

**Risk of Acute Complications of Diabetes among People
with Schizophrenia in Ontario**

by

Taryn Becker

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Graduate Department of Health Policy Management and Evaluation

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ABSTRACT

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Taryn Becker

Health Policy Management and Evaluation

University of Toronto

Diabetes Mellitus (DM) is a complex, chronic disease, associated with potentially devastating complications. The DM-complication rate may be increased among people with schizophrenia. This study evaluated the relationship between schizophrenia and risk of preventable, acute DM-complications. Using administrative data, a retrospective study assessed acute DM complications (emergency department visits or hospitalization for hypo- or hyperglycemia, and hospital admissions for infections) among Ontario residents ages 18-50 with schizophrenia and newly diagnosed DM between 1995 and 2005, comparing people with and without pre-existing schizophrenia. People with schizophrenia had a 74% greater risk of requiring a hospital visit for hypo- or hyperglycemia (HR =1.74, 95% CI 1.42-2.12) compared to those without. The risk was similar when the outcome included infection (HR=1.62, 95% CI 1.39-1.89). Outcomes remained significant after adjustment for baseline characteristics.

Understanding this relationship will direct future studies assessing barriers to care, and implementation of individualized approaches to care for this population.

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1. Background

1.1 Overview

Diabetes mellitus (DM) is a serious chronic condition associated with potentially devastating complications. The prevalence of DM has been dramatically increasing worldwide, making it an extremely costly chronic disease, both in terms of patient morbidity and healthcare expenditure. The impact of DM certainly has affected Canada. Between 1995 and 2005, the prevalence of DM in Ontario increased by 69 percent, exceeding the global rate that was predicted for 2030 (1). The increasing prevalence of DM contributes significantly to the increasing prevalence of DM complications. Although the risk of complications has actually improved due to improved management strategies or earlier detection, the number of individuals experiencing complications is increasing because of the very large growth of DM cases. DM is the leading cause of end-stage kidney disease and dialysis, blindness and limb amputation in Canada. Cardiovascular disease is 2-4 times greater in people with DM compared to people without, and is the leading cause of death among people with DM. Effective management of DM is supported by evidence-based clinical practice guidelines (2). A multi-disciplinary approach provided primarily through primary care and other outpatient services (ambulatory care) can prevent both acute and long-term DM complications (3-5). Despite the publication of evidence-based guidelines, diabetes targets still are not being met. There are many reasons why DM care may be compromised. Certain subpopulations of individuals with DM have poorer DM control and more difficulty managing their condition, which puts them at higher risk of developing DM-related complications and

may lead to more emergency department visits or hospitalizations. Risk factors for poorer DM control and DM complications include non-white ethno-racial groups, low socio-economic status (SES) and certain geographic locations (3, 6-10). Another potentially vulnerable group includes people with other serious medical conditions, such as schizophrenia. People with schizophrenia have an increased risk of developing DM compared to the general population (11-14). Many reasons, including the wide usage of atypical anti-psychotics, have been postulated as to why the risk is increased in this group. People with schizophrenia are also less likely to receive adequate care for other medical conditions (15). Therefore the current study will examine the relationship between acute complications of DM in individuals with schizophrenia and DM, compared to people of similar SES and other risk factors who have diabetes but do not have schizophrenia. The relationship between DM and schizophrenia is complex, and incorporates a number of factors (Figure 1), including the understanding and management of DM, its complications and potential pitfalls with the current model of care. While there are several social, economic and cultural barriers to optimal DM care, the co-existence of schizophrenia may have an additional impact on occurrence of acute DM complications. A brief background to each of these issues will be provided in the sections that follow.

2. Diabetes Mellitus

2.1 Definition

DM refers to a group of diseases that lead to elevated blood glucose levels (hyperglycemia) due to defects in insulin secretion or the action of insulin or both (16). DM is a complicated condition, with multiple risk factors that contribute to development

of the condition, including but certainly not limited to obesity, age, race, and genetic factors. Although DM is treatable, there is currently no cure. One of the key objectives in the management of DM is to lower blood glucose into or close to the normal range. However, optimal management includes targeting a range of other cardio-metabolic risk factors, such as hypertension, dyslipidemia, obesity and smoking cessation. DM management is achieved through a number of interventions. These include lifestyle modification involving diet, physical activity, and maintaining a healthy body weight. Medications include several anti-diabetic oral agents, insulin, as well as agents which address cardiovascular risk factors as needed.

2.2 Diabetes Complications

2.2.1 Acute Complications

Morbidity from DM and its treatments may result from both acute and chronic complications. The 2008 Report on Ontario's Health System showed that approximately 4% of people with newly diagnosed DM presented to an emergency department or hospital for an acute complication of DM (17). Acute complications include extreme levels of blood glucose, with accompanying symptoms and/or other laboratory abnormalities. These may range from diabetic ketoacidosis and nonketotic hyperosmolar coma to hypoglycemia. Generally, these states are reversible and but if not treated can lead to death. Hospitalizations for acute metabolic decompensation are associated with significant morbidity and mortality, and they are considered preventable with adequate ambulatory care (18). DM is considered an ambulatory-care sensitive condition. Ambulatory-care sensitive conditions include those for which hospitalization is thought

to be avoidable through interventions and early disease management delivered in an ambulatory care setting, such as primary care. High rates of hospital visits for conditions considered “ambulatory-care sensitive” may provide evidence of problems with access to healthcare, inadequate care and resources or disconnection between medical services. In 2001 the Agency of Healthcare Research Quality (AHRQ) published the “Guide to Preventable Quality Indicators (PQIs): Hospital Admission for Ambulatory Care Sensitive Care Conditions” (19). Hospitalization for ambulatory care sensitive conditions (ACSH) is an accepted indicator of access to health care and avoidable morbidity. The premise underlying the ACSH indicators is that greater access to effective healthcare will be associated with lower ACSH rates. The two measures for metabolic decompensation included in the recommendations are hospitalizations for uncontrolled DM and hospitalizations for acute complications of DM. In other words, this form of decompensation includes extreme measures of glucose with the potential for other metabolic derangements, such as electrolyte disturbances or volume depletion and the clinical sequelae that accompany such states (eg. renal failure, hypotension, altered mental status).

