



Special Article

Diabetes and Mental Health

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Key Messages

Living With Diabetes

- The diagnosis and management of diabetes can be a significant life stressor for individuals and their families, and may be associated with challenges regarding illness acceptance and treatment participation. Addressing concerns regarding illness beliefs and participation in treatment recommendations can be helpful.
- The lived experience of diabetes is often associated with struggles specific to the illness and can lead to significant concerns, specifically diabetes distress, perpetuation of stigma, reluctance to initiate insulin when recommended, and the persistent fear of hypoglycemic episodes.

Psychological Reactions to the Diagnosis of Diabetes

- Well-established reactions to diabetes include: perceptions about the seriousness of the disease (either discounting the seriousness of diabetes, which is often seen in those with asymptomatic type 2 diabetes [T2D], or becoming overwhelmed by the diagnosis, often seen in individuals and families with type 1 diabetes [T1D]); not comprehending the extent to which diabetes can be managed; the degree of personal responsibility required for management; and the

perceived benefits and barriers to taking action. Professional support to address these reactions can be helpful in promoting self-management of diabetes.

Stigma Associated With Diabetes

- Weight-based stigma—the perception and experience of being discriminated against due to one's body weight—can be perpetuated by providers in health-care settings. When present, this can lead to worsening distress, diminished quality of life, as well as decreased diabetes self-management behaviours. Health-care providers must be aware of their own biases and be able to communicate in a non-stigmatizing manner about weight-related issues and diabetes management.

Financial Burden of Diabetes

- Diabetes is an expensive illness to live with and to manage well. People living with diabetes should ask their health-care teams for help and health-care providers should recognize the key role they play in accessing financial supports. Advocacy and activism are helpful and often necessary to manage the cost of living with diabetes.
- The costs associated with diabetes can have effects on the physical and emotional well-being of people with diabetes.

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Risks Associated With Diabetes and Psychiatric Conditions

- A wide range of psychiatric disorders (beyond the serious mental illnesses of major depressive disorder [MDD], bipolar and related disorders, and schizophrenia spectrum disorders) put people at higher risk for developing diabetes (usually T2D) compared to the general population.
- People living with diabetes and MDD are at increased risk for earlier all-cause mortality compared to people living with diabetes without a history of MDD.
- Compared to those with diabetes only, individuals with diabetes and mental health concerns are at risk for functional impairment, diabetes complications, and increased health-care costs, often coupled with decreased participation in diabetes self-care and decreased quality of life.

Diabetes in Pregnancy

- Individuals with diabetes in pregnancy are at an increased risk of developing mental health disorders (e.g. depressive and anxious symptoms) and psychological distress throughout the pregnancy. Receiving effective emotional and tangible support, in addition to medical advice, can help buffer these negative outcomes.

Risks for Children and Adolescents

- Youth with diabetes are at risk for having psychosocial symptoms and diabetes self-management difficulties. Regular assessments during routine diabetes care are especially helpful during adolescence and the transition to young adulthood.
- It is important to also assess the emotional functioning of the whole family/home environment—including parent/caregiver distress and fear of hypoglycemia—in order to understand the potential impact of these influences on younger people with diabetes.

Diabetes in Older Adults

- Depressive symptoms in older adults with T2D are an important risk factor for cognitive impairment and are associated with an increased risk of earlier mortality.
- Older people with T2D experience an increased disease burden and are more likely to have multimorbidity (an increased likelihood of complications and other adverse outcomes).

Substance Use and Diabetes

- Substance use is linked with multiplicative health risks and can be a factor in the development of new-onset T2D, as well as worsening health outcomes among those with established diabetes.
- Smoking cigarettes and/or alcohol consumption are risk factors for the development of T2D and adverse cardiovascular events in people with established diabetes.
- People prescribed insulin are more susceptible to the harmful effects of recreational substance consumption, particularly alcohol use.
- Screening for substance use followed by a brief intervention can be helpful, and approved pharmacotherapies for tobacco, alcohol, and opioid use disorders are safe for use in people with diabetes.

COVID-19

- People with diabetes are at higher risk for developing more severe complications from a COVID-19 infection. Preventative measures, such as keeping a safe distance from others, wearing a mask in public, regular handwashing, and keeping up to date on vaccinations, help reduce the risk of acquiring the virus and potentially the severity of the illness.

Screening and Assessment

- All individuals with diabetes, as well as the parents or caregivers of youth with diabetes, should be screened at appropriate intervals for the presence of diabetes distress, as well as symptoms of common psychiatric disorders.
- People with diabetes are at risk for developing a wide array of mental health conditions—especially mood and anxiety disorders—and should be screened regularly for symptoms that may be part of a psychiatric condition.

Psychosocial Treatment Approaches to Managing Diabetes

- Person-centred approaches using motivational interviewing, cognitive behaviour therapy (CBT), acceptance and commitment therapy, stress management, coping skills training, family therapy, and collaborative case management should be incorporated into primary care, wherever possible.
- Building self-management skills, employing educational interventions that facilitate adaptation to diabetes, and addressing co-occurring mental health issues that reduce diabetes-related distress, fear of hypoglycemia, and reluctance to initiate insulin when recommended, are all helpful.

Use of Psychotropic Medications

- There are effective treatments for the disabling symptoms that comprise psychiatric conditions. Regular use of medication can be a crucial element in helping people maximize their function and reduce symptom severity.

Monitoring Metabolic Risks

- Individuals taking psychiatric medications, particularly (but not limited to) atypical antipsychotics, benefit from regular screening of metabolic parameters to identify glucose dysregulation, dyslipidemia, and changes in weight (and possibly other anthropometric measures) throughout the course of the illness so that appropriate interventions can be instituted if necessary.

Key Messages for People With Diabetes

Living With Diabetes

- Living with diabetes can be burdensome and anxiety provoking. The constant demands of having to care for the illness take a psychological toll. As a result, many people struggle to accept the diagnosis or proposed treatment plan and delay actively participating in diabetes care, which only worsens the long-term outlook.

Psychological Reactions to the Diagnosis of Diabetes

- Diabetes is often associated with distress over the need for daily self-care, adding stress to relationships, a significant emotional burden. It is important to be compassionate with yourself and

accept your emotions as valid responses to a chronic condition. In addition to self-care, seeking out support by talking to your friends, family, and members of your diabetes health-care team about how you are feeling can be helpful. Your team can help you to develop effective coping skills and direct you to mental health-care services that can make a difference for you.

Stigma Associated With Diabetes

- Diabetes-related or weight-related stigma (feeling or experiencing social judgement) is common and can lead to a decreased sense of well-being, as well as making you feel less motivated to care for your diabetes.

Financial Burden of Diabetes

- Caring for diabetes effectively can be expensive, and can exceed the ability of many people to manage financially. There may be ways to reduce these costs. So, if your finances are suffering, let your health-care team know—it is possible that something helpful can be done.

Risks Associated With Diabetes and Psychiatric Conditions

- Mood and anxiety symptoms are common in people with diabetes and can be impairing enough to lead to a formal psychiatric diagnosis. Eating, sleeping, and stress-related problems are also common. Speak to your health-care providers about the concerns that you have.
- Mental health issues can affect your ability to cope with and care for diabetes. Caring for your mental health is just as important as caring for your physical health and improves the long-term picture for your diabetes.
- People diagnosed with many psychiatric conditions appear to have a higher risk of developing diabetes than the general population.

Diabetes in Pregnancy

- If you have diabetes and are planning on becoming pregnant (or already are pregnant), your diabetes care team is available to offer psychosocial support and, if necessary, referrals to mental health resources.

Risks for Children and Adolescents

- Younger people often face psychological struggles that negatively impact managing diabetes. Share your physical and emotional struggles with your diabetes care team so they know what to help you with.
- Diabetes care impacts the whole family, so it is important to also discuss parent/caregiver's psychosocial functioning with the diabetes team. There are interventions that can improve everyone's well-being.

Diabetes in Older Adults

- Older individuals with T2D have more complications and adverse outcomes compared to younger individuals with T2D, which can make treatment more challenging and complicated.

Substance Use and Diabetes

- Smoking causes greater health harms in people with diabetes compared to those who do not have the illness. Even 1 cigarette

per day is harmful to your health. If you smoke, consider asking for support from your health-care provider to help you quit. Using a smoking cessation medication (nicotine patches, varenicline, or bupropion) together with counselling more than doubles your chances of quitting successfully.

- If you currently do not drink alcohol, it is a healthier decision to not start. For people who drink alcohol, it is imperative to reduce intake to minimize adverse health outcomes. This may mean consuming a maximum of 2 standard drinks per week, which has been linked with causing the least potential for harm. Consuming over 4 standard drinks per occasion has the potential to negatively affect diabetes care. Ask your health-care provider for support if you wish to reduce your alcohol use.
- Substance use with cannabis, stimulants, or illicit opioids may interfere with your blood glucose levels and your ability to manage your diabetes, particularly if these substances are consumed on a regular basis or in a large quantity over a short time (binges).

COVID-19

- Diabetes puts people at greater risk of having complications if you get infected with COVID-19. Preventative measures, such as keeping a safe distance from others, regular handwashing, and wearing a mask in public places, reduce the chance of acquiring COVID-19. Keeping up with vaccinations may reduce the severity of the infection if you do get it. You must do your best to reduce your chances of developing long COVID.

Screening and Assessment

- Your health-care provider can offer screening questionnaires that you can complete to help better understand your experiences and aid in planning treatment for diabetes. There are questionnaires to screen for diabetes-related concerns, as well as for general psychological distress. Screening questionnaires can be completed prior to your appointment and the results discussed at your visit.

Psychosocial Treatment Approaches to Managing Diabetes

- Diabetes care teams can help you manage the degree of distress that you are experiencing with strategies that are specific to living with diabetes. As well, they can arrange a referral to mental health services for concerns that may not be directly related to diabetes.

Use of Psychotropic Medications

- Medications, when taken regularly, can make a significant contribution to your health and ability to live your life with fewer troubling symptoms. If a medication has been recommended, consider giving it a good trial (taking it long enough as prescribed to determine if it is working) and then reporting the results to your clinician. Hopefully, you can find medications that make a positive impact on your health and are tolerable (few or no side effects).

Monitoring Metabolic Risks

- Your mental health medications may need to be monitored for possible side effects. Monitoring your glucose levels, lipid levels, blood pressure, and changes in weight will give you peace of mind that your major health risks are being covered.

Introduction

Diabetes mellitus is a disease that takes a heavy toll on the lives of people who have received the diagnosis. For those diagnosed with T1D, it is a major life stress (and can become a medical emergency) that often dominates the focus of individuals and their families. T2D can be (often for the first several years) asymptomatic or cause symptoms that are relatively easy to ignore. Yet, minor metabolic aberrations develop into larger ones that eventually can affect most major physiological systems and lead to characteristic end-stage complications that threaten life, limb, and vital functions. Diabetes mellitus can be a challenge for the people who have it, as well as the network of people who seek to offer support.

Irrespective of which type of diabetes an individual has, it can be a significant daily burden from which there is no relief. Research has shown that people who live with T1D must make an estimated 180 health-care decisions *each day* [1].

Managing blood glucose levels within a narrow range is a constant, complex balancing act, and what works well one day may not work the next. Many people who do not live with diabetes don't understand the persistent challenges involved in managing it and, in fact, can sometimes make those who have diabetes feel blamed or shamed for having it. Despite the fact that diabetes is caused by numerous complex factors—not all of which are within an individual's control—many Canadians (with and without diabetes) view a person's own behaviour as the most important contributing factor to the increasing rate of T2D [2].

The mental and emotional burden of living with diabetes can seem overwhelming, but can be reduced when caregivers have a fuller appreciation of this stress. Research has shown an increasingly clear relationship between diabetes and a variety of psychological reactions. These include expectable reactions to being diagnosed with a chronic metabolic illness, which can progress to established psychological syndromes specific to the experience of living with diabetes, finally increasing in severity to diagnosable psychiatric disorders. Another important contributor to psychological burden with diabetes is the social burden stemming from the judgement and stigma that accompanies life with diabetes. The 2018 Diabetes 360 report found that 33% of people with diabetes are hesitant to disclose their diabetes to others and 15% have experienced some form of discrimination, often due to misconceptions about the cause of the illness [3].

The context for understanding mental health issues in those living with diabetes begins with the acknowledgement or reflection that life involves continual challenges requiring daily coping efforts that necessitate sufficient resources and support. A primary drive for individuals is to try to maximize a sense of pleasure, and to minimize pain and distress [4].

When it comes to chronic diseases, such as diabetes, a treatment maxim is that “no one wants to be unwell.” The diagnosis of diabetes confers burdens and challenges that drain resources from other pursuits. One way of understanding this is to examine the relationship between life experiences and emotions, specifically:

- The experience of threat → feelings of anxiety
- The experience of loss → feelings of sadness/depression
- The experience of unfairness → feelings of anger [5]

This perspective offers insight into the mental health issues that people living with diabetes might experience. Inquiring into experiences of threat (e.g. nocturnal hypoglycemia), loss (e.g. recalling the more carefree experience of not having diabetes), and unfairness (e.g. navigating eating in social circumstances) can help empathize with the burden associated with diabetes. Since diabetes self-management affects almost every aspect of daily living, the burden of management is high, since it falls on individuals and their supports [6,7].

Psychological Adaptation/Expectable Reactions to the Diagnosis of Diabetes

Diabetes is a demanding chronic disease for both individuals and their families [8]. It is not surprising that some individuals struggle with acceptance of the diagnosis. If no one wants to be unwell, embracing the illness and its treatment involves a willingness to tackle the behavioural, social, and emotional burdens associated with successful diabetes management. Disease acceptance issues might be more likely to occur during life transitions or illness transitions. Individuals diagnosed with diabetes may follow expectable reactions to receiving bad news (i.e. denial, anger, sadness, bargaining, shock, rationalization, etc.) and get stuck at any of these stages. In order to maximize one's ability to reduce the potential harms from diabetes, individuals must accept the diagnosis and be willing to fully participate in recommended treatments.

Similarly, while we have access to many highly effective medical therapies and supporting technologies in diabetes management, persons with diabetes are the ones who must enact these strategies. Accordingly, attitudes and perspectives are critical to assess and address in any care plan. Treatment acceptance is an important issue that should not be overlooked in supporting individuals living with diabetes. Both disease acceptance and treatment acceptance can be understood through a validated assessment strategy called the Health Belief Model [9,10].

This model involves assessing perceptions of disease susceptibility, disease severity, benefits to action, barriers to action, self-efficacy, and cues to action. Asking questions about these areas and incorporating the person's attitudes into the care plan is both recommended and consistent with contemporary views on person-centred care [11].

The Health Belief Model is also helpful in understanding the acceptance of medical treatments. Specifically, there is strong evidence supporting the needs and concerns analysis regarding any specific recommended medical treatment. Adherence to medical therapies is critical to diabetes outcomes and is often suboptimal, and the needs and concerns analysis can help providers identify reasons for this [12].

Providers are encouraged to ask persons with diabetes at the time of medication initiation/review about the degree to which they believe they need the medication, and the extent to which they have concerns about the medication. Use of the following matrix (Figure 1) can be helpful since providers would benefit from knowing the person's attitude prior to offering a prescription.

Difficulties in accepting the diagnosis and treatment recommendations do not necessarily reflect a pathological process. These reactions are based on specific beliefs of the individual, such as someone on higher doses of medication must be in worse shape. Often clinicians are aware of the importance of psychological issues but feel ill-equipped to address them [13].

One way to support providers in addressing emotional issues is to separate the constructs of distress and psychopathology. Distress can be driven by diabetes-specific issues, problems of living, and/or psychopathology. Diabetes-specific distress should be considered to be within the scope of diabetes care providers to address, where problems arising from living-based distress or psychopathology-based distress (such as comorbid psychiatric disorders) are better managed in collaboration with mental health—care providers [14].

Established Psychological Syndromes Related to the Diagnosis of Diabetes

The significance of diabetes-specific psychosocial issues (and comorbid psychiatric disorders) is that they are associated with reduced participation in self-management activities, decreased quality of life, and poorer treatment outcomes that include diabetes complications and early mortality [15]. There are 3 established psychological conditions associated with the lived experience of

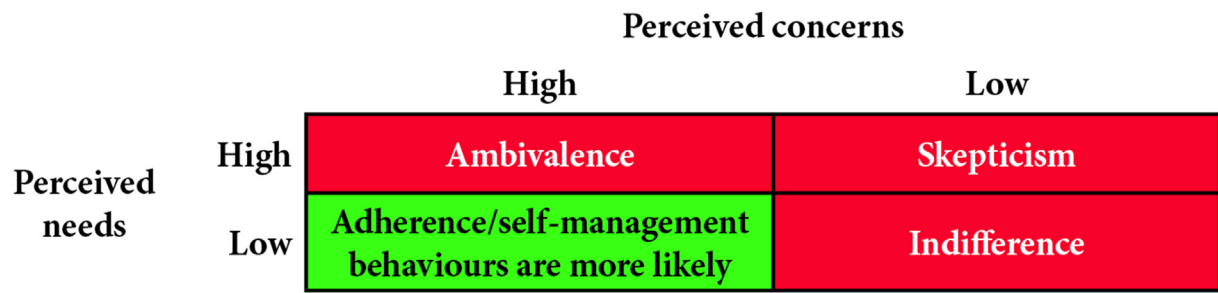


Figure 1. Determining perceived concerns and needs when considering medications.

diabetes that should be monitored and managed: diabetes distress, hesitance to initiate insulin when recommended, and fear of hypoglycemia (for those at risk).

