictors as well as the course of comorbidity. There is a particular need for studies in children and adolescents with diabetes where there is a paucity of knowledge. More detailed description and study of diabetes subtypes, including gestational diabetes mellitus and impaired glucose metabolism, and phenotypes (e.g., age, ethnicity, BMI, diabetes duration, comorbidities, treatment) are needed to clarify the onset and comorbidity of depression and diabetes.

### MECHANISMS AND PATHOGENESIS UNDERLYING THE ASSOCIATION BETWEEN DIABETES AND DEPRESSION

Previous epidemiological studies have demonstrated a bidirectional association between *depression* and diabetes (20,21), with most prior work focusing on understanding potential mechanisms by which diabetes leads to *depression* and vice versa. The presentations at the meeting, however, suggested a novel paradigm shift by considering shared biological and behavioral pathways that may simultaneously predispose to both affective and metabolic disorders. Focusing more on mechanisms common to the development of both *depression* and diabetes rather than focusing on the direction of association may yield novel insights for developing improved approaches to

**Table 1—Mechanisms and pathogenesis: future research needs and recommendations**

Mechanism	Basic science	Clinical, behavioral, and population science
Environmental factors	Develop models of stress/depression in existing diabetic animal models to evaluate genetic and epigenetic factors, developmental stressors, and environmental stressors	Develop longitudinal studies to determine if neighborhood factors modify the association between depression and diabetes Develop lifecourse studies to examine the impact of cumulative early life and environmental stressors on incident depression and diabetes
HPA axis	Design animal studies to elucidate the role of the HPA axis in neuroplasticity, which has implications for development of both depression and cognitive dysfunction in the setting of diabetes	Incorporate static and dynamic measures of HPA axis function into human studies to elucidate the role of the HPA axis in depression and type 1 and type 2 diabetes Use uniform cortisol sampling protocols and analytic strategies across studies to allow comparability Evaluate the impact of corticotrophin-releasing hormone and 11 $\beta$ -hydroxysteroid dehydrogenase-1 antagonists and behavioral interventions on HPA axis function
Inflammation	Conduct preclinical studies of diabetes and cognition/neurogenesis that incorporate measures of inflammation (e.g., acute phase proteins, interleukin-6, inflammatory signaling pathways including nuclear factor- $\kappa$ B and p38 mitogen-activated protein kinase, kynurenine:tryptophan ratio, microglia activation) and tests of depression-like behavior	Conduct studies to determine if anti-inflammatory strategies would be beneficial for the treatment of depression in the context of diabetes Conduct association studies on biomarkers of inflammation and symptoms of depression Conduct studies to determine the degree to which overlapping development conditions—personal, cultural, ecological—explain the comorbidity of diabetes and depression and how central inflammatory processes are to this overlap
Circadian rhythm/sleep disturbance		Conduct studies to elucidate whether the pathogenesis of depression in patients with diabetes is causally linked to obstructive sleep apnea (OSA) or whether the diabetic state is the driving force in the development of depression independent of sleep status Conduct studies to elucidate disruptions in endocrine axes and neurotransmitter pathways common to depression, diabetes, and OSA Design studies to define mechanisms underlying improvement in depression that have been associated with improved glycemic control as well as improved OSA
Behavioral factors	Conduct studies to understand neural circuitry associated with behavioral regulation in diabetes	Evaluate linkage between self-care adherence, hyperglycemia, and onset of depression in adults with type 1 and type 2 diabetes Evaluate mechanisms associated with mood changes resulting from physical activity in adults with type 1 and type 2 diabetes Evaluate types of physical activity and thresholds for duration and intensity to produce mood improvements in adults and children of different ages with type 1 and type 2 diabetes
Treatment factors	Evaluate existing antidepressant and antipsychotic medications in animal models of diabetes to determine mechanisms of action for treatment Evaluate antihyperglycemic therapies (e.g., GLP agonists) as novel experimental treatment for diabetes and depression (via regulation of glycemic control [direct mechanism] and/or regulation of neuroplasticity [indirect mechanism])	Design adequately powered randomized controlled trials of antidepressants that assess metabolic risk and will allow understanding of how psychotropic medications interact with other risk factors for diabetes Examine existing databases for reporting possible adverse metabolic consequences of antidepressant treatment Consider the potential effects of psychotropic medication in future diabetes prevention trials Examine the impact of sociocultural factors on the acceptability and outcome of treatment, preferably using collaborative research allowing an exchange of experience and evidence among countries

prevention and treatment. In turn, this may lead to treatment and preventative strategies to address these two major public health burdens simultaneously.