Severe glucose disturbances are not the only acute DM-related events that lead to hospitalization. It has been demonstrated that people with DM have a greater risk of developing infectious diseases (20, 21). Not only does DM confer a greater than 2-fold risk of being hospitalized for infection, the risk ratio for death from infection is almost double for people with DM compared to people without DM (20). Furthermore, skin and soft tissue infections, namely ulcers and foot infections, are an important and frequent cause of morbidity in patients with DM (22). Foot infections can lead to limb amputation

and increase the risk of mortality (23). Since these infections are considered preventable, the Canadian Diabetes Association has published guidelines on how to manage and prevent such problems (2).

2.2.2 Chronic Complications

In addition to the acute complications described above, serious and often irreversible long-term complications result from chronic abnormalities in blood glucose. These include both microvascular disease (retinopathy, nephropathy and neuropathy) (24-26) and macrovascular disease (atherosclerosis and coronary heart disease). The risk of death from a cardiac or cerebrovascular event is also significantly elevated compared to people without DM (27) (28). Hyperglycemia has been associated with the development and progression of these consequences, as demonstrated in epidemiologic analyses for a number of DM complications (24-26). Moreover, results of multiple randomized trials have demonstrated the importance of tight glycemic control in the prevention of long-term diabetes complications in people with newly diagnosed DM, or those who are early in the course of their disease (4, 5).

2.3 Prevention of diabetes complications

In type 2 DM, disease onset is usually insidious and diagnosis frequently is delayed. As a result, microvascular complications already may be present at the time of DM diagnosis (29), and frequency of complications increases over time. Thus, depending on the duration of disease and other vascular risk factors, long-term complications may be present when screening occurs. There is evidence that for people early in the course

of DM, *long-term* complications may be prevented, or progression can be slowed. While there are no randomized trials demonstrating the role of ambulatory care in the prevention of *acute* complications, there is evidence that DM management improves glycemic control and other metabolic measures. It is likely that the degree of glucose control is a mediator, contributing to the risk of acute DM-complications. However assessment of the acute DM-complications, particularly in vulnerable individuals is important because it results in a direct burden to the patient, the health care system, and likely reflects suboptimal glucose control.

The landmark Diabetes Control and Complications Trial (DCCT) evaluated the impact of differing glycemic targets in the prevention of microvascular complications in patients with type 1 DM who did not have significant microvascular disease. This study examined whether intensive insulin treatment, aimed at maintaining blood glucose concentrations close to the normal range, could decrease the frequency and severity of microvascular complications (30). Patients were randomly assigned to receive either conventional therapy or intensive insulin therapy (4), and followed prospectively. Conventional therapy was defined by one or two insulin injections per day, while intensive therapy consisted of multiple daily injections or an insulin pump. Patients with no retinopathy or nephropathy were evaluated in the primary prevention arm. Those with established microvascular disease were followed for progression of these conditions in the secondary-intervention arm.

Glycosylated hemoglobin (HbA_{1C}) was monitored in this study. HbA_{1C} is a form of hemoglobin used to represent the average plasma glucose over prolonged periods of time. During the nine-year study, mean HbA_{1C} values were 7.2 percent in the intensive

therapy group, versus 9.1 percent in the conventional group. Intensive therapy reduced the mean risk for retinopathy by 76 percent (95% CI 39 to 66%) in the primary prevention cohort, and there was a 54 percent (95% CI 14 to 67%) reduction in the progression of retinopathy in the secondary prevention arm. In both cohorts, intensive insulin therapy significantly lowered the occurrence of microalbuminuria and clinical nephropathy. The DCCT provided conclusive evidence that tight glycemic control delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in patients with type 1 DM. It has been established that a HbA_{1c} level between 4 and 5.9 is considered normal, while each incremental increase has been implicated as a continuous risk factor for increased microvascular complications of DM. A follow-up study to the DCCT, the Epidemiology of Diabetes Interventions and Complications study (EDIC), found that intensive diabetes therapy also decreases the incidence of cardiovascular disease among patients with type 1 DM (31).

The United Kingdom Prospective Diabetes Study (UKPDS) followed over 4,000 patients with newly diagnosed type 2 DM (5). This study demonstrated that strict glycemic control among people with type 2 DM also resulted in a reduction of microvascular complications. There was a 25 percent risk reduction in microvascular disease in the intensive therapy arm of this study (P=0.001).

There is also a well-established relationship between DM and cardiovascular disease, with cardiovascular disease accounting for the majority of deaths among people with DM (32)(33). The prevalence of coronary artery disease is 2 to 3 times greater in people with DM, compared to individuals without DM (34, 35). This relationship is not only impacted by glycemic control, but is multi-factorial. Hypertension and lipid

abnormalities are common in people with DM, and there is compelling evidence from randomized controlled trials that treating these disorders can significantly reduce the risk of cardiovascular complications in this population (36, 37). The Steno-2 trial assessed the impact of intensified multi-factorial pharmacologic intervention (in addition to lifestyle changes) on cardiovascular disease in people with type 2 DM (38). Interventions included behaviour modification and pharmacotherapy targeting hyperglycemia, hypertension, dyslipidemia and microalbuminuria, as well as secondary prevention of cardiovascular disease with the anti-platelet therapy. The study demonstrated a 50 percent reduction in cardiovascular events using intensified intervention simultaneously targeting multiple risk factors among people with type 2 DM and microalbuminuria. A subsequent study demonstrated a reduced death rate from any cause and cardiovascular death in this population (39). In addition to the pharmacologic agents demonstrated to influence diabetes outcomes, there is evidence for the role of physical activity (40)(41) and nutrition therapy (42) in achieving improved glycemic control and other metabolic parameters. There are several recommendations in the Canadian Diabetes Clinical Practice Guidelines pertaining to both of these behavioural interventions (2). One example of such a recommendation is the implementation of “a minimum of 150 minutes of moderate to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise”. Another recommendation encourages people with DM to follow the ‘Eating well with Canada’s Food Guide’ to ensure adequate nutrition.