Diabetes distress (DD) refers to the negative emotions and burden of self-management related to living with diabetes. This term is used to describe the despondency and emotional turmoil specifically related to living with diabetes, in particular, the need for continual monitoring and treatment, persistent concerns about complications, and the potential erosion of personal and professional relationships [16,17].

DD has received extensive research over the last decade. A PubMed search (performed August 5, 2022) of the title term “diabetes distress” yielded 532 publications, including 17 systematic reviews. Evidence is clear that DD is common, affecting approximately one-third (36%) of those with diabetes [18].

DD can be measured using validated scales, both for T1D [19] and T2D [17,20]. Additionally, the Problem Areas In Diabetes (PAID) scale has been validated for use with T1D and T2D [21].

DD is a critically important mental health issue to be aware of, and should be part of regular screening [22]. DD is associated with elevated A1C levels, higher diastolic blood pressure, and increased low-density lipoprotein cholesterol levels [23–25]. Furthermore, individuals with higher levels of DD were found to have a 1.8-fold higher early mortality rate, a 1.7-fold increased risk of cardiovascular disease [26], and a lower quality of life [27]. Risk factors for developing DD include being younger; being female; having a lower degree of education; living alone; having a higher body mass index (BMI); lower perceived self-efficacy; lower perceived provider support; poorer quality diet; greater perceived impact of glycemic excursions; and greater number of diabetes complications [28,29].

Hesitancy to initiate insulin when recommended (also called psychological insulin resistance [PIR] or insulin refusal [IR]) refers to a strong negative response from people with T2D to the recommendation from health-care providers that they would benefit from adding insulin to their regimen. This can be a common reaction, particularly for individuals with T2D who may have previously been successfully managed with oral antihyperglycemic agents. Individuals may hold beliefs that the need for insulin is a sign of personal failure in their self-management, or that their illness has become much more serious. Further, many people report fear or anxiety about having to self-administer injections, and have a low level of confidence in their ability to manage their blood glucose with insulin [30,31]. It is important for diabetes providers to be aware of PIR/IR because it is a major factor associated with diabetes treatment inertia [32].

Identifying the attitudes underlying this reluctance is an opportunity for diabetes providers to ask permission to educate about evidence versus perception. Common underlying beliefs are perception of worsening disease severity, the addition of insulin representing a personal failure, perceived loss of control, injection-related anxiety, anticipation of pain, low self-efficacy, and perceived lack of any positive gains [33].

If health-care providers can reframe the beliefs around initiating insulin, and relate it to the pathophysiology of diabetes, health outcomes can improve.

Fear of hypoglycemia (FoH), for those with the potential for hypoglycemia, is a common occurrence and a major behavioural and emotional burden. Hypoglycemic experiences, especially serious or nocturnal episodes, can be traumatic for both individuals and their family members. A common strategy to minimize FoH is compensatory hyperglycemia, where individuals either preventatively maintain a higher blood glucose level, or treat hypoglycemia in response to perceived somatic symptoms without objective confirmation by capillary blood glucose concentrations [34–37]. This process, if left unmanaged, can negatively impact glycemic target achievement, increase the risk of complications, and reduce quality of life.

Summary of Psychological Syndromes Associated With Diabetes

Challenges accompanying the diagnosis of diabetes include adjustment to the illness, participation in the treatment regimen, and psychosocial difficulties at both a personal and an interpersonal level [38,39]. Stress, deficient social supports, and negative attitudes toward diabetes can impact on self-care and glycemic levels [40–44]. Diabetes management strategies ideally incorporate a means of addressing the psychosocial factors that impact individuals and their families. Both symptom measures (e.g. self-report measures of various symptoms) and methods to arrive at psychiatric diagnoses (e.g. structured interviews leading to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision [DSM-5-TR] diagnoses) [45] have been developed. Given that people with diabetes are directly responsible for 95% of diabetes management [46], identifying significant psychological reactions in diabetes is important since depressive symptoms are a risk factor for difficulties with diabetes self-management [47–49] and outcomes, such as early mortality [50,51].

Distinguishing Diabetes Distress From Major Depressive Disorder

While DD, MDD, and the presence of depressive symptoms (that do not meet the threshold for the diagnosis of MDD) do share similar symptomatology, DD has been most shown to have the strongest effect in causing adverse diabetes outcomes [52–54]. Some of the distinguishing features between DD and MDD are summarized in Table 1.

Stigma: Comorbid Diabetes and Mental Health Issues

Stigma—defined as the experience of perceived or direct social judgement (social stigma)—often results in discrimination or exclusion, including in health-care settings (structural stigma). The reported prevalence of social stigma among adolescents and young adults with T1D has been reported to range between 47%–65%. Stigma has been also associated with both hyper- and

Table 1

Comparison of the main features and assessment methods: Diabetes distress vs major depressive disorder

	Diabetes distress	Major depressive disorder
Assessment instrument	Diabetes Distress Scale (DDS) T1D (28 items) DDS-T2D (17 items) DDS-T2D Revised: Core scale (8 items); Sources (21 items)	Patient Health Questionnaire for Depression: PHQ-9 (9 items) [55, 56]
Format	Self-report using ratings from 1 to 6 based on feelings and experiences over the past week	Self-report using ratings from 0 to 3 based on feelings and experiences over the past 2 weeks
Features	DDS-T1D: Powerlessness, management distress, eating distress, negative social perceptions, physician distress, and family/friends distress DDS-T2D: Emotional burden, physician-related distress, regimen-related distress, interpersonal distress DDS-T2D Revised: Management demands, long-term health concerns, hypoglycemia concerns, health-care access concerns, shame/stigma concerns, health-care provider concerns, and interpersonal demands concerns	Vegetative symptoms, such as sleep, appetite, and energy level changes Emotional symptoms, such as low mood and reduced enjoyment of usual activities Behavioural symptoms, such as agitation or slowing of movements Cognitive symptoms, such as poor memory or reduced concentration or feelings of guilt; thoughts of self-harm

hypoglycemia, as well as reports of a reduced sense of well-being and self-efficacy for managing diabetes [57].

Diabetes-related stigma is often associated with visible diabetes management activities (e.g. use of technology, blood glucose checks, verbalized rationale for food choices), leading to coping by avoidance with regard to diabetes care [57].

Approximately half of adults with T2D report experiencing both general diabetes-related stigma, as well as stigma based on weight status [58].

Endorsement of higher degrees of weight-based stigma (i.e. being discriminated against or experiencing prejudice/differential treatment due to body weight) is associated with increased levels of diabetes-specific distress and weight-bias internalization (self-stigma) in adults with higher weight status and/or T2D [59].

Weight-based stigma may also occur in health-care settings and can negatively impact the quality of the patient-provider interactions [59], as well as health outcomes (i.e. risk of elevated cortisol levels, higher blood pressure, decreased glycemic stability) [60]. Health-care providers need to be aware of their own weight-stigma biases and language in their verbal and written communication [58,60].

Training in the use of motivational interviewing techniques to improve the quality of communication around weight-based discussions can be helpful [60,61].

Financial Burden/Financial Distress of Diabetes

Diabetes is a chronic condition associated with significant direct costs (e.g. medications, diabetes supplies, travel to physician and allied health-care provider appointments, food plans recommended for diabetes, etc.), as well as significant indirect costs (e.g. decreased productivity, management of diabetes complications, hospitalizations related to diabetes, etc.). It has been found that treatment participation in diabetes care is affected by these direct and indirect costs [62,63].

People affected by diabetes tend to have lower incomes than the general population. Depending on location, age, household income, medications, and medical devices used, people with T1D in Canada may face an annual out-of-pocket expense of up to \$18,306 for costs associated with use of insulin pumps and continuous glucose monitoring devices. The average out-of-pocket cost associated with managing T1D may be as high as 20% of the total household income. In the case of people with T2D in Canada, the annual out-of-pocket cost can be as high as \$10,014 and can account for up to 16% of the total household income. When there are multiple members of a

household living with diabetes, the impact will be even greater. Depending on the location of the individual in Canada, there can be significant inequality in the share of these costs being covered by provincial/territorial governments, ranging from 0% to up to 100%. For people with T2D, government plans cover <20% of the costs for almost half the provinces and territories in Canada. The Kirby/Keon Senate Study and the Romanow Royal Commission on the Future of Health Care defined the threshold for catastrophic drug costs as 3% of gross income. This threshold was exceeded in 57% of T1D and 45% of T2D representative provincial and territorial scenarios in a recent update by Diabetes Canada, which suggests that these individuals are highly likely to be non-concordant with their prescriber's recommendations.

Similar to these Canadian statistics, data from other countries also illustrate how financial burden can affect the capacity of a person to manage their diabetes. For instance, people taking insulin (a direct cost) report cost-related underuse of this treatment, and are more likely to have higher glycemic levels as a result [64].

A recent study suggested that young adults with T1D who report increased financial burden of diabetes are far less likely to achieve glycemic targets compared to those that do not report financial burden of diabetes. Cost concerns were described as all-consuming and a source of fear and feelings of isolation. Diabetes cost concerns intensified feelings of limitation and unfairness [65].

A US database study showed that people taking insulin with higher levels of treatment participation/self-management had significantly lower adjusted all-cause total costs than people with lower levels of adherence/self-management. This is despite the fact that the direct drug costs were much higher in the adherent group [66].

Multiple studies have established that the increased costs of diabetes therapy are associated with inadequate adherence, which eventually affects outcomes. Given the deleterious effects of cost-related underuse of therapy and the eventual complications of suboptimally controlled diabetes, it is imperative that health-care providers regularly ask about the affordability of therapy [67].

The 2021 National Health Interview Survey by the Centers for Disease Control and Prevention found that about 16.5% of people with T1D and T2D who use insulin rationed its use. The most common forms of insulin rationing included delaying purchase (all insulin users), followed by taking less than required (T1D more so than T2D) [68].

Members of diabetes care teams should inquire about the financial burden the illness is causing and help with access to fiscal

supports available through government and other community programs (where applicable and available).

Psychiatric Conditions in Adults

Individuals with serious mental illnesses—particularly those with depressive symptoms—and people with diabetes share reciprocal susceptibility and a high degree of comorbidity (Figures 3 and 4). The mechanisms behind these relationships are multifactorial, complex, and only partially understood. Second- and third-generation (atypical) antipsychotic agents are used to treat a wide variety of mental health conditions (including as augmentation agents for major depression, OCD, as well as use as mood stabilizers for bipolar disorder in addition to their use in psychotic disorders), but can increase the risk of T2D [69]. Biochemical or physiological changes due to psychiatric disorders themselves also may play a role [70]. Symptoms of mental health disorders and their impact on lifestyle choices and practices are also likely to be contributing factors [71].

The interplay between psychiatric disorders and diabetes is illustrated in Figure 4. The psychiatric disorders listed here principally (but not exclusively) contribute to the risk of developing T2D.

Neurodevelopmental disorders

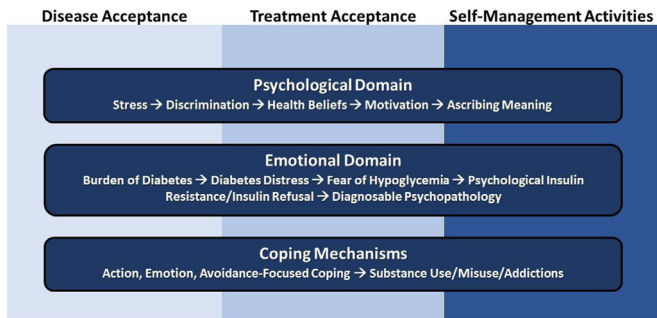
People with intellectual disability or autism spectrum disorder were found to have a 1.6- to 3.4-fold higher age-adjusted odds of having obesity, as well as developing T1D or T2D compared to those without these conditions [72,73].

However, other studies have not established this risk, so these findings should be considered speculative [74].

The prevalence rate of T1D in people with Down's syndrome can be up to 10.6%, which is considerably higher than the general population [75].

A population-based data study in Taiwan found children (average age 8.6 years) diagnosed with attention-deficit/hyperactivity disorder (ADHD) had higher prevalence of T2D than people without ADHD (0.9% vs 0.4%, $p<0.001$). After adjusting for age, sex, index year, geographic location, and body weight, ADHD was significantly associated with a prior diagnosis of T2D (OR=2.75, 95% confidence

Mental Health Issues Arising From the Lived Experience of Diabetes



Diabetes Issues Arising From the Lived Experience of Mental Health Disorders

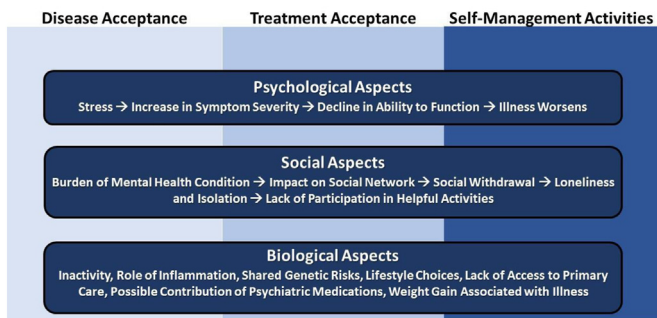


Figure 2. Framework for understanding the intersection of mental health and diabetes.

interval [CI]=1.82–4.16). However, no significant association was observed between ADHD and T1D [76].

Schizophrenia spectrum disorders

A robust finding across many studies is that the prevalence of T2D in people with schizophrenia and schizoaffective disorder is 2- to 3-fold higher than in the general population [77–81].

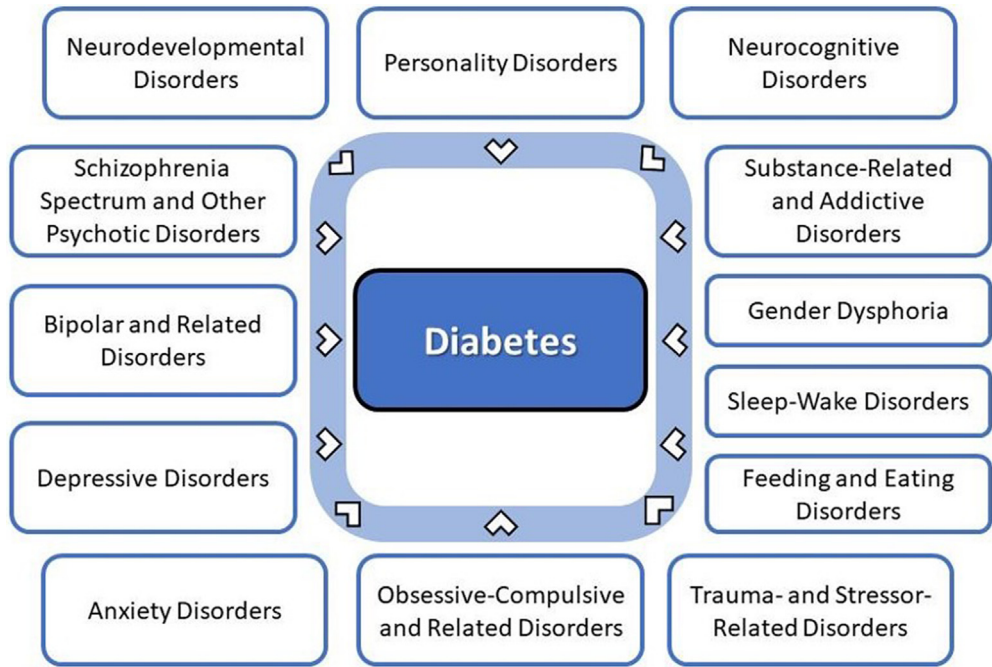


Figure 3. Psychiatric conditions that increase the risk of developing diabetes.