Figure 1 summarizes common pathogenic mechanisms and their interrelations discussed during the conference, although it is acknowledged that other postulated pathogenic mechanisms linking these two disorders may exist.

The traditional view of comorbid diabetes and *depression* assumed that the self-care burden of diabetes, coupled with the knowledge of the diagnosis of diabetes and its complications, rendered the patient with feelings of helplessness and hopelessness that resulted in *depression*. Studies showing higher rates of *depression* in people with diagnosed diabetes compared with undiagnosed diabetes

support this model (22). In addition, the increased rate of diabetes in people with *depression* has been attributed to obesity-promoting health behaviors, such as physical inactivity and poor dietary habits (21). Nonadherence to self-care routines in those already diagnosed with diabetes and experiencing depressive symptoms has also been found, such that a 1-point increase in depressive

**Table 2—Clinical aspects and treatment: future research needs and recommendations**

Phenomenology and prevalence studies	<p>Seek clarity and specificity in future studies in measurement/definition of depressive symptoms vs. depressive disorders (psychiatric diagnoses) vs. diabetes distress</p> <p>Conduct prospective longitudinal studies of diabetes subtypes and phenotypes, especially type 1 and type 2 diabetes, to study inception predictors and comorbidity course</p> <p>Develop cross-culturally applicable assessment instruments allowing the identification of depression comorbid with diabetes</p>
Depression screening	<p>Conduct studies to assess cost-effectiveness in depression screening in the context of intervention trials</p> <p>Conduct studies of electronic medical record surveillance to identify people with diabetes at high risk for depression</p>
Treatment modalities, care delivery, and cost-effectiveness	
Psychotherapy	<p>Determine which psychotherapeutic approaches are most effective for which diabetes subpopulations and in different types of depressive disorders</p> <p>Expand treatment modalities beyond cognitive behavior therapy to include exercise and mindfulness-based stress reduction, etc.</p> <p>    Community-based programs linking non-health care—system resources</p>
Medications	Evaluate mechanisms of depression medication treatments in randomized controlled trials in type 1 and type 2 diabetes
Collaborative care	<p>Identify methodologies and infrastructure to deliver economically sustainable, integrative collaborative care adjusted to the cultural and economic conditions prevailing in different countries and parts of countries</p> <p>Develop technologies to extend collaborative care to patients and providers</p> <p>Develop payment approaches to support case management at national and state level</p>

symptom score was found to be associated with a 10% increased risk of nonadherence to fruit and vegetable intake and foot care (23). This suggests the possibility that there may be a mutually reinforcing relationship between depressive symptoms and decreased adherence to self-care behaviors (23,24).

Current research also supports a contribution of biological changes in diabetes, such as structural, functional, and neurochemical changes in the brain regions responsible for affect and cognition in both type 1 and type 2 diabetes that may increase the risk of *depression* (25). Specifically, animal models have shown that diabetes and hyperglycemia negatively affect hippocampal integrity and neurogenesis, reducing neuroplasticity and contributing to mood symptoms in diabetes (26). In humans, hippocampal neurogenesis can be indirectly assessed via MRI, and hippocampal atrophy has been observed in people with diabetes (26).

#### Intrauterine Environment

The earliest influence is the intrauterine environment and early life conditions, such as fetal undernutrition and stress and maternal stress, which can lead to

low birth weight and a predisposition to adult diabetes (27). Animal studies have shown an adaptive slowing of fetal growth rate and modification of organ structure in response to undernutrition (28). The data about the relationship between adverse intrauterine environment and risk for *depression* in adulthood remain inconclusive, with some studies suggesting a positive association while others have null findings (29). In human studies, both low birth weight and fetal overexposure to cortisol secondary to maternal stress have been associated with hypothalamic-pituitary-adrenal (HPA) axis programming and elevated cortisol reactivity in childhood, adolescence, and adulthood, predisposing the individual to stress-related and metabolic disorders (30).

#### External Environment

Several contextual factors, including childhood adversity (possibly mediated through increased adult C-reactive protein concentration [31]), neighborhood environment, and poverty, also influence the predisposition to *depression* and diabetes.