There is an abundance of recommendations to minimize or prevent the long-term sequelae of DM. Not only are these recommendations complex, but they are associated

with a monetary cost; they are time-intensive, and they require a commitment from both the patient, as well as their health care providers.

2.3.1 Prevention Quality Indicators

As outlined above, several ambulatory care interventions have demonstrated reduction in long-term microvascular and macrovascular complications. Although not as common as micro- and macrovascular disease, hospital visits for acute metabolic complications of DM are also considered preventable with appropriate ambulatory care (18). Accordingly, in 2001 the Agency for Healthcare Research and Quality (AHRQ) published *Prevention Quality Indicators: Hospital Admission for Ambulatory Care Sensitive Conditions* (19). With respect to DM, there were two indicators for metabolic decompensation in the recommendations: hospitalization for uncontrolled diabetes and hospitalizations for short term complications of diabetes (hyperosmolar non-ketotic coma or diabetic ketoacidosis).

2.4 Models of Delivery of Care for Diabetes Management

While evidence that effective management of DM can prevent complications of disease has been available for a number of years, current models of DM care delivery do not always provide the optimal level of management for all patients. As a complex, chronic condition, diabetes management requires ongoing care with individualized treatment plans. The goal of medical monitoring of blood glucose and other metabolic parameters, and preventative services is to reduce the complications associated with DM. This management relies primarily on outpatient services from a variety of medical

disciplines. Successful DM care relies on a daily commitment from the individual with DM to self-manage, as well as medical resources. The Canadian Diabetes Association (CDA) current practice guidelines recommend that DM care be organized around an interdisciplinary diabetes health care team (2). Each team is based around the person with DM, and includes family members, a primary care physician and DM educators. Additional team members may include DM specialists and other medical specialists or non-physician health care professionals. Regular medical care is essential to ensure the appropriate long-term follow-up of people with DM. The CDA guidelines emphasize that the family physician has an important role, ensuring continuity of care, evaluating the person with DM in the context of his/her family, and acting as a resource to meet the varied needs of the person with DM. The guidelines state that “Diabetes care depends upon the daily commitment of the person with diabetes to self-management practices with the support of an integrated diabetes healthcare (DHC) team” (2). The DHC team ideally should be multi- and interdisciplinary, and establish a communication network between the team members and the individual with diabetes. However evidence for models of care is limited, as it is difficult to design comprehensive studies to objectively evaluate these different models.

2.5 Vulnerable Populations with Diabetes

With comprehensive ambulatory care, hospital visits for hyper- or hypoglycemia can generally be prevented (3). In contrast, when individuals have decreased access to health care services, optimal delivery of diabetes care is impeded and potentially avoidable acute diabetes emergencies occur more frequently (3). Booth et al.

demonstrated that among patients with DM in Ontario, a region with universal access to health care, those from low socio-economic status (SES) neighbourhoods experienced an excess of complications that could have been prevented by optimal ambulatory care. For example, the risk of having an avoidable hospitalization or emergency department visit or hospitalization for hyper- or hypoglycemia increased by 10 percent for each successive lower income quintile. Low income is common among people with schizophrenia (43), which poses a challenge as the impact of poverty must be disentangled from the effects of mental illness on DM care and DM outcomes.

Low SES is not the only risk factor for poorer DM control and self-management, leading to DM-related complications and more frequent emergency room visits. Others include non-white ethno-racial groups, language barriers, and geographic location (44)(6-8, 10). Individuals living in rural or more remote regions of Ontario were almost 2-times more likely to visit an emergency department or be admitted to hospital for management of DM than similar people living in urban communities (10). Another important predictor of acute complications of DM is primary care utilization (44). Avoidable hospitalizations and emergency department visits were increased 2-fold among people who had not seen a primary care physician in the year prior to the event. Fewer events occurred among people with more primary care visits or the presence of a usual care provider (44). Access to, and use of outpatient healthcare services, appear to be key issues in preventing acute complications of DM. Lack of healthcare access and utilization is an independent risk factor for such events. However, it is possible that some of the other risk factors (eg. ethnicity and geography) are mediated by access and utilization patterns.

3.0 Schizophrenia

3.1 Relationship between Diabetes and Schizophrenia

Epidemiologic data suggest the prevalence of type 2 DM is at least 3-fold greater in people with schizophrenia than the general population (11-14). Schizophrenia has been identified as an independent risk factor for diabetes (4). The cause of increased risk of DM in individuals with schizophrenia is not fully known, but there are a number of possible explanations for this relationship. One possibility is the increased use of atypical antipsychotic drugs, and associated weight gain, in the treatment of schizophrenia. Weight gain is a significant issue with neuroleptic drugs in general, but is a particular problem with the commonly used second-generation antipsychotic agents (SGA), especially clozapine and olanzapine (45). Numerous authors have reported the association between antipsychotic use, obesity and DM, and a consensus report reviewed the data and provided guidelines for management in this population (45). Recommendations specifically included measurement of fasting lipids and glucose at baseline and after 12 weeks of treatment in all patients with schizophrenia who receive antipsychotic medications.

Although antipsychotic agents are implicated in the increased risk of DM in people with schizophrenia, there may be other possibilities for the increased prevalence, including genetic factors or the illness itself. Several reports, although not all, have suggested that schizophrenia is associated with abnormal glucose metabolism independent of antipsychotic use (46-50). In 1998 Mukherjee et al. reported that unaffected first-degree relatives of people with schizophrenia have higher rates of type 2 DM than the general population (51). This was confirmed by Fernandez-Egea et al. a

decade later (52, 53). Furthermore, the association was reported prior to the widespread use of antipsychotic drugs. Over 15 percent of patients presenting with first-episode schizophrenia have impaired fasting glucose, elevated insulin levels, as well as high stress hormones (eg. cortisol) which may contribute to elevated glucose levels, prior to starting any treatment (47).