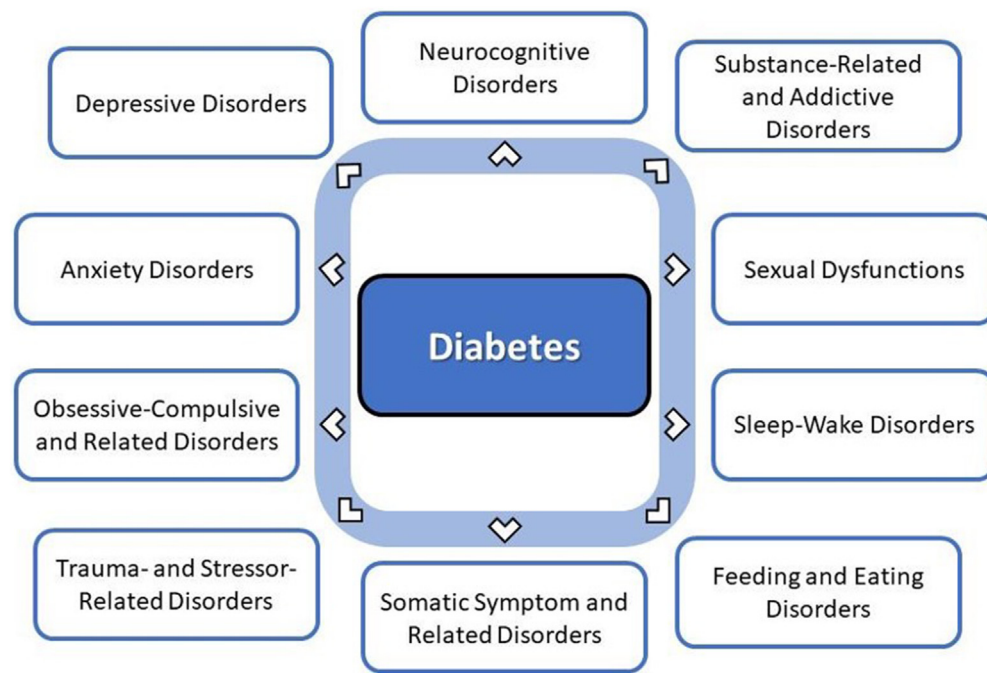


Figure 4. Diabetes increasing the risk of developing select psychiatric disorders.

Schizophrenia and other psychotic disorders may contribute an independent risk factor for diabetes. People diagnosed with psychotic disorders were reported to have had insulin resistance/glucose intolerance prior to the development of antipsychotic medication [82–84]. The Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study found that of the individuals with schizophrenia who participated in the study, 11% had already been diagnosed with diabetes (T1D and T2D combined) [69]. The prevalence of metabolic syndrome was approximately twice that of the general population [85]. Diabetes and schizophrenia together lead to more cardiovascular complications and all-cause mortality compared to people with diabetes alone [86]. Whether the increased prevalence of diabetes is due to the effect of the illness (such as advanced glycation end products), antipsychotic medications, or other factors, individuals with psychotic disorders represent a particularly vulnerable population [87].

Furthermore, repeated relapses in schizophrenia leads to a higher risk of developing diabetes than does the first episode of psychosis. Women also are at higher risk of developing diabetes. Diabetes generally develops 1 to 2 decades after the onset of symptoms in serious mental illnesses, such as schizophrenia [88–92].

Bipolar disorders

The dominant finding from studies suggests that the prevalence of T2D in people with bipolar disorder is 2 to 3 times higher than in the general population [81–84], along with at least double the risk of metabolic syndrome [14,93].

One study demonstrated that over half of people with bipolar disorder were found to have impaired glucose metabolism, which was found to worsen key aspects of the course of the mood disorder [94]. In this same study, impaired glucose tolerance (IGT) was found to be an associative factor (and possibly the precipitating step) in the development of bipolar disorder [94]. While insulin resistance or IGT does not cause bipolar disorder, the associated inflammation may unmask bipolar disorder in people predisposed to developing it. Insulin resistance is associated with a less favourable course of bipolar illness, more cycling between mood states, and a poorer response to lithium [95].

Significant work has gone into unravelling the role of inflammation as an important etiologic factor in mood disorders (more so for bipolar disorder than for MDD) [96].

Depressive disorders

The prevalence of clinically impactful depressive disorders among people with diabetes is approximately 30% [97–99]. The prevalence of MDD is approximately 10% [100,101], which is double the overall prevalence in the general population. The risk of developing MDD increases the longer a person has diabetes [102]. Clinically identified diabetes was associated with a doubling of the number of prescriptions for antidepressants. People with undiagnosed diabetes were not given an increase in prescriptions for antidepressants. This strengthens the hypothesis that the relationship between diabetes and depression may be attributable to factors related to diabetes management [103]. Individuals with MDD have approximately a 40% to 60% increased risk of developing T2D [103–105]. The prognosis for comorbid MDD and diabetes is worse than when each illness occurs separately [106]. MDD in people with diabetes amplifies symptom burden by a factor of about 4 [107]. Episodes of depression in individuals with diabetes are likely to last longer and have a higher chance of recurrence compared to those without diabetes [108]. Episodes of severe hypoglycemia have been correlated with the severity of depressive symptoms [109,110]. MDD has been found to be underdiagnosed in people with diabetes [111].

Studies examining differential rates for the prevalence of depression in T1D vs T2D have yielded inconsistent results [97,112]. One study found that the requirement for insulin was the factor associated with the highest rate of MDD, regardless of the type of diabetes involved [113]. Treatment with metformin may enhance recovery from MDD in T2D [114].

Risk factors for developing MDD in individuals with diabetes are as follows [115–119]:

- Female sex
- Adolescents/young adults and older adults

- Lower socioeconomic status
- Few social supports
- Stressful life events
- Glycemic instability, particularly recurrent hypoglycemia
- Higher illness burden
- Longer duration of diabetes
- Presence of long-term complications

Intensive lifestyle intervention designed to induce weight loss by providing intensive group and individual support for people with T2D with overweight or obesity reduced the risk of depressive symptoms by 15% [120].

Risk factors (with possible mechanisms) for developing diabetes in people with depression are as follows:

- Physical inactivity [121], having overweight, obesity [120], which leads to insulin resistance
- Psychological stress leading to chronic hypothalamic-pituitary-adrenal dysregulation and hyperactivity stimulating cortisol release, also leading to insulin resistance [122–127]
- Hippocampal atrophy and decreased neurogenesis [128]

Some of the mechanisms underlying this association are thought to be autonomic and neurohormonal dysregulation, hippocampal structural changes, inflammatory processes, and oxidative stress [128].

Comorbid MDD worsens clinical outcomes in diabetes, possibly because the accompanying lethargy lowers the energy available for self-care, resulting in lowered physical and psychological fitness, higher use of health-care services, and reduced participation in medication regimens [129,130]. MDD is also associated with increased cardiovascular mortality [131–133]. Treating depressive symptoms more reliably improves mood than it does glycemic stability [134–137].

MDD increases the risk of all-cause hospitalizations for persons treated for diabetes. This increased risk is independent of medication self-management difficulties, or other potential factors [138]. Inadequate social support increases the risk of MDD in people with T2D [139].

There does not appear to be a significant association between the severity of depressive symptomatology and higher A1C levels. However, increased depressive symptomatology was associated with higher A1C values among participants with fewer social supports [140].

Anxiety disorders

Anxiety is commonly comorbid with depressive symptoms [141]. One study estimated that 14% of individuals with diabetes experienced generalized anxiety disorder (GAD), with double this figure experiencing a subclinical anxiety disorder, and triple this figure having at least some anxiety symptoms [142]. Anxiety disorders were present as comorbid conditions in one-third of people with serious mental illnesses and T2D, and were associated with increased depressive symptoms and decreased level of function [143]. A 21-year follow-up study in Australian women suggests that long-term anxiety has been associated with an increased risk of developing T2D across the reproductive span [144].

Alternately, in an epidemiological study with 10-year follow-up, no significant relationship was found between anxiety and development of diabetes-related complications among those with prevalent T2D. This large study showed that anxiety disorders were not associated with a greater risk of developing T2D or the risk of diabetes complications in people already diagnosed with diabetes [145].

A multicentre international study spanning 15 countries looked at people aged 18 to 65 years with T2D treated in outpatient settings who were administered the Mini-International Neuropsychiatric Interview. The study found that female gender, the presence of diabetes complications, longer duration of diabetes, and more glycemic instability were significantly associated with comorbid anxiety disorders [146].

Obsessive-compulsive and related disorders

Individuals with obsessive-compulsive disorder (OCD) have an increased risk of T2D compared with the general population (adjusted hazard ratio = 1.22; 95% CI 1.13–1.31). Compared to people with OCD who do not take serotonin reuptake inhibitors, those taking higher doses of these medications and who had a longer duration of treatment demonstrated significantly diminished risks of metabolic and cardiovascular complications, irrespective of whether they were also taking antipsychotic medications [147].

Stress, trauma, abuse, and neglect

A history of significant psychological adversity or trauma—particularly early in life—increases the risk for developing obesity, diabetes, and cardiovascular disease [148]. Higher BMI, leptin, blood pressure, fibrinogen, and decreased insulin sensitivity have been found in people with significant trauma histories [149]. Post-traumatic stress disorder (PTSD) was found to cause a 40% increased risk of developing T2D, while those with subsyndromal traumatic stress symptoms had a 20% increased risk [150].

Traumatic symptoms may increase the risk for developing diabetes and other cardiovascular illness through reduced physical activity, poorer diet, greater likelihood of tobacco consumption, escalating BMI, and MDD [140].

There is a significant association between psychological trauma and higher A1C values. Adequate social support can attenuate the association between psychological trauma and A1C values [151].

Dissociative identity disorder

No conclusive evidence could be found at the time of writing regarding an association between dissociative identity disorder and diabetes, apart from a case report about hyperglycemia-associated dissociative fugue (organic dissociative disorder) in an older male [152].

Somatic symptom disorders

Non-specific premonitory symptoms can be prodromal signs of illnesses well before actual onset, and this includes T2D [153].

Somatic symptoms prior to the onset of T2D are chiefly related to hyperglycemic states and acute metabolic disturbances, with key symptoms being polyuria, polydipsia, weight loss (sometimes along with polyphagia), and blurred vision. People reporting these symptoms are at increased risk of developing T2D [154].

Feeding and eating disorders

Anorexia nervosa, bulimia nervosa, and binge eating disorder (BED) have been found to be more common in individuals with diabetes (both T1D and T2D) than in the general population [155]. Eating disorders are common and persistent, particularly in females with T1D [156,157]. Elevated BMI is a risk factor for developing both T2D and MDD [158].

Depressive symptoms (not severe enough to be MDD) are highly comorbid with eating disorders, affecting up to 50% of individuals with eating disorders [159].

Night eating syndrome (NES) is characterized by the consumption of >25% of daily caloric intake after the evening meal and waking at night to eat, on average, at least 3 times per week. NES has been noted to occur in individuals with T2D and depressive symptoms. NES can result in weight changes, poor glycemic management, and an increased number of diabetes complications [160].

Up to 20% of people with T2D have an underlying eating disorder, the most common being BED. The prevalence of BED in people with T2D can be up to 25%, which is significantly higher than the 2%–3.5% prevalence seen in the general population.

T1D with disordered eating (T1DE)—often called diabulimia—is an eating disorder that only is seen in people with T1D when they decrease or stop taking their insulin in an attempt to lose weight. Although diabulimia is not a formal diagnosis, it has garnered significant exposure in the media that medical and psychiatric communities acknowledge the term. Offering psychological support is the mainstay of treatment for people with diabulimia. Clinicians should consider each individual's concerns about weight or physical appearance, challenges in adjusting to diabetes, past traumatic experiences, and the value of supportive relationships in order to deliver effective psychological treatment [161–163].

Elimination disorders

People with diabetes commonly experience problems with bladder and bowel control. However, no conclusive evidence is presently available to support a more formal association between elimination disorders and diabetes.

Sleep–wake disorders

The risk of developing T2D is associated with alterations in sleep pattern, including <6 h and >9 h total sleep time, initial insomnia, sleep maintenance problems, obstructive sleep apnea (OSA), and erratic sleep. The elevated risk is comparable to traditional risk factors for T2D, such as having excess weight, having a positive family history, and physical inactivity. Pooled relative risks (RRs) of total sleep time are:

- ≤5 h total sleep time → RR 1.48 (95% CI 1.25–1.76)
- 6 h total sleep time → RR 1.18 (95% CI 1.10–1.26)
- ≥9 h total sleep time → RR 1.36 (95% CI 1.12–1.65)

Poor sleep quality, OSA, and shift work were associated with greater risk of developing T2D, with a pooled RR of 1.40 (95% CI 1.21–1.63), 2.02 (95% CI 1.57–2.61), and 1.40 (95% CI 1.18–1.66), respectively. In comparison, the pooled RRs of living with overweight, having a family history of diabetes, and being physically inactive were 2.99 (95% CI 2.42–3.72), 2.33 (95% CI 1.79–2.79), and 1.20 (95% CI 1.11–1.32), respectively [164].

Sexual disorders

Both T1D and T2D are established risk factors for sexual dysfunction in men [165–168].

There is a 3-fold greater risk of erectile dysfunction (ED) in men with diabetes compared to those who do not have it, likely due to vascular causes [165,169].

Men with diabetes have a lifetime ED prevalence of between 35% and 75% [170].

Women with either T1D or T2D have been found in some studies to have an increased prevalence of sexual dysfunction compared to women without diabetes [167,171,172].

Female sexual dysfunction appears to be more likely due to secondary social and psychological impacts of diabetes rather than the direct physiological consequences [167,172,173].

There is no robust evidence available at this time showing that other sexual or paraphilic disorders have an association with diabetes [174].

Gender dysphoria

An increased prevalence of T1D in transgender children and adults has been described (up to 9.5 times in one study) [175].

However, the correlation of T1D with gender dysphoria appears to exist equally for all transgender populations [176,177].

Various factors may explain the increasing prevalence of T1D in transgender populations, including psychological stress. Clinicians should attempt to look for environmental triggers, such as psychological minority stress (defined as the relationship between minority and dominant values and resultant conflict with the social environment experienced by minority group members) experienced by young people with gender dysphoria. Such sources of stress may affect the pathogenesis and management of T1D. Better clinical outcomes may result with early detection and adequate support.

A Dutch case-control study found an increased prevalence of T2D among transgender populations when compared to both age-matched, non-transgender males and females, though this study did not adjust for other risk factors [177,178].

In a study of the effects of administering gender-affirming hormones on insulin sensitivity in transgender populations, transgender women (those receiving estrogens or anti-androgens) evidenced a reduction in markers of insulin sensitivity; there was no change in transgender men (those receiving androgenic medications) [179].

People with established diabetes undergoing gender-affirming surgeries constitute a special group for whom efforts to effectively manage glucose levels is desirable. Genital surgeries and breast/chest surgeries involve microvascular techniques, and healing, avoidance of infection, functionality, and cosmetic enhancement all have better outcomes with optimization of glycemic stability. Although the diagnosis of diabetes in itself may not be a contraindication for any of these procedures, interprofessional coordination between the surgical team and the clinicians managing the diabetes is advisable [180].

At present, there appears to be no significant relationship between receiving gender-affirming hormone therapy and diabetes risk, or impact on established diabetes. Accordingly, no specific recommendations can be put forth at this time for diabetes screening in transgender populations, regardless of hormone administration status.

Impulse-control disorders

In a study of 50,000 people using data from 19 countries, the authors identified 2,580 cases of adult-onset diabetes diagnosed in individuals aged 21 years and older. After factoring for the presence of comorbid MDD, this study found that, among impulse-control disorders, only intermittent explosive disorder appeared to be an independent risk for diabetes (OR 1.6; 95% CI 1.1–2.1) [181].

People whose weight is in the obese range but who do not have T2D have been found to have somewhat more rigid behaviours along with more compulsive personality traits compared to people with both obesity and T2D, who may demonstrate more impulsivity with their decisions, which may negatively influence diabetes self-management [182].

Substance use disorders

The exact prevalence of substance use disorders among individuals with diabetes is difficult to establish, and the presence of substance use disorders may contribute to unique challenges in this population. Recreational substance abuse is associated with increased rates of hospitalization and readmissions for diabetic ketoacidosis (DKA) [183]. Furthermore, substance abuse and psychosis among individuals with T1D and T2D increases the risk of all-cause mortality [184–186].

Neurocognitive impairment/disorders

T2D is a recognized risk factor for the development of various subtypes of dementia and mild cognitive impairment [187].

MDD is an important risk factor in the development of cognitive impairment in people with T2D, the risk being 2.5 times compared to people with diabetes without MDD. Although certain inflammatory markers, such as C-reactive protein and interleukin 6 (IL-6), are associated with MDD, there is presently no clear link supporting the hypothesis that systemic inflammation mediates the relationship between MDD and dementia [188].

Personality traits/disorders

Personality traits or disorders that put people in constant conflict with others or engender hostility have been found to increase the risk of developing T2D [189]. People with chronic, significantly negative mood states and social inhibition were less likely to follow a healthy diet or to consult health-care professionals when problems developed with their diabetes management. They report more barriers surrounding medication use, diabetes-specific social anxiety, loneliness, and symptoms of depression and anxiety [190].

A population-based, matched cohort study in Denmark found an increased risk of personality disorders (unspecified) in only girls with a diagnosis of T1D. An Australian study confirmed an overall increase in the risk of personality disorders of more than 2-fold following T1D onset, but did not differentiate between sexes [191].