Poorer neighborhood physical environment (e.g., physical disorder, traffic,

noise, decreased walkability) is associated with worse diet, lower physical activity patterns, obesity, and diabetes (32–34). Furthermore, worse neighborhood social environment (e.g., lower social cohesion and social capital, increased violence, decreased residential stability) is associated with higher rates of depressive symptoms and mental health problems (35). Cross-sectional data sets have indicated that resources promoting physical activity and healthy diets are associated with lower diabetes risk (36). Adverse neighborhood environments have also been associated with dysfunctional HPA axis activity and disruption of its normal circadian rhythm (i.e., blunted profile) (37–41) as well as enhanced inflammation (42,43).

#### Common Interrelated Biological Pathways

Both diagnosed major depression and diabetes are associated with HPA axis dysfunction, which manifests as subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity, and increased inflammation (44–47). Disrupted sleep patterns are seen in people with major depression (48), and poor sleep quality and altered circadian rhythms are

**Table 3—Public health and prevention: future research needs and recommendations**

Preventing comorbid depression and diabetes	<ul style="list-style-type: none"> <li>Identify and implement best practice into routine health care for integrated health services for comorbid depression and diabetes in different types of service and in different countries</li> <li>Expand economic studies of depression–diabetes comorbidity to non-U.S. countries</li> <li>Incorporate non-health care–related costs into cost-effectiveness analyses</li> </ul>
Preventing diabetes in depression	<ul style="list-style-type: none"> <li>Develop studies to understand the effect of depression and antidepressants on diabetes preventive interventions</li> <li>Determine if prevention or treatment of depression can reduce type 2 diabetes incidence</li> <li>Validate diabetes risk engines in individuals with depression</li> </ul>
Preventing depression in diabetes	<ul style="list-style-type: none"> <li>Conduct future depression intervention studies in individuals with diabetes in primary and subspecialty care settings               <ul style="list-style-type: none"> <li>Evaluate effectiveness</li> <li>Target health care providers as intervention focus</li> </ul> </li> <li>Conduct health services studies to determine the optimal way of delivering depression interventions, including the use of nonprofessional workers (e.g., peer support) and new technologies</li> <li>Use alternative research methodologies to model more closely the clinical care setting (e.g., practice-based research networks, pragmatic trials, systems science, longer-term observational studies)</li> </ul>
Primary prevention of depression and diabetes	<ul style="list-style-type: none"> <li>Develop and test in randomized trials population-based interventions to reduce etiological factors associated with comorbid diabetes and depression, within and across cultures and countries</li> </ul>

associated with insulin resistance and type 2 diabetes risk (49). All these biological pathways are activated in major depression and are associated with insulin resistance. A recent meta-analysis showed that depressive symptoms are weakly associated with insulin resistance, providing a potential link to incident type 2 diabetes (50).

#### Pathways Related to Medications for Depression

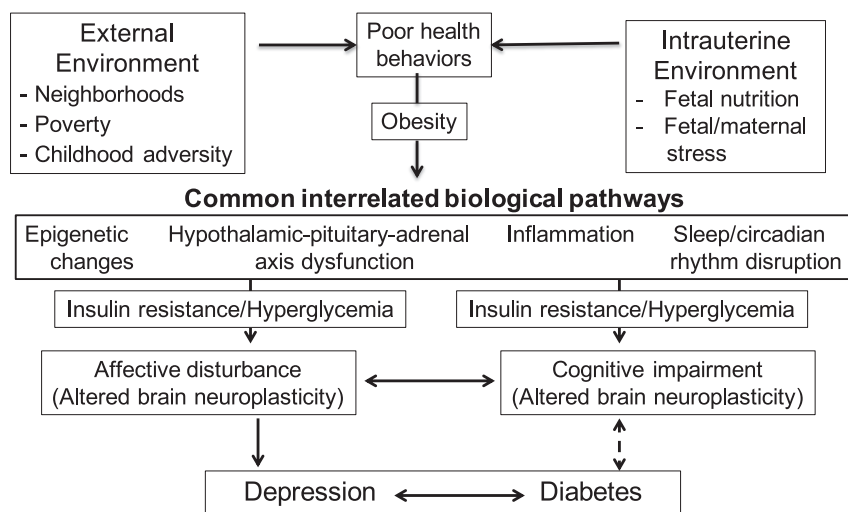
While there have been concerns that certain antipsychotic medications, particularly some of the “atypical” or second-generation antipsychotic medications, are associated with a two- to threefold increased risk of diabetes (51), recently, a role of antidepressants in the development of diabetes has also been postulated (52). Cohort studies show a small increased risk of diabetes in those receiving antidepressant medications. Randomized controlled trials, however, have emphasized that antidepressants vary considerably in their propensity for weight gain (53) and glycemic effects, ranging from hyperglycemic to hypoglycemic effects (52). It

remains unclear whether the weight gain results from poorly treated *depression* or a medication side effect. The precise mechanisms by which these drugs may lead to weight gain and altered intermediate metabolism are unknown, not least because they may affect multiple neurotransmitter receptors simultaneously (52,53).