3.2 Schizophrenia and Medical Illness

Patients with co-morbid mental illness and medical illness represent a high-risk population with complex treatment needs. A consensus review of schizophrenia reported that mortality rates in people with schizophrenia are 2-3 times higher than the general population, with an increased risk of excess mortality in younger patients with schizophrenia (45). Compared to the general population in the United States, the lifespan of people with schizophrenia and affective disorders is at least 30 percent shorter (54). The high death rate is not fully explained by increased suicide, but also is attributable to natural causes. These include circulatory, respiratory, digestive and genitourinary disease, as well as adverse events during medical and surgical hospitalizations (45, 54-56).

Cardiovascular disease and DM are the leading cause of death in people with schizophrenia. Compared to the general population, people with schizophrenia have an increased prevalence of several major risk factors for cardiovascular disease, many of which are modifiable. These include cigarette smoking, substance abuse, dyslipidemia, hypertension, a sedentary lifestyle and a diet which is low in fiber and high in fat (57-59). The increased mortality related to coronary heart disease is likely multi-factorial, but may

partly be due to under-monitoring and under-treatment of cardiac risk factors in patients with psychiatric disorders (60-62). A recent study in the U.S. compared the rates of lipid and glucose testing in patients receiving antipsychotic medications before and after 2004, when the American Diabetes Association (ADA) issued guidelines recommending testing (63). They found that despite significant improvements after the guideline's publication, less than 22 percent of patients received baseline glucose testing and only 18 percent received repeat testing at 12 weeks after medication initiation.

3.3 Impact of Schizophrenia on Diabetes Care

People with schizophrenia represent a high-risk, vulnerable population, as they are less likely to receive adequate care for other medical conditions (15) and they have complex, ongoing treatment needs. Studies evaluating the impact of schizophrenia on diabetes care have yielded inconsistent results (64-68). Current studies assessing quality of DM care in people with schizophrenia have focused primarily on quality of care indicators, including the following recommended services: retinal eye and foot examination, blood pressure checks, and measurement of HbA_{1C}, lipid and urine profiles.

Dixon et al. conducted a cross-sectional study of DM care among 300 people with and without *serious* mental illness recruited from community mental health centers in Baltimore (64). A third of the patients had schizophrenia, another third had a major mood disorder and the remainder had no identified severe mental illness. The authors found that there was no difference between groups in DM-related outpatient visits, but those with serious mental illness were likely to receive fewer recommended services. They concluded that receipt of DM care was poorer among people with serious mental

illness, despite equal access to care. They report lower HbA_{1C} compared to other studies, and the authors comment that mental health services could have contributed to stability and adherence to DM treatment. However, all of these patients were recruited from a mental health centre, and the mean HbA_{1C} values were all above the recommended target. It is difficult to know how these findings would compare to a population of people with DM who do not require treatment at a mental health centre, and are without mental illness (severe or not); particularly given that the population included in this study had specific treatment needs, differing medications and perhaps vastly different contact with the medical system than those in a general diabetes population.

Three studies were conducted within the U.S. Department Veterans Affairs (VA) health care system. The first of these studies concluded that patients with mental disorders were somewhat less likely to receive some DM secondary prevention recommendations compared to similar patients without mental illness (65). However, only 4.3 percent of this cohort had a diagnosis of schizophrenia or other psychotic disorder. A second study by Frayne et al. concluded that there is poor adherence to quality-of-care measures (glycemic and lipid testing, and retinal examination) among patients with mental illness (68). This study also found that the group with mental illness was more likely to have poorer glycemic control. In this cohort, only 5.3 percent had a psychotic disorder. The study with the largest population having both mental illness and diabetes assessed over 36,000 people. Several quality-of-care measures and DM outcomes were evaluated. The authors found no significant difference in rates of testing of HbA_{1c} or lipid levels, and diabetes outcomes among patients with and without serious mental illness (66). However this population was predominantly male, with a mean age

of 58 years, and they were all receiving care in the VA health care system. This is a uniquely integrated system, which contains an electronic communication system among providers, and actual physical integration of health care services. Therefore, the results of these studies may not be generalizable to a Canadian population of people with DM and schizophrenia.

There have been several publications quantifying the relationship between serious mental illness and access to medical services, providing mixed results (69-72). Some of these American studies have suggested that patients with DM and serious mental illness have similar hospitalizations and outpatient visits related to diabetes. Brantford et al. combined results of two national health surveys in the U.S., and found that people with psychotic disorders had a significantly reduced odds of having a primary care physician compared to people without mental illness (Odds Ratio =0.55. 95% Confidence Interval 0.44-0.69) (73). Another study concluded that mental illness was associated with receipt of a greater number of diabetes-related services (67). Although the number of visits may be comparable to or even higher in people with mental illness, the appropriateness of diabetes care provided to these patients may be suboptimal (67). In the aforementioned cross-sectional analysis of 300 people, study participants were interviewed and provided with information about DM education. The authors found that in addition to receiving less recommended DM quality of care indicators, those with serious mental illness were also less likely to receive any DM education. This illustrates another disparity in DM care among individuals with mental illness. Interestingly, those in the mental illness group who were smokers were more likely to meet performance measures for tobacco counseling compared to those without serious mental illness (74). Therefore it appears

that mental illness did not discourage healthcare providers from providing patient education for behavioural change *in general* to people with serious mental illness. However, there may have been recall bias, as the study relied on self-report of education. Given the sampling strategy employed in this study, patients may have received diabetes services in somewhat specific environments that are not generalizable.

4. Challenges Faced by Healthcare Providers for Individuals with Schizophrenia

4.1 Challenges in achieving Diabetes Targets in People with Schizophrenia

As outlined above, people with sub-optimal control of DM are at a significantly increased risk of adverse complications related to DM. In people with schizophrenia and DM, there may be an added challenge to control glucose levels and other metabolic parameters while taking antipsychotic medications. The relationship between antipsychotic use and weight gain is not limited to altered glucose metabolism, but also increases the risk of developing a “metabolic syndrome”, a constellation of factors including increased abdominal girth, hyperglycemia, dyslipidemia and hypertension (75). It is estimated that the metabolic syndrome, which is associated with an increase in cardiovascular disease, affects up to 50 percent of people with schizophrenia (76, 77). Thus the use of antipsychotics may make it more difficult for patients to reach glycemic targets, as well as achieve targets of secondary prevention such as blood pressure, lipids and reduction of central adiposity.