In T2D, impaired personality functioning, as manifested by greater difficulties in personal relationships, mood dysregulation, impulse-control problems, and problems with interpersonal communication were correlated with deterioration in plasma glucose levels during the first 6 months of a standardized disease management program. However, the degree of depressive symptoms did not show this correlation [192].

Neuroticism—the disposition to experience negative emotions—including anger, anxiety, self-consciousness, irritability, emotional instability, and depression is associated with decreased T2D risk, even after controlling for ethnicity, age, depressive symptoms, and BMI.

Type A behaviour is characterized by a constant sense of time pressure, a strong appetite for competition, and the achievement of goals. Extraversion and Type A behaviours do not appear to be significant risk factors for T2D [193–195].

A descriptive cross-sectional study examined 294 participants (104 with T1D and 190 controls). People with high levels of resiliency estimated their degree of diabetes management inaccurately by reporting a high degree of perceived adherence, which was not in keeping with their more objective A1C levels (suggesting overconfidence). With respect to psychological health factors, people who demonstrate more resilience appear to have better overall adjustment, demonstrating fewer emotional problems in managing T1D.

People exhibiting controlling traits (sometimes referred to as “overcontrolled”) with A1C levels indicative of adequate metabolic

management in T1D, however, were found to have the most accurate adherence estimation. Factoring in people's personality styles can help predict participation in self-care recommendations (overcontrolled personalities) and whether their estimation of successful diabetes management is likely to be accurate [196].

Psychiatric Disorders and Adverse Outcomes

Two independent systematic reviews with meta-analyses showed that MDD significantly increases the risk of all-cause mortality among individuals with diabetes compared to those with diabetes without MDD [197,198]. Older adults with diabetes and MDD may be at particular risk [184]. Individuals with bipolar disorder, schizophrenia, or other psychotic disorders, and who have comorbid diabetes, are at increased risk of rehospitalization following medical-surgical admissions [199].

A large prospective cohort study determined that the presence of MDD in people with both T1D and T2D is associated with greater risk of developing chronic kidney disease compared to people without MDD [200].

Comorbid MDD or anxiety are associated with significantly longer hospital length of stay, as well as for adolescents with T1D hospitalized for DKA [201].

A meta-analysis of 11 cross-sectional and prospective cohort studies showed that MDD is significantly associated with higher incidence of diabetic retinopathy in individuals with T2D. However, it is unclear if this is a causal association [202].

Impact on length of hospital stay

Two studies reported an increase in length of stay of close to 4 days in individuals with diabetes and a comorbid mental illness [203,204].

Individuals with T2D are more likely to have a longer length of stay in inpatient mental health settings compared to people with T1D. Those with T2D are likely to have more comorbid conditions, increasing illness severity and necessitating longer hospital stays. More resources are likely to be needed to ensure a safe and seamless hospital discharge. The needs of people with T2D may be different than those with T1D, but it is unclear if the difference in pathophysiology alone accounts for differences in length of stay [205].

Considerations in Pregnancy

Gestational diabetes mellitus: A recent systematic review of the associations between gestational diabetes mellitus (GDM), anxiety, and depression in pregnant individuals found a bidirectional relationship in that anxiety and depression (as well as other stressors, such as a history of childhood sexual abuse and experiencing intimate partner violence) during pregnancy resulted in a higher incidence of GDM [206]. Additionally, a diagnosis of GDM increased the subsequent incidence of anxiety and depressive disorders [207].

Another meta-analysis indicated that the highest levels of depressive symptoms for individuals with GDM occur right around the time the condition is diagnosed [208]. This may be due to the increased psychological strain of having a new diagnosis that could negatively impact pregnancy outcomes and the increased demands in diabetes self-management tasks [207].

However, a population-based study in Canada explored mental illness rates (including anxiety and MDD) in individuals prior to pregnancy, during pregnancy, and postpartum. It was found that, although the prevalence of mental health issues was higher in those with GDM versus those without GDM, there appeared not to be a temporal relationship between GDM and subsequent

incidence of psychiatric diagnoses [209]. Differences were hypothesized to be more likely related to gestational increases in weight [210]. Additionally, there did not appear to be significant mental health differences in those diagnosed with GDM early in pregnancy versus during the typical screening period for GDM in pregnancy [211].

Despite these disparate findings, the consensus is that there is a higher prevalence of psychiatric symptomatology in individuals with GDM and that the symptoms are often underdiagnosed [212].

Optimized pregnancy outcomes can be seen with:

- Increased health-care provider awareness of the potential impact on mental health at diagnosis of GDM
- Regular screening throughout the pregnancy and postpartum period (e.g. potentially at each prenatal visit following the GDM diagnosis)
- Routine referrals for mental health interventions (both traditional therapy and other options)
- Culturally sensitive measures [213–215]

Screening instruments and rating scales, such as the single-item Self-Rated Mental Health Question (SRMHQ), can be helpful in individuals with GDM [216]. A study using mindfulness-based counselling interventions has demonstrated some initial effectiveness in decreasing anxiety in individuals with GDM, but more research is needed to compare this treatment with other evidence-based approaches [217], as well as examine whether lifestyle-based interventions that address weight fluctuations during pregnancy are effective at reducing depression symptoms [218].

Pregestational/pre-pregnancy diabetes: For those individuals with pregestational/pre-pregnancy diabetes (PGM), such as premorbid diagnosis of T1D or T2D, a Canadian-based population study found that there was a modestly higher incidence rate of mental health disorders (including MDD and GAD) in the pregnancy and postpartum periods than for those without PGM [219]. Another study examined the trajectory of depressive and anxious symptoms in a group of individuals with PGM only, and the results indicated that these symptoms remained unchanged from early to late pregnancy [220]. Optimal support for this population would involve:

- Early mental health screening, peer support options, and timely referrals for mental health treatment both during pregnancy and during the postpartum period
- Proactive psychosocial strategies from health-care providers on managing mood and anxiety symptoms prior to potential conception, as well as any individual with PGM during the perinatal period for all individuals with diabetes (regardless of pregnancy status) [221]
- Medical support beyond primarily focussing on reducing the risk of pregnancy complications (e.g. preterm delivery) [222]

Diabetes in pregnancy: GDM, PGM, and postpartum depression: A population-based study examining postpartum depression (PPD) rates in individuals with diabetes in pregnancy (DIP), which includes individuals with either GDM or PGM, found a 1.5-fold increased risk for those with a history of MDD prior to pregnancy [223]. Another recent meta-analysis replicated the association between those with DIP and PPD but cautioned that when those with GDM versus PGM were compared, the individuals with GDM were the ones more at risk for developing PPD [224]. Another study found that although individuals with DIP all had significant levels of distress, the highest level of negative pregnancy outcomes was found in those with PGM and

negative psychological outcomes were found in individuals with GDM [225].

Clinically significant DD (upwards of 58% in one study) can be present even if no diagnosable psychiatric conditions were found in individuals with DIP [212].

The SARS-CoV-2 (COVID-19) pandemic can also worsen symptoms. One study of individuals with DIP found that both anxiety and depression severity were high (approximately 80% and 60%, respectively), which is higher than reported prevalence rates in pregnant individuals without diabetes during COVID-19 [226]. In addition, 2 factors (unintended pregnancies and lower social support) were associated with higher levels of anxious and depressive symptoms for individuals with DIP. This may also be related to the effects of social isolation during the pandemic based on fears of a more severe COVID-19 infection for those with diabetes [226], which may improve with diabetes education and medical support that focuses on the emotional burden of DIP and diabetes regimen-related concerns [227].

Optimal care for people with GDM and PGM would involve:

- Screening practices that include an assessment of one's history of MDD or significant depressive symptoms prior to pregnancy in addition to current mental health functioning
- Targeted diabetes education and tailored medical treatment plans for the different populations of pregnant individuals with GDM and PGM, which may have differing psychological trajectories [225,228]

Individuals with pregnancy in diabetes have a higher prevalence of various psychiatric conditions (particularly mood and anxiety disorders), which are often underdiagnosed [212]. One study found that higher levels of medical support experienced by individuals with DIP significantly reduced levels of anxious and depressive symptoms and may buffer the negative outcomes [229].

Children and Adolescents

T1D in children and adolescents

For children and adolescents, there is a need to identify mental health disorders and psychosocial issues associated with T1D in order to be able to institute early interventions. Children and adolescents with T1D have significant risks for mental health issues, including depressive symptoms, anxious symptoms, altered feeding and eating, and disruptive behaviours [230–232]. These risks increase significantly during adolescence [233,234] and into young adulthood. Studies have shown that mental health disorders predict difficulties with diabetes management and glycemic variability [235–238] and worsen medical outcomes [47,239–241]. The more glycemic levels are not within target range, the probability of mental health issues also increases [242]. Adolescents with T1D have been shown to have rates of DD that are comparable to adults with T1D [16].

The presence of psychosocial symptoms and diabetes self-management issues in children and adolescents with T1D are often strongly affected by caregiver/family distress. It has been demonstrated that while parental/caregiver psychological issues are often related to psychological adjustment issues and glycemic variability [243–249], they also can negatively impact perceptions of the child's ability to manage diabetes [250].

An initial study of parental self-report suggests that the use of hybrid closed-loop systems for insulin delivery in children may help ameliorate some parental FoH and poor sleep quality symptoms that may lead to improved glycemic stability for the child [251]. Maternal anxiety and depressive symptoms are often

associated with higher glucose instability and school absenteeism in younger adolescents with T1D, and a reduction in positive mood and motivation for their own diabetes care in older teens [252,253].

Eating disorders in pediatric diabetes

Ten percent of adolescent females with T1D meet DSM-5-TR criteria for eating disorders [45], compared to 4% of their age-matched peers without diabetes [254]. Eating disorders are also associated with less metabolic stability, in addition to an earlier onset and faster progression of microvascular complications [157]. Adolescent and young adult females with T1D who have difficulty achieving and maintaining glycemic targets—particularly if insulin omission is suspected—may also have problematic eating behaviours (including subclinical disordered eating behaviours and eating disorders).

Individuals with disordered eating behaviours may require different management strategies to optimize glycemic stability and prevent microvascular complications [254]. T1D in adolescent females appears to be a risk factor for development of a formal eating disorder, both in terms of an increased prevalence of established eating disorder features, as well as purposeful weight control through diabetes-specific means, such as insulin omission or restriction (often called “diabulimia”), significant carbohydrate restriction, and disinhibited eating when experiencing symptoms of hypoglycemia [255,256].

Other considerations in children and adolescents with T1D

The prevalence of anxiety disorders in children and adolescents with T1D in one study was found to be 15.5%, and mood disorders was 3.5%, with one-third having a lifetime prevalence of at least one psychiatric condition [257]. Another study of children with early onset (<5 years) of T1D and a diabetes duration of at least 10 years found elevated GAD symptoms in about 10% of the adolescent population, which was associated with both diminished general and diabetes-specific functioning [258]. The presence of psychiatric disorders was related to elevated glycemic levels and a lowered health-related quality of life score in a general pediatric quality of life inventory study [257]. In the diabetes mellitus—specific pediatric quality of life inventory, children with mental health disorders revealed more symptoms of diabetes, higher treatment barriers, and lower self-management behaviours than children without mental health disorders [257]. Adolescents with T1D ranked school as their number 1 stressor, their social lives as number 2, and having diabetes as number 3 [259].

Prevention and intervention in children and adolescents with T1D

Children and adolescents with T1D, as well as their families, benefit from screening for mental health disorders and psychosocial issues (also referred to as person-reported outcome measures [PROMs]) at the time of diagnosis, as well as at regular intervals [260]. Given the prevalence and impact of mental health issues, psychosocial screening of children and adolescents with T1D is just as important as screening for microvascular complications [261,262].

A promising addition to traditional in-person clinic visits is the use of telehealth services, which increased out of necessity during the COVID-19 pandemic but may be a lasting option. Online meeting rooms, such as virtual group appointments or digital health interventions (e.g. mHealth apps) demonstrate improvements in diabetes-related distress [263] and self-efficacy [264], as well as parental ratings of quality of life [265]. In order to prepare for the transition from pediatric to adult diabetes care, a transition plan should be initiated at around 12 years of age so that services (including diabetes education, transition readiness assessments,

setting transition goals, etc.) can occur early enough to prepare adolescents and their families [266,267].

Psychological interventions, which include cognitive-behavioural as well as other complementary psychotherapy approaches (e.g. art therapy), have a positive impact on mental health of children and adolescents with T1D and their families [268, 269], including overall well-being [270], perceived quality of life [271,272], and reduction in depressive symptoms [269,273]. Psychosocial interventions can positively affect glycemic stability [274,275]. Other studies have demonstrated that psychological interventions can increase both diabetes self-management behaviours and frequency of in-target glycemic levels, as well as overall psychosocial functioning [276,277].

T2D in children and adolescents

Mental health concerns play a significant role in children and adolescents with T2D across all ethnic groups, particularly depression [278] and binge eating behaviours [279].

These psychosocial issues, along with disruptive sleep habits [280], are associated with lower diabetes self-management success and quality of life [231,281].

Rates of reported depressive symptoms ranged from 15%–36% in youth with T2D and have been found to be highest among females and youth with fewer social support as well as a family history of T2D [282]. Moderate-to-severe depression rates in young adults who were diagnosed with T2D in childhood have also been associated with high levels of DD [283].

Presently, there is a lack of high-quality research data on the impact of MDD and depressive symptoms in youth with T2D. The majority of the studies in this population do not assess for a formal diagnosis of MDD, although depressive symptoms are common in youth and more likely to be associated with adverse diabetes outcomes [282].

Considerations for Older People With Diabetes

T2D does not appear to be more common in geriatric-aged people with psychiatric conditions than similarly aged controls. The risk of developing a dementing illness in people is increased in those who have MDD (hazard ratio [HR] 1.83), T2D (HR 1.20), or both (HR 2.17) [284]. The presence of depressive symptoms in older adults with T2D is associated with increased mortality risk [285].

Older individuals experience a greater disease burden due to diabetes and are more likely to have multimorbidity and experience the adverse outcomes, including severe complications like diabetic neuropathy, nephropathy, retinopathy, or vasculopathy, which are seen in up to 20% of older people with T2D [286].

Totalling the PHQ-9 scores for the symptoms of diminished interest, sleep changes (increase or decrease), psychomotor changes (retardation or agitation), and diminished concentration symptoms to 4 or above has an enhanced specificity for detecting MDD in older people [287].

Overweight status, limited physical capabilities, and reduced activity level, along with the presence of more than 2 comorbid illnesses, were risk factors for MDD in older people with diabetes mellitus. In a case–control study done in China, metformin was found to reduce the risk of developing MDD in older people with diabetes [288].

Access to ongoing psychosocial interventions through technological platforms may potentially minimize diabetes complications and improve health-related outcomes [289,290]. Telehealth-related technologies can be effective in improving the clinical, behavioural, and psychosocial outcomes in people with diabetes above 50 years of age.

Prescription choices for older people with diabetes mellitus and MDD should factor in antidepressants with a higher likelihood of safety and tolerability [291].

Recreational Substance Use

Recreational substance use is common in Canada. Among the general population, the prevalence of consumption is: [292,293]

- 15% for problematic alcohol consumption
- 11% for daily tobacco
- 4.3% for daily cannabis
- 3% for opioid use for recreational/non-medical purposes
- 2% for cocaine use
- 0.2% for methamphetamine use

Most studies find that prevalence of substance use among people with diabetes mirror the prevalence rates found in people without diabetes. Excess substance use leads to physical health complications in major organ systems leading to increased morbidity and premature mortality. This makes substance use among people with diabetes of particular concern because of the additive health risks.

Evidence suggests that substance use has a complex effect on diabetes. In people without diabetes, consumption of tobacco or alcohol increases the risk of developing diabetes [294,295]. In persons living with diabetes, substance use is linked with adverse health outcomes, particularly complications of diabetes [296,297]. These observations can be partly explained by the deleterious effects of the substance directly on glucose homeostasis. There are indirect effects of substance use on one's capacity to perform health-maintaining behaviours that are needed for prevention and self-management of diabetes [298].

Substance use and risk for developing diabetes

A large body of literature suggests that substance use is associated with greater risk for the development of T2D [294,295]. However, there is no evidence at present to suggest that substance use plays a role in the development of T1D, as many cases appear in childhood/adolescence prior to substance exposure.

Tobacco: A meta-analysis of 25 cohort studies found an increase in the relative risk for new-onset diabetes among people who smoke cigarettes (RR 1.44, 95% CI 1.31–1.58). The potential risk appears to be dose-dependent, with smokers using ≥ 20 cigarettes per day showing the highest risks [294].

The heightened risk for heavier smokers has a number of hypotheses, including the stimulant effects of nicotine leading to insulin resistance, the potentially toxic effects of substances (e.g. heavy metals found in tobacco) on the pancreas, and the positive correlation between the number of daily cigarettes smoked and abdominal obesity [299].