#### Research Recommendations: Mechanisms

The current state of science in our understanding of the biological and behavioral mechanisms linking *depression* and diabetes from animal and human studies has two important gaps. First, many studies have been cross-sectional, resulting in residual confounding and limiting our understanding of temporal relationships. Second, longitudinal studies typically capture a snapshot in the prospective associations between *depression* and diabetes when, in reality, these associations are influenced by exposures over the lifecourse. To address these critical gaps, as outlined in Fig. 1, prospective lifecourse studies are needed in both animals and humans with detailed phenotypic characterization

of the intrauterine environment and the external environment in which individuals are raised, with simultaneous longitudinal assessment of behavioral and biological pathways influenced by these early exposures (e.g., HPA axis function, inflammation, sleep/circadian rhythms). In animal studies, the intrauterine environment can be directly manipulated by impairing placental blood flow, and in both animal and human studies, assessment of epigenetic markers and DNA methylation patterns can reflect the degree of fetal stress (28). These studies should also longitudinally assess 1) metabolic measures reflecting insulin resistance and hyperglycemia, 2) brain morphology to assess the influence of biological and metabolic factors on neuroplasticity implicated in affective and cognitive disturbances, and 3) the presence/onset of specific depressive disorders using a standardized approach. In animal studies, neuroplasticity can be directly assessed in the amygdala, but this cannot be directly and noninvasively assessed in human studies, which is an important area for future research. In animal studies, researchers can assess



**Figure 1**—Summary of shared pathogenic mechanisms in the depression–diabetes association covered at the International Conference on Depression and Diabetes.

development of depressive behaviors (26). What will be required in human studies is to perform standardized psychiatric interviews in the context of lifecourse studies to allow depressive disorders to be correctly characterized. This will ultimately allow us to link depression phenotypes more specifically to the biological and behavioral pathways altered, while determining phenotypes that are more strongly related to diabetes onset. Finally, these studies will determine which depression phenotypes in the setting of diabetes are related to poor health behaviors, onset of complications, and increased mortality. Accomplishing these lofty goals will require international collaborations to exploit resources and existing research infrastructure, but lifecourse studies will be critical to enhancing our current understanding. Such studies also will help us to understand the cumulative effect of multiple environmental stimuli, how they interact with intrinsic biological changes, and how they influence vulnerability or resilience to mental health and metabolic disorders. Ultimately, the studies will help to identify potential intervention periods and targets.

Future interventional studies in animal models and humans should examine the impact of experimental therapies on proposed biological and behavioral pathways common to *depression* and diabetes by incorporating measures of biological, behavioral, and brain function. Therapies targeting the implicated pathways may lead to more effective prevention and

treatment approaches for both diabetes and *depression*.

### TREATMENT OF DIABETES AND DEPRESSION

Until recently, people with diabetes were specifically excluded from *depression* treatment trials in the general population, and consequently, there are relatively few studies examining antidepressant and psychotherapy treatment of *depression* that specifically focus on diabetes.

#### Psychotherapy

Psychotherapy treatment protocols for *depression* in people with diabetes have predominantly used cognitive behavioral therapy (CBT) delivered individually by mental health providers or trained nurse case managers and are effective in reducing depressive symptoms in adults. Although there are mixed effects on glycemic control, interventions that combine diabetes self-management education reported benefits for glycemic control (54).

Although a small research base exists, more research is needed to test alternative behavioral intervention approaches for treating diabetes and *depression* (e.g., electronic-based health [eHealth] intervention, exercise, mindfulness-based stress reduction). For example, trials of eHealth and mobile technology-based health (mHealth) interventions suggest that these are less effective than face-to-face psychotherapeutic treatments (55).