Associations between cognitive impairment and both DM *and* schizophrenia have been reported (78, 79). Dickinson et al. compared cognitive performance in three groups of patients: one group with schizophrenia and diabetes, another group with diabetes only

and the third group with schizophrenia only (80). Results indicated that people with both diabetes and schizophrenia had greater cognitive impairment compared to the other groups. Furthermore, these impairments were positively associated with diabetes severity markers. Thus cognitive deficits in individuals with schizophrenia likely pose a further challenge in diabetes management, as impaired cognition can impair capacity to understand DM education and the patient-role in DM self-management; and to follow through with medical instructions. It may contribute to whether or not a healthcare provider even offers such DM education or instructions.

4.2 Challenges in Providing Medical care for people with Schizophrenia

Although people with mental illness are at high risk for developing comorbid somatic illnesses, the general health care needs of this population are commonly neglected (71).

Schizophrenia is a psychotic disorder which if not controlled will lead to delusional thoughts and behaviour. For some patients, it is challenging to find the correct medications or adhere to prescribed anti-psychotic medication. When this occurs, and the primary psychiatric disorder is poorly controlled, it is conceivable that adherence to DM medication and treatment plan instructions will be abandoned, further increasing the risk of adverse consequences of DM.

People with schizophrenia may have a lack of resources outside of the medical system which hinders their success in deriving benefit from generic models of diabetes care. This vulnerable subpopulation may have more difficulty navigating the medical system, and translating and integrating information conveyed through generic diabetes

education models. Multiple factors may contribute including lower socioeconomic status (SES) (81, 82). Economic limitations may impede their ability to use transportation to attend appointments, to buy healthier foods, or to follow appropriate exercise programs. Economic constraints may be combined with an often unstable social environment. For example, patients may not have a fixed address or telephone number, thus disrupting follow-up and communication. Family support may also be fragmented and inconsistent and, where present, may be more focused on supporting the management of the psychiatric condition rather than the seemingly less important medical comorbidities.

Another factor which adds to the complex relationship between DM and schizophrenia and which may contribute to adverse events is the co-existence of other psychiatric disorders, including depression and substance abuse. It has been demonstrated that individuals with a diagnosis of substance use disorders have worse glycemic control than individuals with schizophrenia or other mental disorders (65). Several studies have reported that depression is associated with poor adherence to self-management recommendations, poorer glycemic control, greater social impairment and an increased use of health care services (83-85). Major depressive disorder may also represent a risk factor for cardiovascular disease (86, 87). Among people with stable coronary artery disease, the presence of anxiety and depression predicts major cardiac events such as cardiac death and myocardial infarction (88). Thus, the presence of comorbid mental diagnoses may pose additional barriers in achieving positive outcomes.

4.3 Potential gaps in the Medical System

The disparity in DM care and outcomes related to schizophrenia may be explained by factors relating not only to the individual with schizophrenia, but also by provider and health system factors. This could affect self-management, provider management and ultimately impact clinical outcomes. Health care providers who are not experienced in caring for the special needs of schizophrenia may lack the skills to effectively communicate with this group. Health care professionals may misinterpret somatic complaints and delay diagnosis and treatment, especially if a patient is displaying psychotic or aggressive behaviour, or if a patient is sedated secondary to their psychotropic medication. A study assessing nurses' attitudes toward a standardized patient demonstrated that the group randomized to evaluate a patient believed to be taking antipsychotics was less likely to attribute chest pain to a cardiac etiology than the group evaluating a patient who was not taking psychotropic drugs (89). Daumit et al. demonstrated that patients with schizophrenia were at least twice as likely to experience an adverse in-hospital event during a medical or surgical hospitalization compared to people without schizophrenia (55).

Many healthcare professionals are not adequately trained to address physical and mental health issues, and they may not believe that health and wellness are achievable in people with serious mental illness. However, this preconception has been challenged by a study by Menza et al. (90). This group demonstrated that among people with schizophrenia or schizoaffective disorder, receiving atypical antipsychotic agents, the adherence rates to a weight loss program and mean weight loss at 1 year were comparable to people without mental illness.

While the CDA practice guidelines outline a chronic care model to achieve clinical and biochemical targets that reduce DM-related complications, there still remains a gap between recommendations and clinical practice (91). It has been demonstrated that people from socially disadvantaged populations have significantly higher rates of diabetes complications, health services utilization and poor glycemic control (92). The review by Glazier et al. indicated that short-term didactic teaching aimed at improving DM knowledge, a widely-used method in DM management, may be of limited value in disadvantaged populations. Tailored interventions, addressing aspects such as community and culture, may be more effective. Yet these interventions require expertise, input and resources which extend far beyond what is offered in traditional DM programs. This may contribute further to an inequality in DM care and outcomes.

Currently, it is known that people with schizophrenia are at increased risk for developing DM, and that they are also at increased rates of morbidity and mortality from medical conditions. It also has been demonstrated that despite universal access to health care in Ontario, the recommended chronic care model for DM management still results in inequalities in DM care. The current model of DM management within the primary care setting is yielding still results. Most primary care systems have not fully adopted a “chronic care model”, though they are in the process of doing so, particularly in family health teams when there is funding. Therefore primary care is still organized largely around the treatment of acute problems; thus patients with chronic conditions, especially comorbid chronic diseases, are difficult to manage in the typical primary care setting. The medical needs of people with schizophrenia have yet to be elucidated. Therefore, receiving *equal* access and treatment may not result in equitable care. Current studies

assessing the relationship between schizophrenia and quality of DM care have focused primarily on the American healthcare system, and specifically on the VA population. Results of these studies have not been consistent, and they are not easily generalizable to other healthcare systems and populations. In addition, quality of care has been represented by markers which are intermediary and reflect process of care, such as HbA_{1C} or the number of followed recommendations. These are likely surrogates for negative outcomes, but they may not reflect adverse events directly. On the other hand, measuring acute events, such as acute diabetes emergencies, may be more useful. These acute events not only tax the healthcare system, they have a direct negative impact on the patient. Thus it is important to evaluate this aspect of quality of DM care, preventable hospital visits, among people with schizophrenia, a vulnerable and high risk population in Ontario. As represented in figure 1, the relationship between schizophrenia and acute DM complications is complex. Studies are certainly necessary to assess the impact of altering potential risk factors such as medication use, weight modification and social support. However, the relationship between schizophrenia and adverse clinical events has not been demonstrated among a Canadian population.