Quitting smoking, while having a myriad of health benefits, paradoxically appears to be associated with a transient increase in the risk of new-onset diabetes. In the first 2–6 years after quitting, the hazard ratio for new-onset diabetes in successful quitters is higher than with active smokers (HR 1.22; 95% CI 1.12–1.32). The risk is higher in people who gain weight after quitting smoking, with those who gain the most weight (>10 kg) having the highest risk. This risk peaks 5–7 years after quitting and declines over time [300]. The modest elevation in risk for new onset of diabetes after quitting does not negate the benefits of quitting smoking on cardiovascular health, as evidenced by a decrease in the incidence of acute coronary events and death [300].

Alcohol: On a cross-sectional level, the lowest risk for new-onset diabetes appears to be among those with moderate alcohol consumption. People who consume about 1 standard drink per day (10–14 grams of alcohol) showed an 18% reduction in relative risk compared to abstainers. The relationship was curvilinear, with highest risks observed in those with alcohol consumption over 4.5 standard drinks per day and people who abstain [295].

Events such as acute pancreatitis that follow heavier episodes of alcohol consumption are an established risk factor for new-onset diabetes [301].

Some studies suggest that the type of alcohol consumed may also influence the health benefits, with wine conferring greater risk reduction benefits than beer or spirits [302]. In the absence of high-quality literature linking alcohol consumption to reduced risk of diabetes, most scholars suggest that the purported benefit from alcohol consumption, if any, may be modest at best and conclusions from observational studies may have been exaggerated or biased by methodological factors such as the inclusion of people who quit alcohol due to health reasons being included in the abstainers' group (often referred to as "sick abstainers") [295].

Other substances: Compared with tobacco and alcohol, there is less evidence regarding the association of cannabis use and new-onset T2D. Two cross-sectional studies actually detected a modest reduction in the prevalence of obesity and diabetes among people who use cannabis [303,304], while 2 cohort studies reported conflicting results; one showing an increase in risk for pre-diabetes among those who consume cannabis that was not observed in the other [305,306].

Limited evidence exists regarding the risk of T2D in people who use opioids for non-medical purposes. Prescription opioids do not appear to be associated with an increase in the risk of new-onset diabetes [307].

Nevertheless, people with opioid use disorders who receive opioid agonist therapy (OAT) with methadone appear to be at a higher risk for developing diabetes compared with those receiving naloxone-buprenorphine [308].

Adverse effects of substance use on diabetes-associated comorbidities and complications

It is well-established that regular, sustained substance use is associated with unfavourable health outcomes. Among persons with diabetes, those with heavy substance consumption patterns exhibit higher rates of diabetes-related morbidity and earlier mortality [309]. The deleterious effects of substance use vary with age and type of diabetes. In people <30 years, most of whom have T1D, complications such as DKA and hypoglycemic events have been observed to be more common in those who consume substances [296,297]. In older people >30 years with T2D, micro- and macrovascular complications are associated more commonly with substance use [310,311]. The propensity of substances to worsen glycemic stability has been attributed to a direct effect on glucose homeostasis and an indirect effect mediated through diminished levels of diabetes self-management [298].

T1D

Cigarette smoking can interfere with glucose homeostasis among persons with T1D. Smoking is linked with greater odds of hypoglycemic events (OR 2.4; 95% CI 1.30–4.40) and greater variability in blood glucose levels [312].

Compared with non-smokers, smokers spent greater time in either hypoglycemic or hyperglycemic states and less in normoglycemia [313].

Hypoglycemia could be partly explained by a co-consumption of cigarettes and alcohol [314] and by inadequate diabetes self-management found among smokers [315].

In persons with T1D, alcohol reduces plasma glucose levels and interferes with hypoglycemic counter-regulatory mechanisms. The onset of hypoglycemia usually appears 6–8 hours following alcohol consumption. The sedating effect of alcohol may also reduce the awareness of hypoglycemia. Together, these effects of alcohol can increase the risk of severe hypoglycemic events [296].

Alcohol use among people with T1D can interfere with disease self-management and lead to missed doses of insulin [297], which may explain the greater risk of DKA among young people with T1D who misuse alcohol [183,316].

Managing alcohol consumption can be a challenge for young people in an environment that promotes alcohol use, such as post-secondary institutions [317].

Stimulants (e.g. cocaine, methamphetamine) are linked with hyperglycemic events though their stimulation of sympathetic transmission. Elevated catecholamine levels counter the effects of insulin, and, in combination with missed doses of insulin, can lead to DKA [318].

There is limited evidence available currently in the way of studies regarding the effect of cannabis use on people with T1D. Cannabis can interfere with glucose homeostasis indirectly via its appetite-promoting tendencies, and directly by an effect on gastrointestinal motility that can lead to vomiting. Cannabis may also interfere with self-management routines [319].

A recent study using the T1D Exchange Clinic Registry found that adults with T1D who reported moderate cannabis consumption had 2.5-fold greater risk for DKA [320].

Frequent events of hypoglycemia, hyperglycemia, and/or DKA that are related to substance use take a substantial toll on the health of young people with T1D. This group was associated with a 4-fold earlier mortality rate compared to the general population [321], with substance use being identified as a significant contributor [322,323].

T2D

A recent meta-analysis of longitudinal observational studies confirmed the deleterious effects of smoking on the health of people with diabetes. Compared with people who have never smoked tobacco, smoking had greater relative risks for early mortality (RR 1.55; 95% CI 1.46–1.64), coronary heart disease (RR 1.51; 95% CI 1.41–1.62), stroke (RR 1.54; 95% CI 1.41–1.69), and peripheral artery disease (RR 2.15; 95% CI 1.62–2.85) [310].

People who had quit smoking showed lower levels of risk for cardiovascular events and death compared with active smokers, but still had higher rates compared with lifetime non-smokers [310].

Data analysis by gender suggests that women who smoke have a greater risk for cardiovascular events and death compared with men. However, men and women appear to benefit equally from quitting [324].

The elevated risk for cardiovascular events and death associated with smoking can be attributed to its direct effect on insulin resistance, leading to worsening of glycemic levels as well as the propensity for atherosclerosis [325]. It is also suggested that smoking is associated with more difficulties in diabetes self-management practices [326].

The health effects associated with alcohol drinking among people with diabetes may follow a curvilinear relationship [311]. People who drink 1 standard drink per day appear to have the lowest risk for cardiovascular events, even lower than people who abstain. People consuming over 2 drinks per day have an associated greater risk than abstainers. The associated cardiovascular risk increases linearly with every drink beyond 2 drinks per day [327].

Similar to the association with the risk of developing T2D, scholars have questioned whether moderate alcohol consumption (1 standard drink per day) has a true protective cardiovascular effect or that the results are biased by inclusion of “sick abstainers” in the non-drinking group [328].

Alcohol is thought to be particularly detrimental to health when consumed in higher quantities. People diagnosed with alcohol use disorder experience worse outcomes compared to those without this condition. This includes higher odds ratio for myocardial infarction (OR 1.62; 95% CI 1.06–2.47) and cerebrovascular accident (OR 1.35; 95% CI 0.92–1.98) [309]. Heavy drinking is also linked with negative diabetes outcomes, such as increased odds for diabetic neuropathy (OR 1.27; 95% CI 1.10–1.46) (27%) [309].

Similar to smoking, the effects of alcohol consumption in higher quantities appear greater among women relative to men with diabetes in terms of mortality [327,329].

Engaging in heavier alcohol consumption appears to be particularly detrimental to the health of individuals treated with insulin, who are associated with a 6- to 10-fold greater risk for alcohol-related mortality compared with groups without diabetes matched for alcohol consumption [329].

Beyond the direct effect on glucose homeostasis, alcohol use was also found to predict lower adherence with diabetes self-management behaviours [298].

There is limited evidence that alcohol use disorder may interfere with participation in structured self-management diabetes education programs [330].

Information regarding the effect of other substances such as opioids, cannabis, and stimulants on diabetes-related complications is limited at this time. However, one study found a greater odds ratio for early mortality in people with diabetes who use cocaine (OR 1.61; 95% CI 1.21–2.14) and illicit opioids (OR 1.35; 95% CI 1.02–1.8) [309].

A study examining US Medicaid records found a greater rate of opioid prescriptions among people with diabetes compared to those without (61% vs 31%) [331], which may be related to conditions such as diabetic neuropathy. Dealing with comorbid chronic pain may distract both providers and people with diabetes from focusing on the management of diabetes [332]. This may partially explain why the use of prescribed opioids has been linked with poorer quality of diabetes care, including reduced lipid and glucose monitoring [333].

There is limited evidence of the effect of long-term OAT on persons with diabetes. Stabilization of the opioid use disorder may improve the capacity for diabetes self-management and explain the improvements in A1C seen with buprenorphine/naloxone treatment [334].

Nevertheless, the use of methadone as OAT has been linked with an enhanced preference for sugary or low nutritional quality foods that may promote weight gain and worsen diabetes management (Table 2).

Considerations for reducing harm from substance use

Tobacco: Systemic screening for and documentation of smoking status is widely endorsed in most health-care settings, and smoking cessation is promoted as a key activity for people with diabetes (i.e. ABCDESS: A1C, blood pressure, cholesterol, drugs, exercise, self-management/screening/stopping smoking) [241].

Individuals who smoke tobacco should be offered support for quitting. Brief interventions for smoking (even lasting just 2–10 minutes) include psychoeducation on the benefits of quitting, assessing the level of interest in making a quit attempt, and responding appropriately with treatment or referral for treatment (5As: Ask, Advise, Assess, Assist, Arrange).

Table 2

Recreational substance use and the effects on diabetes

Recreational substance	Risk for developing diabetes	Health effects in people with T1D	Health effects in people with T2D
Tobacco cigarettes	Increased [300]	Greater glucose variability Hypoglycemia	Coronary heart disease Stroke Peripheral artery disease [310]
Alcohol	Increased when drinking over 4 drinks per day [295]	Hypoglycemia Reduced hypoglycemia awareness [296]	Hypoglycemia Reduced hypoglycemia awareness in people treated with insulin or sulphonylurea Cardiovascular risk increases linearly with every drink beyond 2 drinks per day Mortality risk increases when heavy drinking occurs in people treated with insulin [329]
Cannabis	Equivocal [305,306]	DKA [320]	Not available
Opioids	Not available	Not available	Not available
Stimulants	Not available	Hyperglycemia DKA [318]	Increased risk of earlier mortality [309]

For those not ready to quit, a brief intervention can help individuals identify the relevance of quitting to support favourable diabetes and health outcomes. Elucidation of the existing barriers and identification of opportunities for change can be achieved by discussing the 5Rs of smoking: **R**elevance, **R**isk, **R**eward, **R**oad-blocks, **R**epetition. Brief interventions, such as the 5As and 5Rs, increase the odds of quitting successfully [336].

The resources for brief tobacco interventions are made available by the World Health Organization (https://apps.who.int/iris/bitstream/handle/10665/112835/9789241506953_eng.pdf).

People with T1D and T2D have similar success rates to populations without diabetes when using approved treatment for smoking cessation. Quitting success is enhanced when individuals attempt to quit with approved pharmacotherapy (e.g. nicotine replacement therapy, varenicline, bupropion, etc.) combined with behavioural counselling [337,338].

Alcohol screening and brief interventions: Systematic screening for alcohol use in health-care settings can increase identification and timely treatment of alcohol misuse. The most common screening tool for alcohol is the Alcohol Use Disorders Identification Test (AUDIT-C). AUDIT-C screens for the frequency and intensity of alcohol consumption [339].

Scores range from 0–12 and a positive screen is 3 or 4 and above for women and men, respectively. Those with positive screens should be offered a brief intervention for alcohol reduction, which consists of psychoeducation on the risks of excess drinking and the benefits of reducing/quitting for health delivered in a patient-centred manner using a motivational interviewing approach [340].

These brief interventions are called SBIRT (**s**creening, **b**rief **i**ntervention, and **r**eferral for treatment), and have been shown to be effective for both the general population and people with T1D and T2D [340,341].

Recently, SBIRT has been delivered through the internet and found to be effective in reducing alcohol consumption among college students with T1D [342].

Persons who are unable to make changes to their alcohol use on their own should be offered a referral to specialized addiction treatment. Treatment consisting of addiction counselling and anti-craving pharmacotherapy is the mainstay of care for people with an alcohol use disorder. Approved anti-craving pharmacotherapy (e.g. naltrexone, acamprosate, or disulfiram) increase the success of addiction psychosocial counselling and are safe for use in people with diabetes.

The recent 2022 Canadian Low-Risk Alcohol Drinking Guidelines: Final Report from the Canadian Centre on Substance Use and Addiction (CCSA) urges Canadians to “rethink the way we drink”

and reduce alcohol consumption to limits lower than those published in their 2018 guidelines. The lowest risk for health-related harm was seen in people who consume 2 or less standard drinks per week [343].

Alcohol consumption at a level of 3–6 standard drinks per week is associated with increased risk for cancer, and 7 drinks per week or more increases cardiovascular risk [310,344].

Cannabis: Legalization of cannabis in Canada in 2018 led to an increase in use amongst all age groups, but young people in particular. Legalization was followed by a position paper in 2019 from Diabetes Canada [345]. For persons with diabetes who choose to use recreational cannabis, potential harm can be reduced by following recommendations made by Canada's Lower-Risk Cannabis Use Guidelines [346]. These recommendations include avoiding cannabis use during adolescence, avoiding high-potency THC products (i.e. concentrates) and synthetic cannabis (e.g. “spice”), avoiding smoking cannabis to protect lung health, and avoiding daily/regular use. Following these recommendations may also reduce diabetes-related adverse effects that have been associated with cannabis, such as poor diabetes self-management, glycemic instability, and DKA [345].

Individuals who are unable to decrease their cannabis use on their own should be offered a referral to specialized addictions treatment. To date, there are no approved medications for the treatment of cannabis use disorder, and addiction counselling is considered the mainstay of care [347].

Most recently, there is some evidence to suggest that glucagon-like peptide-1 (GLP-1) receptor agonists may play a beneficial role in the treatment of a number of substance use disorders, including tobacco and alcohol. Since this class of medications is currently approved for use in people with T2D, it may be helpful in the treatment of persons with co-existing T2D and substance use disorders [348], however, conclusive evidence is lacking at this point in time.

Suicide

A review article found that people with both T1D and T2D had increased rates of suicidal thoughts, suicide attempts, and completed suicide compared to the general population [349].

T1D: A systematic review and meta-analysis of more than 50 studies reported that individuals with T1D have a risk of completed suicide 2.25 times that of those without T1D [350].

T2D: People with newly diagnosed T2D had a rate of suicide attempts of almost 10%, which is twice the rate estimated in the

general population. The rate of past suicide attempts in individuals with diabetes and comorbid depression was reported at over 20% [351].

Adolescents and young adults: A study of Canadian adolescents and adults reported that individuals with T1D had a higher lifetime prevalence of suicidal ideation (15.0%) as compared with people without T1D (9.4%) [352].

A thorough literature review with practical recommendations for providers (e.g. staff training, screening implementation, brief interventions, prevention efforts, and education and support tools) for reducing suicide risk in youth and young adults with T1D is available [353].

COVID-19 and Mental Health

Acute infections

The COVID-19 pandemic involved the institution of unprecedented public health measures, depleted an already overburdened health-care system, and set off highly polarizing misinformation wars. Among the plethora of other physical and psychological symptoms and the impact on lifestyle-related behaviours, COVID-19 appears to be a causative factor in the development of both T1D and T2D [354]. A meta-analysis reviewing over 3,700 individuals found a pooled proportion of 14.4% for newly diagnosed diabetes in people recently hospitalized with COVID-19 infections [355]. The CoviDiab Registry (covid diab.e-dendrite.com) is a project developed by researchers and clinicians to record features of new-onset, COVID-19–related diabetes as well as severe metabolic disturbances in pre-existing diabetes (i.e. DKA, hyperosmolarity, severe insulin resistance).

A bidirectional relationship appears to exist between COVID-19 infections and diabetes [356].

A United States Department of Veterans Affairs study of over 180,000 participants with no prior diagnosis of diabetes and who tested positive for COVID-19 found that beyond the first 30 days of infection, survivors demonstrated increased risks and burdens for diabetes, and an increased use of antihyperglycemic agents [357].

Pre-morbid diabetes is also associated with an increased risk of COVID-19 complications. Outcomes for people who had COVID-19 and diabetes but were without other comorbidities found an increase in severe complications, including pneumonia, excessive uncontrolled inflammation, a hypercoagulable state, and escalated glucose metabolism dysregulation. The authors concluded that diabetes was a risk factor that would lead to rapid progression of symptoms and more severe negative health outcomes of COVID-19 infections [358].

Long COVID

Post-infection syndromes are common with other viruses, such as Epstein-Barr, cytomegalovirus, West Nile, and enteroviruses, and we must now add COVID-19 to the list. Debilitating symptoms that persist well past the acute phase of a COVID-19 infection have been reported with increasing frequency in the general population [359].