There is a lack of evidence for psychotherapy that specifically addresses *depression* in children with type 1 or type 2 diabetes. Brief behavioral interventions with families of children with type 1 diabetes have been found to be effective in improving adherence to self-care behaviors and glycated hemoglobin, suggesting that this approach could serve as a model for the development of a depression-specific treatment intervention (56).

#### Antidepressants

Antidepressant medications lead to amelioration of depressive symptoms and resolution of major depression in people with either type 1 or type 2 diabetes, but have mixed effects on glycemic control ranging from hyperglycemic effects with tricyclic antidepressant medications to euglycemic or slightly hypoglycemic effects with selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors (54). Fewer than half of the commonly prescribed medications of these types have been tested for their effects on glycemic control in people with diabetes. Trials have not been designed to assess differences in the effectiveness of these medications by diabetes type.

#### Collaborative Care

Multidisciplinary team approaches to the identification and treatment of *depression* within primary care settings incorporate identification of high-risk cases, problem-solving therapy delivered by

trained nurse case managers, and medications using a stepped-care approach (57). The Pathways study indicated positive improvements in *depression* outcomes among adults with type 1 and type 2 diabetes but no changes in glycemic control (57). The subsequent TEAM-care approach combined behavioral and pharmacological treatment of *depression* with diabetes management, leading to positive outcomes for *depression* and glycemic, systolic blood pressure, and LDL-cholesterol control and reduced health care costs (58).

#### **Research Recommendations: Treatment of Diabetes and Depression**

**Depression Screening.** Depression screening is an important first step for the identification of individuals that could benefit from treatment. The use of locally standardized screening instruments, such as the Patient Health Questionnaire-9, that may be widely used in primary care and provide consistent definitions of what constitutes depressive symptom thresholds or cases of “depression” would facilitate comparative studies of depressive disorders in different cultures within and across countries. However, this approach must be evaluated in concert with intervention trials to assess clinical and cost-effectiveness (59). In the context of U.S. health care reform, there is an opportunity to develop routine surveillance using electronic medical records for the risk of major depression and alert providers to intervene proactively. Such surveillance of the quality and patterns of diabetes care would allow large-scale evaluation of natural experiments that occur in health care delivery systems (60).

**Treatment Modalities and Delivery.** Despite well-understood differences in the etiology and pathophysiology of type 1 and type 2 diabetes, existing treatment studies have examined mixed populations making generalizations about treatment efficacy of antidepressant medications or psychotherapy by diabetes type difficult (54). Sample sizes for subgroups of people with type 1 diabetes within existing studies are too small to allow stratified analyses to determine similarities or differences in treatment modalities and outcomes compared with adults with type 2 diabetes. Studies that highlight

whether differences occur between diabetes types are needed.

The most common psychotherapeutic approach used to treat comorbid diabetes and depression is CBT. A total of eight randomized controlled trials have evaluated the efficacy of psychotherapeutic interventions on *depression* in mixed populations of adults with type 1 and type 2 diabetes. Similar beneficial effects of low to moderate effect size have been observed across the studies, indicating the value of this approach in the context of multiple variations in length and format of delivery (e.g., eHealth, individual face-to-face psychotherapy, group psychotherapy) and audience (55). Further research is needed to improve the efficacy of CBT and determine the minimum meaningful “dose” needed to have the greatest cost-benefit for people with diabetes and health providers. It is also important to identify which of the constituent elements of CBT are important for the therapeutic effect. In addition, much work remains to examine treatment strategies for adults with type 1 diabetes, whose unique needs and developmental history with diabetes have gone unaddressed in the current depression treatment literature. Research is also needed to examine how CBT strategies can be adapted to the needs of specific subgroups with *depression* and diabetes, such as young people feeling stigmatized, older adults for whom cognitive decline plays an increasingly important role, or for those with complications and functional loss.

There is also a need to expand treatment modalities beyond CBT to include additional approaches, such as exercise and/or community-based programs, that link treatment to community resources beyond health care systems, such as in-home (61) or community-based treatment programs (62). For example, there is a significant body of evidence from the general population that exercise is an effective treatment for depression. There is also evidence that exercise contributes to diabetes management. Yet, there are few trials that have evaluated this approach as potentially synergistic in treating comorbid *depression* and diabetes. Attention bias modification could be developed to target the HPA axis, which has been implicated in the increased recurrence risk

of depression in people with diabetes. Empirically validated treatment approaches that make use of support systems (e.g., ecological approach) are needed to treat both depressive disorders as well as diabetes-related distress, making use of all possible mental health partners and allied health advocates whose expertise may be complimentary to the health care system and may be incorporated into multidisciplinary approaches to treatment.