5. Context for the current study

Therefore the current study will evaluate quality of diabetes care among people with schizophrenia in Ontario, by examining risk of acute DM complications that should be avoidable in the presence of optimal DM care (3).

6. Research Methods

6.1 Design

This was a population-based retrospective matched cohort study evaluating the relationship between schizophrenia and acute complications of DM in people with newly diagnosed DM in Ontario. Acute complications of DM included emergency department visits or hospitalizations for hypo- or hyperglycemia, or hospitalization for infections more commonly found in people with DM. Administrative databases were used to identify individuals within the cohort and link them to event occurrence.

6.2 Data Sources

Subjects were identified using the Ontario Diabetes Database (ODD), the Ontario Health Insurance Claims database (OHIP) and the Canadian Institute for Health (CIHI) discharge abstracts database (DAD). Data on outcomes of acute complications of DM were tracked using claims to OHIP (physician visits), the CIHI DAD (hospitalizations) and the National Ambulatory Care Reporting System (NACRS –emergency department visits). Demographic data were obtained from the Registered Persons Database (RPDB). Census data were used to determine the median neighbourhood income for the residence of the subjects. Anonymous records for all subjects were linked between the separate databases using a unique, reproducibly scrambled numeric identifier.

6.3 Study Population

6.3.1 Inclusion criteria

The study population included Ontario residents ages 18 to 50 years, who were diagnosed with DM between April 1, 1996 and March 31, 2005. The study population was limited to people up to age 50 to minimize medical comorbidity which may lead to ED visits, making it difficult to assess DM outcomes. Individuals were drawn from the ODD, a validated database of all Ontario residents diagnosed with DM at a physician visit or during a hospital admission since 1992. Incident cases were defined as persons who have been under observation for at least four years with no evidence of DM (no prior physicians' claims or hospital records bearing a diagnosis of DM) who subsequently met the case definition during the study accrual window. In the ODD, a case of DM is defined by either two claims to the Ontario Health Insurance Plan (OHIP) with a diagnosis of DM in a two year period or one hospital discharge abstract with a diagnosis of DM. The incidence date is defined by the first of those records. This case definition algorithm has been validated (93) by comparison to data abstracted from primary care charts and found to have a sensitivity of 86% and a specificity of greater than 97%. For the purpose of this study, the index date was the date of diagnosis of DM. No subjects were included after March 2005, to allow for at least one year of follow-up.

Within this population, two cohorts were identified –one of patients with pre-existing schizophrenia at the time of diagnosis of DM and one of matched persons with DM but free of schizophrenia. Cases of schizophrenia were identified by using one of two methods. Either they had at least two hospitalizations for schizophrenia or one hospitalization and one physician service claim (OHIP billing code 295) not related to the

hospitalization for schizophrenia, after April 1, 1992 and before the diagnosis of DM or March 2005, whichever occurred first. Hospitalizations were identified in the CIHI database. A hospitalization was attributed to schizophrenia if the most responsible diagnosis recorded in the diagnostic field of the discharge abstract was for schizophrenia using ICD-9 CM = 295.0-295.9 or ICD-10 = F20.0X-F20.9X coding. This case identification method for schizophrenia has face validity but its positive predictive properties await results of an on-going validation study (94).

Matched controls were identified as persons without OHIP or CIHI records for schizophrenia at any time during the observation period (April 1, 1992 through March 31, 2006). They were matched to schizophrenia cases on age (+/- two years), gender, geographic region (LHIN) and both area and individual-level socioeconomic status (SES). Ecologic attribution of SES from census data was used to match neighbourhood level SES of cases and controls. To do so, a validated algorithm using 1996 Canadian Census data was used (81). In addition, an individual-level indicator of low SES was used for matching. Persons on social assistance (welfare and disability support) qualify for coverage under the Ontario Drug Benefit Program (ODB). Coverage thus provides a binary measure of low SES at the patient level. Persons were considered to have qualified for coverage if they received any reimbursed drug benefits under the ODB in the year prior to the index date or within 6 months after the diagnosis of DM. Cases and controls also were matched on this individual indicator of low SES. Up to three matched controls were sought for each case of schizophrenia.

These cases and controls formed the cohort of persons in whom the outcome was measured.

6.3.2 Exclusion Criteria

People were excluded if there was an OHIP claim for diabetes in the four years prior to the index date. Those whose age was less than 18 years or greater than 50 at the time of index also were excluded. People who did not meet the case definition for schizophrenia but had any hospitalization or OHIP claim for schizophrenia were not included. People who did not meet the case definition for schizophrenia, but had evidence of another psychiatric psychotic diagnosis were excluded. This was identified by the presence of one or more of a set of diagnostic codes recorded in OHIP or CIHI records (appendix 1).

6.4 Study Outcome

6.4.1 Primary Outcome:

The time to an acute complication of DM was defined by hospitalization or emergency department visit for hyper- or hypoglycemia in persons with schizophrenia compared to matched controls without schizophrenia.

6.4.2 Secondary Outcome:

- a) Time to the first event of *either* hospitalization or emergency department hyper- or hypoglycemia *or* hospital admission for any of the following infections: skin and soft tissue infection, bacteremia, pneumonia, or urinary tract infection.
- b) Time to infection.
- c) Time to skin and soft tissue infection.
- d) Time to bacteremia.
- e) Time to pneumonia.