COVID-19 infections can be divided into 3 phases: acute (lasting up to 4 weeks), sub-acute (lasting between 4 and 12 weeks), and chronic (starting after 12 weeks). It is known by a variety of names, including post-acute COVID-19 syndrome (PACS), post-COVID condition, post-acute sequelae (PASC) of COVID-19, and—an emerging favourite—long COVID, with those who experience it identifying themselves as “COVID long-haulers” [360].

While there is currently no standardized definition of long COVID, it can be at least conceptualized as the lack of a return to pre-infection state of health by 4–12 weeks (depending on the definition used). It appears to be triggered by a reaction to the virus that either does not resolve or causes new symptoms to appear after the acute phase of exposure to the virus.

Lacking formalized criteria for the diagnosis, pathognomonic symptoms, or definitive laboratory findings, long COVID involves a prolonged recovery that includes persistent physical and psychological symptoms. Long COVID has no set pattern to the development of symptoms and a variable course. Those who experience it can have difficulty convincing others of their struggles with serious and persistent symptoms.

The risk of developing long COVID involves only an *exposure* to the virus and has not yet been found to be related to the severity of the acute infection (except for an intensive care unit admission, which is a predictive factor on its own). End-organ damage in the acute phase and pre-existing illnesses (especially respiratory) appear to increase the risk. Other factors found to increase risk are advanced age, high BMI, and certain ethnicities [361].

In the general population, females outnumber males by about 3 to 1 in experiencing long COVID symptoms. Being unvaccinated appears to approximately double the risk of developing long COVID as well [362,363].

The most commonly reported symptoms of long COVID are dyspnea, fatigue, cognitive impairment, and anxious and depressive symptoms, which can significantly impair the ability of individuals who also have diabetes to participate fully in diabetes self-management behaviours [364,365].

In summary, diabetes is associated with an increased risk of COVID-19 complications [357]. COVID-19 vaccinations reduce the risk of developing long COVID [362]. The symptoms of long COVID significantly reduce an individual's ability to manage diabetes [359] and overlap with prominent symptoms in MDD and GAD [366].

Screening and Assessment of Mental Health in Diabetes

Mental health symptoms

Because of the prevalence of DD and psychiatric comorbidity, and the negative impact that these factors have on glycemic management, early morbidity, and quality of life, it is recommended that individuals with diabetes be regularly screened with validated questionnaires or clinical interviews. The available data do not currently support the superiority of any particular depression screening tool [367]. Currently available screening instruments have a sensitivity of between 80% and 90% and a specificity of 70% to 85% [367]. Scales that are in the public domain are available at www.outcometracker.org/scales_library.php. Patient Health Questionnaire (PHQ-9) screeners are available at www.phqscreeners.com. PHQ-9 (for MDD) scores of ≥ 10 and Generalized Anxiety Disorders (GAD-7) scores ≥ 10 have been associated with increased diabetes complications [368,369]. The DD scales can be accessed through <https://diabetesdistress.org>.

Screening instruments fall into 3 categories:

- Diabetes-specific measures, such as the Problem Areas in Diabetes (PAID) Scale or the Diabetes Distress Scales (DDS), including the T1D scale or either version of the T2D scales [370,371].
- Quality-of-life measures and function, such as the WHO-5 screening instrument [372] and Sheehan Disability scale.

Table 3

Features of psychological treatments that can be integrated into diabetes treatment

Cognitive behaviour therapy
Cognitive component: → Record keeping to identify distressing automatic thoughts → Understanding the link between thoughts and feelings → Learning the common “thinking errors” that mediate distress (e.g. all-or-nothing thinking, personalization, magnification, minimization, etc.) → Analyzing negative thoughts and promoting more functional ones → Identifying basic assumptions about oneself (e.g. “unless I am very successful, my life is not worth living”) and being encouraged to adopt healthier ones (e.g. “when I am doing my best, I should be proud of myself”)
Behaviour component: → Strategies to help get the person moving (behavioural activation) → Scheduling pleasant and meaningful events → Learning assertive and effective communication skills → Focusing on feelings of mastery and accomplishment → Learning problem-solving strategies → Exposure to new experiences → Shaping behaviours by breaking them down into smaller steps to develop skills
Motivational interviewing
→ Establish a change-based relationship that is based on bond, task and goal alliance → Demonstrate nonjudgemental curiosity and comfort with ambivalence → Use the Ask, Listen, Summarize, Invite framework to normalize the person’s experience, establish collaboration, seek the person’s ideas, and then ask permission to provide your ideas
Acceptance and commitment therapy
→ Focus on acceptance of present-moment experiences and defusing from thoughts (choosing not to be guided by present cognition) → Commitment to flexibility in perspectives → Determine committed action based on values

- Depressive/anxiety symptoms, such as the Hospital Anxiety and Depression Scale (HADS) [373], the PHQ-9 [55,56], the Centre for Epidemiological Studies-Depression Scale (CES-D) [374], or the Beck Depression Inventory (BDI) [375].

Table 1 outlines the principal features and assessment methods to differentiate DD from MDD.

In addition, it is recommended that diabetes providers assess for attitudes that underlie PIR and FoH in those for whom it appears to be appropriate.

Treatment

Psychosocial (non-pharmacological) treatments: Efforts to promote well-being to mitigate distress should be incorporated into diabetes management for all individuals [376]. Systematic reviews and meta-analyses have validated:

- Motivational interviewing [377,378]
- Cognitive behaviour therapy (CBT) [270,379]
- Acceptance and commitment therapy [380–385]

Furthermore, coping skills, self-efficacy enhancement, stress management [386,387], and family interventions [388–391] all have been shown to be helpful [18,392–394].

Case management by a provider working with the primary care provider and providing guideline-based, person-centred care resulted in improved A1C, lipid levels, blood pressure, and depression scores [384,395–397].

Individuals with depressive symptoms and/or psychiatric disorders benefit from professional interventions, either some form of psychotherapy or prescription medication. Evidence from systematic reviews of randomized controlled trials supports CBT and antidepressant medication, both individually or in combination [273,398,399], for treating depression. No evidence presently shows that the combination of CBT plus medication is superior to these treatments given individually. A pilot study of 50 people with T2D who initially had a moderate level of depression at baseline showed an improvement in the severity of their depression (moving to the mild range) with a 12-week intervention of 10 CBT sessions combined with exercise in the form of 150 minutes of aerobic activity weekly. This effect was sustained at 3 months [273].

Table 3 illustrates some of the major features of motivational interviewing, CBT, and acceptance and commitment therapy as applied to diabetes care. Gains from treatment with psychotherapy are more likely to benefit psychological symptoms and glycemic levels in adults than will psychiatric medications (which usually reduce psychological symptoms only) [400]. Meta-analyses of psychological interventions found that they improved glycemic levels (A1C) in children and adolescents with T1D [401], and adults with T2D [402]. Furthermore,

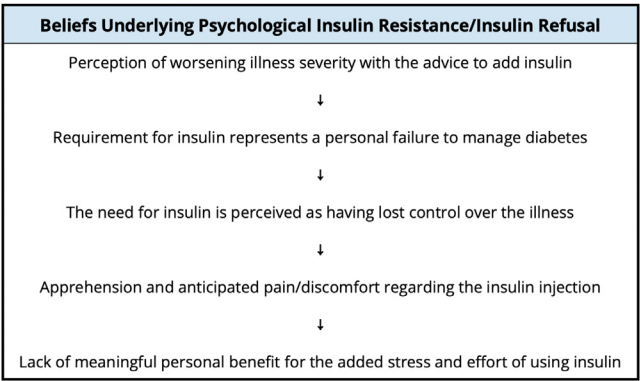


Figure 5. Features of psychological insulin resistance/insulin refusal.

evidence suggests interventions are best implemented in a collaborative fashion and when combined with self-management interventions [400]. Recent evidence also supports the effectiveness of mindfulness-based CBT [403,404].

Among adults with T2D and subclinical depression, CBT resulted in reductions in DD and depressive symptoms compared to controls [405]. Lower diabetes regimen distress (produced by an intervention combining education, problem-solving, and support for accountability) led to improvements in medication adherence, physical activity, and decreased A1C over 1 year [406,407].

Recent research suggests that CBT can be used to address PIR by specifically addressing the beliefs that underlie it [33,106,408,409] (Figure 5). FoH is amenable to treatment, such as with the behavioural desensitization process illustrated in Figure 6 [36,37,409,410].

Since diabetes outcomes are heavily dependent on the sustained participation of the individual with the illness, motivational and behavioural change strategies can be effective. Diabetes care providers can enhance successful behaviour changes through motivational interviewing strategies, such as assessing/promoting readiness to change, having individuals weigh the advantages and disadvantages

of making a self-management change, as well as encouraging their sense of self-efficacy/confidence in making the behavioural changes needed to improve their health [411–413]. Optimism and compassion from providers has also been shown to be helpful [414,415].

Although information and technology-based psychological treatments for the management of depression in people with diabetes appear to be effective in decreasing depressive symptomatology, this unfortunately may not translate into significant improvements in glycemic levels [416].

Psychological treatments delivered by non-specialists may be effective in improving glycemic levels. These treatments have some great potential of improving the quality of life for persons with T2D, particularly in low- and middle-income countries [417].

Finally, there is limited evidence to support art therapy and yoga in managing emotional distress and improving diabetes control [268,418].

Pharmacological Treatments

Psychiatric medications treat a wide array of symptoms and conditions. They have the capability of making profound improvements in symptom severity and enhancing level of function and quality of life. For many people, prescription medications provide essential and even lifesaving treatments. Response (efficacy/effectiveness) and tolerability can only be established by an adequate trial of the pharmacological agent(s). These medications can also have effects on metabolic parameters, causing changes in weight, glycemic stability, and lipid profile, and have even been found to have immunomodulating effects [419–422].

Antidepressant Medications

Introduction and overview

There are well over 20 antidepressants currently available in Canada. These are versatile medications that principally have an effect on monoamine transmission (serotonin, norepinephrine, or

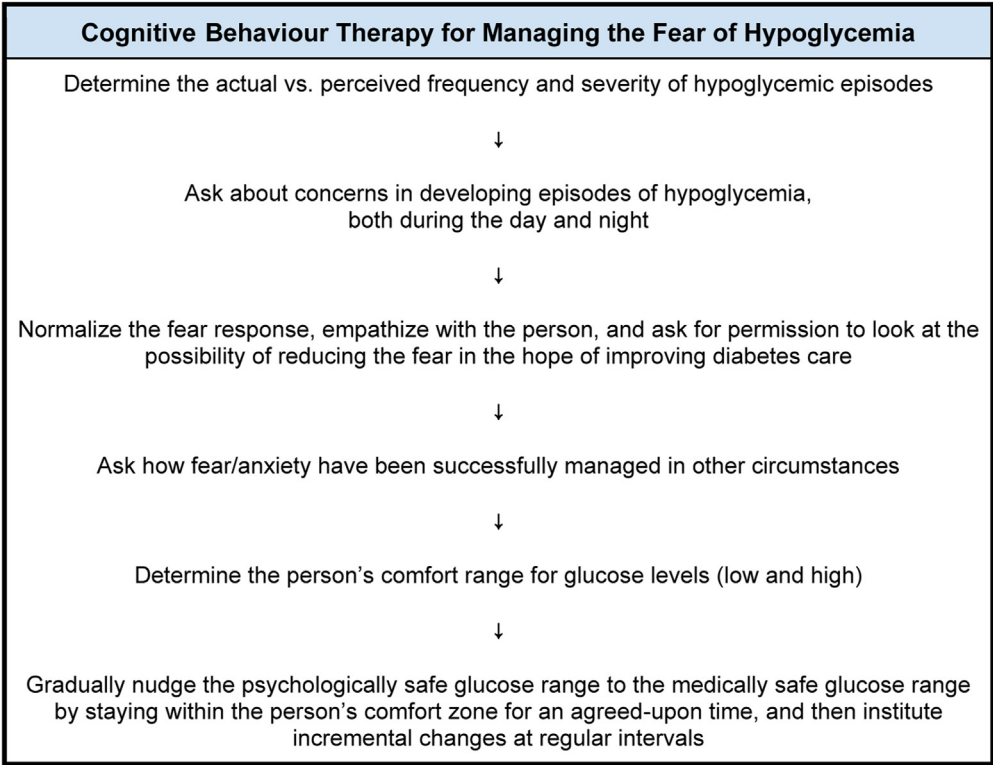


Figure 6. Suggested cognitive behaviour therapy for fear of hypoglycemia.

dopamine), with many having Health Canada-approved indications beyond MDD that include anxiety disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, and feeding and eating disorders.

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) generally have unfavourable side effects that are not tolerated well by people with diabetes (particularly sedation and weight gain) [423] and have been linked to an increased risk of developing diabetes [136,424,425].

Mirtazapine is a noradrenaline and serotonin specific antagonist (NaSSa) that contributes to the risk of weight gain, partly through its blockade of histamine receptors [423].

Selective serotonin reuptake inhibitors (SSRIs) currently comprise 6 medications that are available in Canada and are the most prescribed family of antidepressants. They are generally better tolerated and much safer to use than TCAs (particularly in overdoses) [426].

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are generally more active on the serotonergic component than noradrenergic, with levomilnacipran having the strongest preference among the group for inhibiting norepinephrine reuptake. Bupropion is a norepinephrine and dopamine reuptake inhibitor. Desipramine is the TCA with the strongest action in blocking norepinephrine reuptake [427]. Glucose homeostasis theoretically could be disrupted by norepinephrine reuptake inhibition, but use of these medications has generally found this risk to be speculative, and agents causing norepinephrine reuptake inhibition can be used in treating depressive or anxious symptoms in people with diabetes [428].

Antidepressant use and diabetes risk

Depressive symptoms and their severity can act as confounding factors in assessing the relationship between antidepressants and diabetes risk. Antidepressants may have an impact on mental illness-related factors relevant to the risk for diabetes, such as physical activity and diet. There are several variables involved in the onset and control of depressive symptoms in people with T2D, which include:

- Presence/identification of depression symptoms
- Antidepressant medications
- Severity and duration of depressive symptoms
- Current diabetes medications
- Recreational substance use (alcohol, tobacco, cannabis, etc.)
- Weight/BMI [426]

Individuals who have depressive symptoms and disorders are at risk for developing T2D. It is challenging to separate what may be the metabolic effects of MDD versus the consequences to glucose regulation caused by antidepressant medication. Not surprisingly, there are discrepant data on the risk of diabetes.

Antidepressant use contributes to glucose dysregulation

Some reports [126,130–132] found that the administration of TCAs and SSRIs in moderate or higher doses appeared to increase the risk of glucose dysregulation or diabetes [94,424,429–432].

Length of antidepressant administration for MDD is another consideration. In one study, people treated with moderate-to-high antidepressant doses appeared to have an increased risk of developing diabetes [231].

Other studies have linked antidepressant use with an increased risk for T2D, particularly in people who take moderate-to-high doses and who have taken antidepressants for longer than 2 years. The risk was similar for TCAs and SSRIs [424,433,434].

Antidepressant use does not contribute to glucose dysregulation

Other studies have not found an association between antidepressants and diabetes risk [134,135]. One meta-analysis showed that A1C was 0.32% lower in people with diabetes and MDD who were treated with an antidepressant (and no additional psychological and pharmacological intervention) compared to those treated with placebo. This effect was shown to be more pronounced in pooled analysis of studies with only T2D compared to pooled data of all studies [434–436].

Short-term use of SSRIs appeared to stabilize or even reduce glucose levels, while the use of TCAs was associated with worsening of glycemic levels [437].

Another study even found that certain SSRIs appeared to improve metabolic parameters while others appeared to induce hyperglycemia and worsen glucose levels in people with both diabetes and MDD [438].

Ultimately, it may be that the risk of antidepressant-induced diabetes, which varies substantially even between medications of the same class, may not be a mechanism-based adverse effect, but due to an individual's susceptibility [439].

Weight gain

A comprehensive review and meta-analysis looked at the effect of antidepressants on body weight [47]. These findings are incorporated in Table 7, which categorizes the potential impact on weight of all currently available antidepressants in Canada. Obesity has been associated with a decreased physiological response to antidepressants [440].

Lipid abnormalities

Although weight gain is a risk factor for lipid abnormalities, the data presently indicate that these agents are unlikely to contribute to dyslipidemia [441].

Lithium: The most robust data linking lithium to diabetes is for diabetes insipidus [442], but it does not appear to increase the risk of developing diabetes mellitus. One study looked at the effect of lithium on fasting blood glucose over a 6-year span in people with bipolar disorder. This study concluded that lithium did not the development of diabetes mellitus [443].

Another analysis found that lithium had a lower-than-average risk among 102 medications for its potential contribution to the onset of T2D [444].

Increases in weight occur more often with lithium than placebo (31). If there is to be an increase in weight with lithium, it generally happens in the first 2 years. In contrast to antipsychotic-induced weight gain, a higher weight at the start of lithium treatment appears to predict a greater overall increase in weight. Weight increase is believed to result from increased appetite, lithium-induced hypothyroidism, and nephrogenic diabetes insipidus, leading to increased thirst (which may be satiated with sugary beverages) [445].