There is a need to evaluate mechanisms of pharmacological treatment using adequately powered clinical trials. Greater understanding is needed about the way psychotropic medications interact with other risk factors and the effects of antidepressants on diabetes prevention, metabolic risk, and patient safety in discrete samples of people with different types of diabetes. Such studies should permit comparisons of the impact of the factors listed above in people belonging to different sociocultural groups.

#### **PREVENTION AND PUBLIC HEALTH CONSIDERATIONS**

The high prevalence of comorbid diabetes and *depression* has a number of public health ramifications, particularly at the present time when many health care systems are becoming increasingly fragmented and specialized. This disadvantages individuals with comorbid physical and mental illness. The U.K. Disability Rights Commission has highlighted the concept of “overshadowing,” where health care professionals focus solely on the mental disorder and fail to take note of physical health needs, despite the greater need for this care (63). This translates into poorer diabetes care as those with mental illness are less likely to be screened for diabetes, leading to higher rates of undiagnosed diabetes (64). People with comorbid mental illness are less likely to be offered screening for glycosylated hemoglobin or cholesterol, statin therapy, or diabetes education or be examined for microvascular complications, despite more clinic visits. By contrast, depressive and other mental disorders are often missed and inadequately treated if the focus of care is the medical condition (65,66). These types of systematic deficiencies within health care systems may contribute significantly to the poorer health

outcomes in those with comorbid diabetes and *depression*.

A recent systematic review has highlighted the increased health service utilization and cost associated with comorbid diabetes and *depression* (13). In addition to direct health costs, adverse impacts on workforce participation and absenteeism were also found. A limitation of these studies is that most were undertaken in the U.S., with few examining the impact beyond 1 year or outside the health care system.

### Prevention of Diabetes in People With Depression

Recent studies have shown that diabetes can be prevented, or at least delayed, by either lifestyle or pharmacological interventions (67). The development of diabetes risk engines now allows a reasonably accurate assessment of diabetes risk in clinical practice. This combination of better identification and affordable interventions has made diabetes prevention a realistic and cost-effective proposition (68).

Neither the risk engines nor diabetes prevention interventions have been evaluated in people with *depression*. This is important because the risk of diabetes is increased in people with *depression* and may involve different etiological factors, while a number of barriers may impede the successful implementation of lifestyle interventions. In the Diabetes Prevention Program (DPP), a population with prediabetes at enrollment, those taking antidepressants had a higher risk of developing diabetes than those not taking antidepressants in the placebo and lifestyle intervention arms, while the risk was lower in people in the metformin arm who did not receive lifestyle intervention (69,70). In the same study, elevated depressive symptoms did not predict development of diabetes (69,70). This study excluded those with severe depression and the wide confidence intervals of the findings make it unclear whether these findings can be extrapolated to a broader population of people with *depression*. Nevertheless, it should not be assumed that risk identification and prevention will be equally effective in people with *depression* in the absence of scientific evidence.

### Prevention of Depression in People With Diabetes

Many risk factors that predict the onset of *depression* in the general population

are equally applicable to people with diabetes, but there are several diabetes-specific factors, such as the development of complications (11) and the need for insulin treatment in people with type 2 diabetes (71), that are associated with an increased prevalence of *depression*. Despite our understanding of the epidemiology, there has been little research into the prevention of *depression* in people with diabetes. This is also true in people without diabetes, where most interventions have focused on secondary prevention. A recent systematic review concluded that there was inadequate evidence to determine the clinical effectiveness or cost-effectiveness of low-intensity psychological interventions to prevent relapse or recurrence of *depression* (72).

The large numbers of people with diabetes at risk for *depression* demand efficacious and cost-effective interventions. This may involve the use of nonprofessional workers (e.g., peers) or new technologies to deliver the preventative interventions.

### Primary Prevention of Depression and Diabetes

There are many shared risk factors for diabetes and *depression*, suggesting that diabetes and *depression* may be two manifestations of a common set of psychological, lifestyle, and biological perturbations. It is therefore possible that population approaches that focus on the common ground between diabetes and *depression* and the behaviors that relate to both may allow the effective prevention of both conditions, but this area is largely not researched.