- f) Time to urinary tract infection
- g) Time to death from any cause

Prior to 2002, emergency department visits were available only from OHIP claims. From 2002 onward, more detailed records are available from NACRS. Accordingly, the primary event of the first date of diagnoses of hyper- or hypoglycemia as the primary reason for the ED visit was using code 250 and 251 from the OHIP Emergency Services file. Given that 250 encompasses Diabetes Mellitus, without providing details of the nature of the visit, it is not possible to reliably distinguish whether the reason for the ED visit was for hypo- or hyperglycemia. From April 1, 2002 onward, ED visits were determined from the NACRS record, in which any position contained the following (E10-E14).0 or (E10-E14).1 (see appendix 2). Hospitalizations were determined using the CIHI-DAD record, using the following codes: before April 1, 2002 records in which the most responsible diagnosis was 250.0-250.3; from April 1, 2002 onward, records in which the most responsible diagnosis was (E10-E14).0 or (E10-E14).1. It is not possible to distinguish between hypo- or hyperglycemia when only OHIP data was available, as both diagnoses are coded as 250.

The secondary outcome was identified as the first date for which a patient either developed the primary event (as outlined above) or had a hospital admission with one of the listed infections as the most responsible diagnosis. (See appendix 3 for coding of infection).

Outcomes were measured from the index date (date of diagnosis of DM) until the end of the observation period (March 31, 2006). Patients were censored at death,

migration out of province or development of the outcome of interest. Death was determined using the enriched RPDB, which includes deaths that occurred in hospital.

6.5 Covariates

6.5.1 Demographic Variables

Baseline demographic covariates at index (date of DM diagnosis) included age, gender, neighbourhood income quintile, and ODB coverage. Again, persons were considered to have qualified for coverage if they received any reimbursed drug benefits under the ODB in the year prior to the index date or within 6 months after the diagnosis of DM. Age in years at diagnosis of DM was obtained from the RPDB. The same database was used to obtain postal codes at index, allowing for estimation of neighbourhood income quintile. Other baseline variables were recorded including number of visits to a primary care physician in the year preceding index date and presence of a usual care provider. A usual care provider was considered to exist if in the two years prior to the index date there were more than two physician visits *and* at least fifty percent of these visits were to the same physician.

6.5.2 Comorbidity

A measure of comorbidity was developed and included in multivariate statistical modeling to control for any effects on the outcome that may be attributable to comorbidity and not from the problems that arise directly from schizophrenia. Comorbidity was estimated using the Johns Hopkins Collapsed Aggregated Diagnosis Groups (CADGs) (95). An ADG is a grouping of diagnosis codes that are similar in terms

of severity and likelihood of persistence of a health condition over time. All ICD-9 codes used by physicians over an extended period, such as a year, are assigned to one of 32 ADGs. The collapsed scores are predictive of certain illness categories. In this study, CADG category 5 was recorded, as it represents a chronic unstable medical disease. Lastly, Resource Utilization Bands (RUB) was recorded. The RUB incorporates the diagnostic groups, placing people into one of 6 categories (from lowest to highest) that predicts the healthcare expenditure for a given individual.

6.5.3 Health Care Utilization

It was not known whether people with schizophrenia would have greater or fewer outpatient visits to physicians. As outlined previously, some studies suggest that in select American populations, persons with psychiatric illness and DM tend to have more frequent visits. However, it is conceivable that they may have fewer visits given that persons with schizophrenia have impaired motivation, poor social support, and may be less capable of navigating the medical system and obtaining care. To address this, the number of specific physician visits was recorded between the index date and both the first primary and secondary outcome event. These data were obtained from physicians' claims recorded in the OHIP database and included visits to primary care physicians (physician code "00"), psychiatrists (physician code "19") and internal medicine specialists. (Internal medicine specialists all bill under the same physician billing code "13", so it was not possible to differentiate endocrinologists or other diabetes specialists within this broader group of internists.)

6.6 Statistical Analyses

All statistical analyses were performed using SAS version 9.1 and statistical significance was set at a 2-sided P-value less than 0.05.

6.6.1 Power calculation

The power calculation for this study was intended to show a minimum hazard ratio (HR) that could be estimated confidently given the sample size. The calculations were based on evaluating two cohorts using the long-rank test, using the approach of Schoenfeld and Richter (96). Calculations included 1262 people with schizophrenia and DM and three times as many people with DM but without schizophrenia. The accrual time was 10 years, with additional follow-up time of one year. The power calculation was conducted with the assumption that the hazard ratio (HR) between the two groups would be a minimum of 1.2. The Type I error probability associated with this test of this null hypothesis is 0.05. The null hypothesis was tested with respect to a two-sided alternative hypothesis. These calculations yield a power of 99 percent to detect a minimal HR of 1.2. Given that the hazard ratio derived in this study was actually greater than 1.2, these calculations imply that the sample was more than adequate to estimate the key HR in the model.

6.6.2 Descriptive Data

Overall proportions or means, medians, ranges, and 95% confidence intervals were calculated for the covariates. These were calculated separately for the group with

and without schizophrenia. Comparisons were made between the groups using t-tests or chi-square analyses accounting for strata, as the groups were matched in a ratio of 1:3.

Annualized rates of physician visits were calculated for the people who had an event. This was done by dividing the number of visits to each specific type of physician (primary care, psychiatrist and internal medicine specialist) between the index and event date by the number of days between the two dates. This value was then multiplied by 365 to achieve an annualized rate.

To manage the irregular distribution of physician visits, the many individuals with no visits and a right-skewed distribution among those with one or more visits, a dichotomous variable (indicating whether the individual had any physician visits during this window) was created and used in some analyses.

Collinearity between variable pairs in predicting the outcome was assessed using the variance inflation factor (VIF). An estimated VIF of greater than 10 prompted the exclusion of one of the two collinear variables from multivariable modeling.

6.6.3 Primary Outcome

Frequency of a first hospitalization or visit to an emergency department for hypo- or hyperglycemia by schizophrenia status was described. Survival analysis using a Cox proportional hazard model was estimated using the number of days from index to the first relevant event as the outcome. A series of univariate Cox models were fit in order to assess the individual effects of each of the covariates (including schizophrenia) on the outcome. A multivariable Cox model then was fit to determine the hazard ratio associated with co-existence of schizophrenia after adjustment for potential confounders.