Anti-seizure medications: The effect of anti-seizure medications (often referred to as “mood stabilizers”) on weight change is not as common as with antipsychotics, but can still be significant. Weight increases occur more with valproate than with lamotrigine or topiramate [446], with three-quarters of people taking it reporting weight gain of up to approximately 6 kg [447].

Valproate, used in mental health for a variety of purposes, has also been found to contribute to the risk of insulin resistance [448].

Valproate is associated with weight gain in up to 50% of people taking it, and can be detected within 3 months after initiation. Average weight gain also appears to be approximately 6 kg, and does not appear to be dose dependent [449].

Carbamazepine appears to have a lower risk of weight gain than lithium or valproate [450].
Topiramate and lamotrigine (at higher doses) are weight neutral or may contribute to minor weight loss (found to be up to 1.2 kg) [449].

Antipsychotic medications

The family of medications known as “antipsychotics” can be sub-divided into 3 generations. The first generation, also known as “typical” or “conventional” agents, largely function as dopamine receptor blockers and have demonstrated efficacy for reducing the more florid (also known as positive) signs of psychosis and, accordingly, received Health Canada–approved indications to treat psychotic disorders. However, these agents bind to a much wider variety of receptors than just dopamine and are useful in treating a wide array of symptoms and other (non-psychotic) conditions [423]. The second-generation antipsychotics, often called “atypical” or “novel,” have a more complex pharmacology, interacting principally with serotonin (5-HT_{2A}) and dopamine receptors, but also binding to a wide array of other types of receptors. Several have Health Canada–approved indications for the manic/hypomanic/mixed phases of bipolar disorder in addition to psychotic disorders. However, the range of unofficial or non-approved uses is quite broad, and includes treating insomnia, anxiety, depressive symptoms, etc. The third-generation antipsychotics are known by their mechanism of action—partial agonists—and are described more fully below.
The first-generation antipsychotics cause a variety of adverse reactions, including prolactin elevation and a suite of neurological symptoms, including abnormal movements and movement disorders. They have also been shown to impair glucose metabolism and increase the risk of developing T2D [451].

Second-generation antipsychotics have generally been found to cause fewer adverse neurological reactions, but certain medications are capable of making a significant impact on metabolic parameters. One meta-analysis [452] found a 1.3-fold higher risk for developing diabetes in people with schizophrenia taking second-generation antipsychotics over first-generation medications. A more recent meta-analysis determined that there was insufficient evidence to draw a firm conclusion about this risk [453].
The first and second generations of antipsychotics are not homogeneous (as a family or class) for metabolic risks, and the use of any particular agent will have varying effects on a population basis.
Antipsychotic medication use during pregnancy has been found to be associated with a slightly higher risk of GDM [454]. Accordingly, this risk should be considered when making prescription decisions. If these medications are continued, then health-care providers should ensure enhanced monitoring of glycemic levels in these pregnant individuals in anticipation of the potential development of GDM over time [454,455].

Development of diabetes with antipsychotic medications

Olanzapine and clozapine have been associated with the greatest risk of glucose dysregulation or T2D in people with schizophrenia or bipolar disorder. Quetiapine, risperidone, and low-potency first-generation antipsychotics (e.g. chlorpromazine) are generally the agents that appear to have the next highest level of risk [456,457].
Antipsychotics have been reported to induce T2D even in people who do not experience weight increases from these medications [458,459].
There appears to be an indirect path to the development of T2D when weight increases occur, and possibly a more direct route via contributing to insulin resistance, which involves muscarinic cholinergic receptors. There are 5 subtypes of muscarinic receptors that have been identified presently, and M₃ receptors in particular are thought to play a key role in the regulation of insulin secretion [458].

Olanzapine and clozapine, the 2 second-generation antipsychotic medications with the greatest risk of inducing diabetes, also have the highest M₃ receptor-binding blocking affinity, interfering with insulin secretion and disrupting glucose homeostasis. This leads to insulin resistance and the development of T2D, especially during prolonged antipsychotic medication treatment [460].

Potential mechanisms for antipsychotic-induced diabetes

The major antipsychotic effect of first-generation or typical antipsychotics occurs by blocking dopamine D₂ receptors in the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular tracts. Both first- and second-generation antipsychotics have variable effects on muscarinic, histamine, and adrenergic receptors [461–463].
A large meta-analysis found that the prevalence of T2D in people prior to antipsychotic treatment was 2.9% and increased to an overall prevalence of 11.3% among those receiving treatment with a first- or second-generation antipsychotic. The reported risk of developing diabetes was highest in people taking olanzapine or clozapine and the lowest risk was associated with aripiprazole [88].
Antipsychotics can be obesogenic medications, with between 15%–72% of people taking second-generation antipsychotics experiencing weight gain of 7% or more. Increases in weight, should this occur, generally takes place in the first 6–8 weeks after initiation of antipsychotic therapy [464,465].
Antipsychotics can have a multifactorial contribution to increases in weight. They lead to increased appetite largely due to antagonism of the serotonin 5-HT_{2C} receptors and/or histamine H₁ receptors. Dopamine antagonism leads to increased craving and hedonic eating. Animal studies with atypical antipsychotics have reported alteration of gut microbiome. Finally, energy expenditure can be reduced due to the sedative effect of antipsychotics, further contributing increases in weight [458,466–469].
Although a major contributor, increases in weight are not the only factor contributing to an elevated risk of developing T2D. Antipsychotics are thought to cause downregulation of intracellular insulin signalling, leading to insulin resistance. At the same time, there seems to be a direct effect on the pancreatic β cells. Antagonism of the dopamine D₂, serotonin 5-HT_{2C} and muscarinic M₃ receptors impairs β cell response to changes in blood glucose. In addition to the pharmacological effects, cell culture experiments have shown that antipsychotics increase apoptosis of β cells.
Increased weight and concomitant development of T2D is seen particularly in agents that exhibit high muscarinic M₃ and histamine H₁ receptor blockade [451] (Table 4).

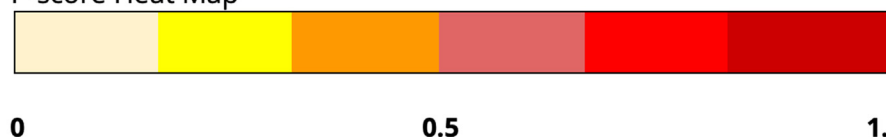
Table 4
Possible mechanisms of antipsychotic contributions to the development of type 2 diabetes [458,470–472]

Factor	Possible mechanism
Weight increase	Increased appetite due to histamine H ₁ receptor antagonism and serotonin 5-HT _{2C} receptor antagonism; increased hedonic eating due to dopamine antagonism; decreased energy expenditure due to sedative effect of antipsychotics; possible gut microbiome alteration
Increased insulin resistance	Direct effect on intracellular insulin signalling and glycogen depletion
Decreased insulin secretion	Decreased β cell responsiveness to glucose levels due to antagonism of dopamine D ₂ , serotonin 5-HT _{1A} , and muscarinic M ₃ receptors; increased apoptosis of β cells
Cholinergic pathway disruption	Muscarinic M ₃ receptor antagonism has been proposed as a mechanism

Table 6
Antipsychotic adverse effects on metabolic parameters [478]

Medication	Weight gain	Glucose	LDL cholesterol	Triglycerides
Haloperidol	0.10	0.59	N/A	0.63
Ziprasidone	0.10	0.42	0.12	0.33
Aripiprazole	0.26	0.55	0.48	0.33
Lurasidone	0.32	0.09	0.27	0.26
Cariprazine	0.37	0.70	0.07	0.28
Fluphenazine	0.38	N/A	N/A	N/A
Flupenthixol	0.44	N/A	N/A	N/A
Brexipiprazole	0.45	0.40	0.66	0.23
Asenapine	0.56	0.22	N/A	N/A
Risperidone and Paliperidone	0.58	0.46	0.54	0.39
Quetiapine	0.65	0.47	0.91	0.71
Olanzapine	0.92	0.67	0.96	0.83
Clozapine	0.90	0.97	N/A	0.97

P-score Heat Map



Footnote for Table 6: Results are ranked by propensity for increase in weight and reported with a P-score heat map, which ranks the likelihood of an adverse event on a scale from 0 to 1. A higher P-score indicates a larger increase in the metabolic parameter. The results were edited for antipsychotic medications presently available in Canada at the time of writing.

Use of aripiprazole and topiramate have evidence to support their use for managing antipsychotic-induced weight increases [449].

Augmentation with aripiprazole (to assist with symptom control in psychotic or mood disorders) can lead to a reduction in A1C levels, albeit minor [484].

Aripiprazole has also been reported to have a minor impact on body weight in children and adolescents [485].

Brexipiprazole

In a pooled analysis of phase 3 studies, the proportion of brexpiprazole-treated individuals with unfavourable shifts in metabolic parameters was low and like that of placebo-treated individuals, and unrelated to dose. In the short-term studies, mean (SD) increase in body weight was 1.2 (3.4) kg in the brexpiprazole group vs 0.2 (2.7) kg in the placebo group [486].

An open label study using brexpiprazole with data collected to 26 or 52 weeks involving an enrolment of over 1,000 people with schizophrenia found a mean change in body weight during long-term treatment of 2.0 (5.9) kg at week 26 and 3.2 (7.6) kg at week 52 [487].

Another pooled analysis of phase 3 studies looked at the effects caused by brexpiprazole used as an adjunct to treat MDD, specifically

weight and metabolic parameters. Mean changes from baseline in lipids were small in the 6-week trials, with triglycerides showing the most significant increase. In most cases, the incidence of unfavourable shifts in metabolic parameters was lower than the incidence of favourable shifts. Mean body weight increase in the 6-week studies was 1.5 kg (with antidepressant being co-administered) compared to an antidepressant+placebo showing a weight increase of 0.3 kg. Studies of over 1 year found a mean body weight increase of 3.8 kg.

An analysis comparing changes in body weight using brexpiprazole and aripiprazole as monotherapy for schizophrenia or as adjunctive treatment to antidepressant treatment (MDD) summarized both short-term (4–6 week) trials and long-term (≤ 52 weeks) studies. Clinically relevant changes in body weight ($\geq 7\%$) were similar for brexpiprazole and aripiprazole, with no statistically significant differences [488].

In short-term schizophrenia studies, the mean weight increase was 1.2 kg for brexpiprazole and 0.6 kg for aripiprazole. In short-term MDD studies (adjunctive to antidepressants), the mean weight increase was 1.5 kg for brexpiprazole and 1.6 kg for aripiprazole. In the long-term schizophrenia studies, at week 52, the mean weight increase was 2.1 kg for brexpiprazole and 3.0 kg for aripiprazole. In long-term MDD studies (adjunctive to antidepressant therapy), at week 52, the mean weight increase was 3.2 kg for brexpiprazole and 4.0 kg for aripiprazole [486].

Effects on glucose and lipids have generally been found to be minor. A mean gain of ~1 kg greater than placebo was observed in short-term studies. The mean change in body weight decreased for both brexpiprazole and placebo in longer-term studies. Weight gain is generally reported to be higher in people taking brexpiprazole as an adjunct for MDD than for schizophrenia [489,490].

Cariprazine

A meta-analysis reviewing 9 randomized controlled studies involving over 4,300 people taking cariprazine found that people taking cariprazine were more likely to have a clinically significant increase in weight (RR 1.68, 95% CI 1.12–2.52), but no statistically significant differences in results were found in other metabolic parameters or cardiovascular-related events [491].

A double-blind, placebo-controlled phase 3 study examining the effectiveness of cariprazine in the depressed phase of bipolar disorder found that mean metabolic parameter changes were low, with a mean weight increase of ≤ 0.5 kg for all groups [492].

Antipsychotic summary

Switching to an antipsychotic with a lower tendency to cause weight gain can be an effective intervention for some, though reversal of any added weight does not always occur when medications are switched [473,493].

Recent guidelines have established the importance of mitigating potential increases in weight in individuals with T2D. These guidelines suggest that weight management is as important as maintaining glucose levels and cardiorenal risk reduction [494,495].

Given the ongoing change in the understanding of increases in weight and its association with the risk of developing T2D, a metabolically safer approach involves starting with medications that have a lower propensity for weight gain, and the partial agonists/third-generation antipsychotics as a family presently have the best overall data.

Antipsychotic use in children and adolescents

Antipsychotics should be used with caution in children and youth. One study found a 3-fold increased risk of diabetes in children and youth who were given antipsychotic medications compared to other classes of medications. The most frequently recorded diagnoses for which the medications were used were mood disorders, ADHD, and conduct disorder. The risk was already increased within the first year of medication administration, increased with cumulative lifetime dose, and remained elevated even 1 year after antipsychotic discontinuation [471,496,497].

Other studies have confirmed that children and adolescents using antipsychotics had a 2- to 3-fold increased risk of T2D [497,498], which was apparent within the first year of follow-up. Metformin has been shown to have a modest ability to reduce weight gain due to antipsychotic medication [499].

Although T2D seems rare in youth taking antipsychotic medications, cumulative risk and exposure-adjusted incidences were significantly higher than in healthy controls and controls with psychiatric conditions but not taking antipsychotic medications. Olanzapine treatment and antipsychotic exposure time were the main modifiable risk factors for T2D development in youth exposed to antipsychotic medications [500].

Children and adolescents appear to experience a greater degree of weight gain than adults when taking antipsychotic medication [501].

The medications that cause the greatest risk of weight gain in adults is the same as it is for children [502].

Children and adolescents who use antidepressants also appear to be at an elevated risk for developing diabetes [395,503].

Of note, atypical antipsychotic medications are often associated with increased weight, insulin resistance, impaired fasting glucose, and T2D in children and adolescents [504]. The risk of developing T2D may be higher in adolescents taking both antipsychotic and antidepressant medications, and should be considered when making psychopharmacological decisions to address mental health needs [505].

Effects of psychiatric medications on the risk for diabetes and weight gain

Should medical problems arise during a course of psychiatric medication, clinical judgement will dictate on a case-by-case basis whether healthy behaviour interventions, such as diet or physical activity, adding a medication to address the emergent issue (e.g. side effect or medical complication), or changing the psychiatric prescription, is the most reasonable step [506,507]. Resources are available to help clinicians quickly review the major side effect profiles of psychiatric medications [423,508].

The CATIE study investigated 4 aspects of the effectiveness of antipsychotic medications: efficacy, tolerability, emergence of medical problems, and individual choice [69]. The results indicated that some antipsychotic medications were more likely to cause weight to increase, worsen glycemic stability, and induce unfavourable changes in lipid profile (consistent with the results in Tables 5 and 6). All 4 aspects are important and reinforce the need for regular and comprehensive metabolic monitoring. Non-pharmacological interventions can be effective in reducing medication-associated weight gain and glucose changes [509].

Significant differences have been reported in the susceptibility to gain or lose weight with the same antipsychotic [31,38,477,510].

Irrespective of which antipsychotic medication is taken, changes can range from weight loss to weight neutrality to weight gain. Monozygotic twin and sibling studies indicate that genetic factors may be the dominant factor in medication-induced weight gain [473,510–513], with estimates as high as 60%–80% for antipsychotic-related weight gain [103].

Genetic factors control the expression of various receptors and compounds, including serotonin (5-HT_{2C}) receptors, dopamine D₂ receptors, brain-derived neurotrophic factor (BDNF), insulin-induced gene, leptin, and ghrelin (among many others) [77,447,458,473,478,514–516].

People with serious mental illnesses (SMI) usually experience weight gain, if it is to occur, early in the course of taking antipsychotics. The trajectory of weight gain usually flattens out within a year. The degree of weight gain in the first few weeks is usually a good predictor of the likelihood of longer-term weight gain and associated metabolic abnormalities [493].