#### Research Recommendations: Prevention and Public Health Considerations

**Prevention.** It is unclear whether effective prevention or treatment of *depression* can reduce incidence of type 2 diabetes. Future trials are needed to address this issue while validation of diabetes risk engines in people with *depression* is needed to identify those at high risk of diabetes. The interaction of *depression* and antidepressants on interventions to prevent diabetes also merits further study.

Future research should examine when and how interventions to prevent *depression* can be introduced in people with diabetes. Such research should be conducted in people with diabetes in both primary and specialty care settings to evaluate the effectiveness of interventions

using established methods and functional outcomes. The timing of these interventions in relation to the diagnosis of diabetes should be considered. Given the burden of diagnosis, interventions aimed at health care professionals providing care at the time of diabetes diagnosis should be considered. Research into the facilitators of and barriers to health care professionals' engagement with comorbidity is needed. Health services research is required to find the optimal way of delivering interventions.

Currently researched models of care often do not match the reality of primary care and so alternative methodologies, such as practice-based research networks, pragmatic trials, systems science, and longer-term observational studies that include patient-reported outcomes, should be considered.

Population-based interventions to reduce common etiological factors for diabetes and *depression* should be developed and tested in experimental studies.

**Public Health Considerations.** Translating basic and clinical research findings into improved treatment and outcomes remains a substantial challenge. While multidisciplinary team care approaches have shown efficacy for both diabetes and *depression*, much work remains to identify the methodologies and infrastructure needed to deliver and implement best practice into routine health care in an economically sustainable manner. Given the cross-specialty nature of comorbid diabetes and depression, further research is needed to identify how health care professionals working across different disciplines can provide integrated health services for people with comorbidity. Additional work to develop technologies to extend collaborative care (e.g., telemedicine, patient registries, eHealth, mHealth) to patients and providers is needed while weighing the relative benefits of *depression* control in light of multiple health outcomes (e.g., glucose, blood pressure, lipid, and tobacco control). National and local initiatives to develop payment approaches to support case management are needed to insure the successful implementation of large-scale integrated care interventions.

Most of the published economic analyses of the comorbidity of diabetes and *depression* have been undertaken in the



U.S.; further research is needed in other parts of the world. Collaborative studies using cross-culturally applicable assessment methods would be valuable because they would clarify the impact of culture on the presentation, course, and outcome of *depression* and diabetes and allow the development of different yet effective interventions and models of service. Longer-term studies that take a broader view of the costs, including non-health care–related costs, are needed to evaluate cost-effectiveness as cost benefits are not usually realized immediately.

### TRAINING FOR RESEARCH AND CLINICAL CARE

Training is needed to enhance the workforce involved in both research and clinical care of diabetes and depression. Many researchers and practitioners currently work within single disease fields. It is critical that training moves research and practice to account for the complexity of multiple comorbid diseases that are the norm for real-world patients. Training should promote the development of cross-disciplinary researchers who can work in teams to understand the mechanisms of comorbid conditions better and to develop effective prevention and treatment approaches. Researchers with basic science and clinical research expertise in neuroscience, neuroendocrinology, neuroimmunology, behavioral science, clinical psychology, public health, clinical trials, and medicine (e.g., psychiatry, internal medicine, pediatrics) will all be necessary to advance this field. As well as working across disciplines, training is needed to develop researchers who can move across different levels of the translational continuum from basic to applied clinical, behavioral, and population science and back again. As in many fields, scientific advancement is stunted without a cadre of researchers that can span the translational chasms between the basic, applied, and population sciences.

Training to expand the workforce health care professionals and extenders (e.g., community health workers, peer supporters) adept in managing comorbid *depression* and diabetes is needed. However, given the scope of the needs in high-, middle-, and low-income countries, cost-efficient approaches to expanding the workforce will be critical. Mental health providers, diabetes

behavioral researchers, diabetologists, diabetes educators, primary care providers, nursing and midlevel provider staff, and community-based providers are some examples of professions where additional training in detection, prevention, and treatment related to comorbid diabetes and *depression* could be beneficial.

### CONCLUSION

The association between diabetes and depression or depressive symptoms is a major public health problem. A more detailed understanding of the association is needed, with greater clarity and precision in the terminology used to differentiate between depressive symptoms and formal clinical diagnoses of depression. These advances in understanding should be coupled with the introduction of evidence-based interventions into health care if we are to resolve the challenge of the comorbidity and to improve the outcomes for people with comorbid diabetes and depression.

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