Monitoring Metabolic Risks

Health risks for people with SMI include:

- Increased weight/overweight/obesity
- Dyslipidemia
- Diabetes
- DKA
- Hypothyroidism (lithium only)
- Syndrome of inappropriate antidiuretic hormone release (SIADH)
- Hypertension
- Heart disease and stroke
- Sudden cardiac death
- Pneumonia
- Liver disease
- Leukocytopenia/agranulocytosis
- Thrombocytopenia

Table 7
Psychiatric medications and risk of weight increase

	Unusual		Not unusual	Common		Concerning
Anticholinergics	Benztrapine	Trihexyphenidyl	Procyclidine	Amitriptyline	Maprotiline	Diphenhydramine
Antidepressants	Bupropion	Levomilnacipran	Paroxetine	Clomipramine	Mirtazapine	
	Citalopram	Moclobemide	Tranylcypromine	Desipramine	Nortriptyline	
	Desvenlafaxine	Sertraline		Doxepin	Phenelzine	
	Duloxetine	Trazodone		Imipramine	Trimipramine	
	Escitalopram	Venlafaxine				
	Fluoxetine	Vilazodone				
	Fluvoxamine	Vortioxetine				
Antipsychotics	Aripiprazole	Thiothixene	Asenapine	Amoxapine	Pipotiazine	Clozapine
	Cariprazine	Trifluoperazine	Brexpiprazole	Chlorpromazine	Quetiapine	Olanzapine
	Loxapine	Ziprasidone	Fluphenazine	Flupenthixol	Risperidone	
	Lurasidone		Haloperidol	Paliperidone	Thioridazine	
			Methotrimeprazine		Zuclopenthixol	
			Pericyazine			
			Perphenazine			
			Pimozide			
Anxiolytics	Clonazepam	Nitrazepam				
	Clorazepate	Oxazepam				
	Diazepam	Temazepam				
	Flurazepam	Triazolam				
	Lorazepam					
Cholinesterase inhibitors	Donepezil	Rivastigmine				
	Galantamine					
Mood stabilizers/anti-seizure medications	Lamotrigine	Topiramate	Carbamazepine	Lithium		
			Gabapentin			
			Oxcarbazepine			
			Valproate			
Sedatives/hypnotics	Eszopiclone	Lemborexant				
	Zolpidem	Zopiclone				
Stimulants	Atomoxetine	Methylphenidate				
	Dextroamphetamine	Modafinil				
	Lisdexamfetamine					
Substance use disorder treatments	Buprenorphine	Naltrexone	Methadone			
	Clonidine	Varenicline				

Amalgamated from references 218 and 219.

- Osteoporosis
- Kidney disease
- Movement disorders

People with SMI generally have a life expectancy 10–20 years shorter than the general population [517,518].

Despite the significant advances in cardiovascular health made in recent years, the benefits have not generally made an impact on people with SMI [519].

Many persons with SMI either do not have a primary care provider, or, if they do, may be inconsistent with keeping regular appointments and not benefit from cardiovascular monitoring. A shared care model does offer a possible solution, where psychiatric and primary care expertise is available in the same clinical space [520].

While lifestyle choices, genetics, and access to primary care all make an impact on metabolic risks in people with SMI, choice of psychiatric medication is the most easily addressed modifiable risk factor [77,441].

Metabolic syndrome is found at higher rates in individuals with psychiatric illnesses than in the general population [521,522]. Individuals with diabetes and comorbid psychiatric illnesses are at an elevated risk for developing metabolic syndrome, possibly due to a combination of the following factors [523]:

- Person-level factors (e.g. health behaviour choices, diet, tobacco consumption, recreational substance use, exercise, obesity, low degree of uptake of education programs)
- Illness factors (e.g. pro-inflammatory states from MDD or depressive symptoms, possible disease-related risks for developing diabetes) [524,525]

- Medication factors (e.g. psychotropic medications have variable effects on glycemic levels, weight fluctuations, and lipids)
- Environmental factors (e.g. access to health care, availability of screening and monitoring programs, social supports, education programs)

The main impact on lipid profile is an increase in triglyceride and total cholesterol levels, especially with clozapine, olanzapine, and quetiapine [69,526]. Table 7 lists the likelihood for weight gain with use of psychiatric medications. If a person is prescribed a medication that poses a higher risk for metabolic consequences, or has pre-existing uncontrolled dyslipidemia and is initiated on a higher-risk medication, then monitoring lipid levels as soon as 1 month is recommended. For all other circumstances, rechecking lipids at 3- to 6-month intervals is appropriate.

Regular, comprehensive monitoring of metabolic parameters is recommended for all persons who receive antipsychotic medications, whether or not they have diabetes. A1C was shown to be a more stable parameter in identifying psychiatric persons with diabetes [527]. Table 8 outlines a psychiatric medication metabolic monitoring protocol.

Because weight gain with medications tends to happen most quickly during the first few weeks, then slows and usually plateaus within 1 year [528], more frequent monitoring is recommended early in the course of treatment. Results indicate that the first year of antipsychotic treatment is a critical period for weight gain and metabolic abnormalities, as initial rapid weight gain is a significant predictor of the potential for long-term weight gain and obesity [458,529].

Table 8
Metabolic monitoring schedule for people taking psychiatric medications

Biometric parameters	Comments
Blood pressure	Check at baseline (ideally before medication is taken) and preferably at every visit . As a modifiable risk factor, it is important to monitor BP as often as possible to treat if it becomes problematic.
Waist circumference	Measure at baseline (ideally before medication is taken) and at regular intervals (monthly to quarterly) in the first year when the risk of weight gain is the highest. Semi-annually to annually after the first year is appropriate.
Weight	Check at baseline (ideally before medication is taken) and preferably at every visit . As a modifiable risk factor, it is important to monitor as often as possible. Should weight increase occur, it is often greatest in the first year.
Hematologic tests	Comments
Fasting glucose or random glucose	Measure at baseline (ideally before medication is taken) and at regular intervals (monthly to quarterly) in the first year when the risk of weight gain is the highest. For higher-risk medications or individuals, take more often during the first year and q3 to q12 monthly afterwards based on clinical circumstances.
A1C	Measure at baseline (ideally before medication is taken) and at q3 monthly in the first year when the risk of weight gain is the highest. After the first year, q3 to q12 monthly afterwards, based on individual circumstances.
Lipid profile	Measure at baseline (ideally before medication is taken) and at regular intervals (possibly monthly in high-risk circumstances or quarterly otherwise) in the first year when the risk of weight gain is the highest. Elevation in lipids may be found before weight gain occurs. For higher-risk medications or individuals, take more often during the first year and q3 to q12 monthly afterwards based on clinical circumstances. This test no longer requires people to fast before blood samples are taken.
Medical history	Comments
Personal history	Take the information at baseline (ideally before medication is taken) and update this at least annually or more often based on clinical circumstances. Key questions are about tobacco use, alcohol use, recreational substance use, sleep patterns, amount of exercise, sexual health, and challenges faced with taking medications regularly .
Family history	Take the information at baseline (ideally before medication is taken) and update this at least annually or more often based on clinical circumstances. Key questions are about psychiatric illness in the extended family, metabolic illness in the extended family, and the family philosophy towards chronic illnesses .

Recommendations

Reactions to the illness of diabetes

1. Assess individuals with diabetes for psychological reactions to the diagnosis that may impair diabetes self-management [Grade D, Consensus].
2. Health-care providers are advised to be aware of their own weight-based biases [Grade C, Level 3 [61]].
3. Motivational interviewing techniques can be used to improve discussions focusing on weight to minimize weight-based stigma in health-care settings [Grade C, Level 3 [60,61]].
4. Health-care providers are encouraged to regularly assess, counsel, and offer health-care resources to help individuals with diabetes to reduce the indirect and direct costs of diabetes management and improve self-management [Grade D, Level 4 [65]].

Screening

5. Individuals with diabetes may be screened at each pregnancy-related follow-up visit for common psychiatric conditions (particularly mood and anxiety disorders), psychosocial stressors, and to assess social support [Grade D, Consensus].
6. Children and adolescents with type 1 diabetes may benefit from screening at diagnosis and routine assessment to identify and address the mental health aspects of living with diabetes, specifically:
 - a. Major depressive disorder [Grade C, Level 3 [248]],
 - b. Psychosocial difficulties, family/caregiver distress, and/or mental health disorders [Grade D, Consensus],
 - c. Fear of hypoglycemia [Grade C, Level 3 [248]], and
 - d. The processes of transition to adult care services [Grade D, Consensus].

7. Adolescents with type 1 diabetes may benefit from being regularly screened using non-judgemental questions about:
 - a. Weight and body image concerns, and
 - b. Dieting, binge eating, and insulin omission for weight loss [Grade D, Level 4 [256]].
8. Children and adolescents with type 2 diabetes should be screened at diagnosis and regularly thereafter (at least twice per year) for major depressive disorder, binge eating disorder, and other psychosocial difficulties (e.g. diabetes distress and stigma) [Grade C, Level 3 [278,530]].
9. Individuals with diabetes, as well as the parents or caregivers of youth with diabetes, should be screened when newly diagnosed, as well as regularly afterwards, for diabetes-related psychological distress and psychiatric disorders using validated self-report questionnaires or clinical interviews [Grade C, Level 3 [248,531]].
10. Older people with diabetes should be screened for major depressive disorder and offered psychotherapy options, such as cognitive behaviour therapy, to improve physical health parameters, such as body weight [290], systolic blood pressure [290], glycemic management [289], and diabetes distress [289] [Grade B, Level 2].
11. Health-care providers should use open and non-judgemental communication with adults with diabetes who are recreational substance users to facilitate implementation of strategies to reduce potential harm from substance use [Grade C, Level 3 [532]].
12. People with diabetes may benefit from being screened for potential misuse of alcohol [Grade D, Level 4 [533]].
13. For people with diabetes who have comorbid mental health concerns, inquiries about thoughts or plans for self-harm should be assessed regularly [Grade C, Level 3 [349]], and, when present, necessary steps should be taken to ensure the safety of the person [Grade D, Consensus].

Treatment

14. For children and adolescents with type 1 diabetes, individual and family interventions, including mobile health (mHealth) and telemedicine resources, can be beneficial when included to address stress and/or diabetes-related conflict [Grade D, Consensus].
15. Individuals with diabetes benefit from being counselled about the emotional and interpersonal impact of diabetes to improve their engagement in diabetes self-management recommendations [Grade D, Consensus].
16. The following groups of people with diabetes may warrant referral to specialized mental health–care professionals:
 - a. Significant distress related to diabetes management [Grade D, Consensus],
 - b. Persistent fear of hypoglycemia [Grade D, Consensus],
 - c. Psychological insulin resistance [Grade D, Consensus], and
 - d. Psychiatric disorders (i.e. depression, anxiety, eating disorders) [Grade D, Consensus].
17. Collaborative care by interprofessional teams should be provided for individuals with diabetes and depression to improve:
 - a. Depressive symptoms [Grade A, Level 1 [396,397]],
 - b. Adherence in taking antidepressant and non-insulin anti-hyperglycemic medications [Grade A, Level 1 [396]], and
 - c. Glycemic stability [Grade A, Level 1 [397]].
18. Interventions may be provided by a multidisciplinary diabetes team (including a mental health professional) to support behaviour change and coping with lifestyle changes for individuals with diabetes [Grade D, Consensus].
19. Psychosocial interventions should be integrated into diabetes care to improve adaptation to living with diabetes and engagement in self-management, including:
 - a. Motivational interviewing [Grade A, Level 1A [378]],
 - b. Cognitive behaviour therapy [Grade A, Level 1A [379]],
 - c. Acceptance and commitment therapy [Grade A, Level 1 [380]],
 - d. Stress management strategies [Grade A, Level 1A [18,392,393]],
 - e. Coping skills training [Grade A, Level 1A [534] for type 2 diabetes; Grade B, Level 2 [535] for type 1 diabetes],
 - f. Family therapy [Grade A, Level 1B [388,390,536]], and
 - g. Case management [Grade A, Level 1 [394]].
20. Cognitive behaviour therapy should be used to treat depression in individuals with depression alone [Grade B, Level 2 [137]] or in combination with antidepressant medication [Grade A, Level 1 [273,399]].
21. People currently taking insulin therapy and who consume alcohol, cannabis, stimulants, or illicit opioids may be advised to:
 - a) Accept counselling about the risk, prevention, recognition, and treatment of hypoglycemia, along with their support persons [Grade D, Consensus], and
 - b) Monitor glucose levels frequently for glycemic excursions [alcohol [Grade C, Level 3 [297]]; other recreational substances [Grade C, Level 3 for T1D [297,319]]; Grade D, Consensus for T2D]].
22. Antidepressant medication should be used to treat acute depression in people with diabetes [Grade A, Level 1 [136]] and for maintenance treatment to prevent recurrence of depression [Grade A, Level 1A [135]].
23. People with diabetes or who are at risk for developing diabetes and who would benefit from an antipsychotic medication should be initially prescribed partial agonists/third-generation serotonin-dopamine modulators over first- and second-generation agents to reduce the chance of glycemic dysregulation, weight gain, or sedation [Grade C, Level 3 [474]].

Monitoring

24. All persons (with or without diabetes) who are prescribed psychotropic medications (especially clozapine and olanzapine) should undergo metabolic monitoring at appropriate intervals to reduce the potential risk of adverse metabolic effects [Grade D, Consensus].

Abbreviations

A1C, glycated hemoglobin; BMI, body mass index; BP, blood pressure; CBT, cognitive behaviour therapy; CV, cardiovascular; DD, diabetes distress; DIP, diabetes in pregnancy; DKA, diabetic ketoacidosis; FoH, fear of hypoglycemia; GAD, generalized anxiety disorder; GDM, gestational diabetes mellitus; HR, hazard ratio; IR, insulin refusal; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; PGM, pregestational/pre-pregnancy diabetes; PHQ-9, Patient Health Questionnaire; PIR, psychological insulin resistance; PPD, postpartum depression; PTSD, post-traumatic stress disorder; SMI, serious mental illness (generally includes schizophrenia and other psychotic disorders, bipolar disorder, and major depressive disorder); T1D, type 1 diabetes; T2D, type 2 diabetes

Author Disclosures

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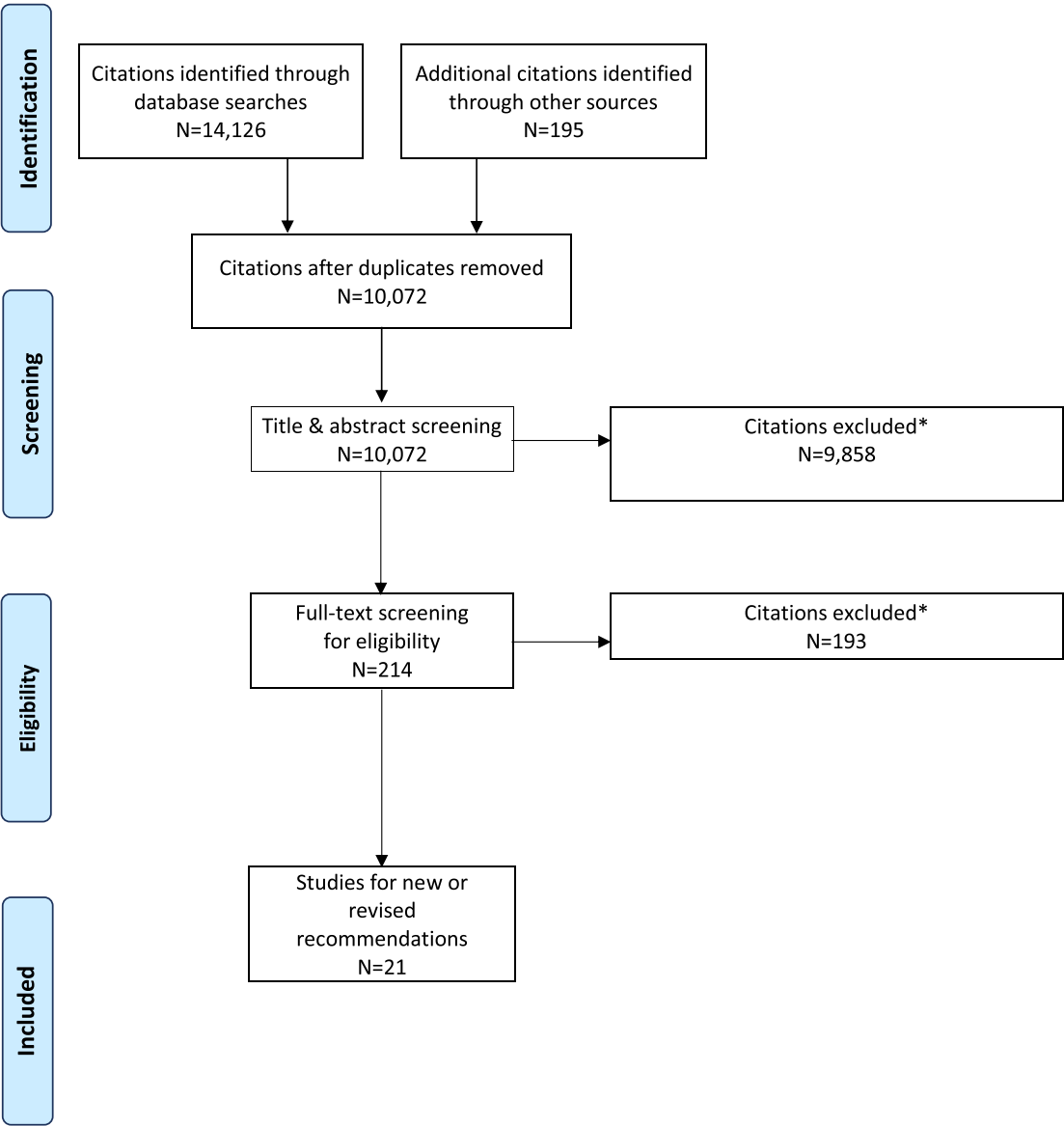
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Updated Literature Review (2017-2022) Flow Diagram: Diabetes and Mental Health



*Excluded based on: population, intervention/exposure, comparator/control, or study design.