The Cox proportion hazards assumption (that the ratio of the hazard functions of developing the primary outcome over time was constant) was tested using Schoenfeld residuals. For each candidate variable of the multivariate model, scaled Schoenfelds were plotted against time, and the resultant plots were inspected visually. Variables for which the residuals appeared to have a time trend were assumed to have violated the proportional hazard assumption. This analysis was supplemented by examining whether each variable had a time-varying effect. If there was a significant interaction between survival time (defined as the event-free period) and the variable in question, then the proportional hazards assumption was rejected. Any covariate violating this assumption was managed by allowing the effect of this variable to be modeled as having a time-varying covariate effect in subsequent modeling.

6.6.4 Secondary Outcomes

The above steps were repeated for the secondary outcome of first event of either the primary outcome or hospitalization for infection.

The frequency of death was calculated and proportions calculated for each group.

6.7 Ethical Considerations

Prior to study initiation, ethics approval was obtained from the Institutional Review Board at Sunnybrook Health Sciences Centre, Toronto, Ontario.

7. Results

7.1 Subjects

There were 1262 newly diagnosed cases of diabetes among people with previously diagnosed schizophrenia in Ontario between 1996 and 2005. There were a total of 3771 matched controls. There were 1251 people with schizophrenia matched to 3 people in the comparison group without schizophrenia (99.13%), 7 people with schizophrenia matched to 2 people in the comparison group (0.55%) and 4 people with schizophrenia matched to 1 person in the comparison group (0.32%). The final number of individuals included in the analysis was 5033.

7.2 Baseline Characteristics

Baseline data for the groups with and without schizophrenia are presented in Table 1. The mean age at index (date of diagnosis of diabetes) was 38.8 years and about 47 percent of the cohort was female. Over 60 percent of the people were in the lowest two income quintiles and almost 80 percent of people had received ODB coverage. The two groups were well matched on the matched variables (age, gender, ODB coverage and income quintile).

Compared to people without schizophrenia, those with schizophrenia were more likely to have seen a primary care provider in the year preceding the diagnosis of diabetes (median 11 versus 7 visits) (figure 3), but less likely to have a usual care provider. They were significantly more likely to be placed in a higher resource utilization band than similar people without schizophrenia. There was no significant difference in the proportion of people with a chronic unstable medical illness.

7.3 Follow-up

The mean duration of follow-up in the analysis to primary event was 4.0 years in the schizophrenia group, compared to 4.4 years in the non-schizophrenia group (Table 2). With regard to analysis for the secondary outcome (primary outcome or hospitalization for infection), the mean follow-up was 3.8 years in those with schizophrenia compared to 4.2 years in those without.

Of people who suffered the primary event, the mean duration between the index date and the primary event was 0.91 years in the group with schizophrenia and 0.93 years in the group without schizophrenia. For those who suffered a secondary event, the mean duration between the index date and the secondary event was 1.21 years among individuals with schizophrenia and 1.21 years among those without schizophrenia.

7.4 Descriptive Data

In the group of people with schizophrenia, there were 158 (12.52%) people who required *at least* one hospital admission or emergency department visit for hypo- or hyperglycemia, compared to 277 (7.35%) people in the group without schizophrenia (Table 2).

When the outcome included the *first* of the primary outcome or hospitalization for infection (ie. secondary outcome), 268 (21.24%) individuals were considered to have had an event in the group with schizophrenia, compared to 513 (13.60%) events in the group without schizophrenia. When assessing the individual infection rates, the most significant difference was in the percent of people requiring hospital admission for pneumonia (Table 2).

During the follow-up period, those with schizophrenia had an almost 2-fold increased death rate ($P < 0.0001$).

7.5 Health Services Utilization

Among the people who had an event, there was a significant difference between the number of annualized visits to a primary care physician between index and the primary outcome *and* between index and the secondary outcome (Table 3), indicating that individuals with schizophrenia had higher utilization rates. The same relationship was found when evaluating annualized visits to a psychiatrist between the index and each outcome. With respect to annualized visits to an internal medicine specialist, there was no significant difference between the groups for either event. However, there was a trend suggesting those with schizophrenia received more visits to an internist than those without.

The annualized visits to a primary care physician between index and the primary or secondary event among those who had an event was much lower than the number of visits in each group overall in the year preceding the diagnosis of diabetes, suggesting a different distribution in the people experiencing these outcomes. In Table 4, only the people who had at least one visit to the respective physician groups are displayed. Greater than 40 percent of people with and without schizophrenia did not have any visits to a primary care physician between index date and the primary outcome. More than 60% of the people with schizophrenia did not see a psychiatrist during this period. The results are similar for the period between the index date and the secondary outcome.

7.6 Cox Proportional Hazard Analysis

The results of the univariate Cox proportional hazards analyses comparing the rate ratio of developing the primary event are presented in Table 5 and the results comparing the rate ratio of developing the secondary event are presented in Table 6. Compared to controls, presence of schizophrenia was associated with an unadjusted hazard ratio (HR) of 1.74 (95% confidence interval (CI) 1.42-2.12, $P < 0.0001$) of developing the primary event (figure 4). Schizophrenia was associated with a HR of 1.62 (95% confidence interval (CI) 1.39-1.89, $P < 0.0001$) of developing the secondary event (figure 4). Of note, in many cases the date of DM diagnosis was case finding, rather than detected via screening. As seen in figure 4, the index date and event occurred within days of each other. This should be prevented in a population that is being screened for DM, rather than the diagnosis being made because the patient has become symptomatic from the DM.

Collinearity of potential predictor variables was tested using the variance inflation factor (VIF) for both the primary and secondary outcome. For each outcome, the VIFs were all less than 10, indicating that there was no collinearity between variables in predicting either outcome. Therefore all covariates could be added to subsequent multi-variable models.

Cox proportional hazards assumption was tested for each covariate and both the primary and secondary outcome. When the Schoenfeld residual variables were graphically plotted against time, the only variable which appeared to potentially violate the assumption of proportional hazards for the primary event was annualized visits to a primary care physician. However, since this variable was calculated only for people who

actually had an event, it was not included in subsequent models. With respect to the secondary outcome, the resource utilization band category “3”, as well as the presence of a usual provider before diagnosis of DM appeared to violate the assumption. To overcome this violation, subsequent multi-variable survival models included an interaction term between the time-to-event and each of these variables.

Multivariate analyses were performed to adjust for variables that may influence the association between schizophrenia and each outcome. Table 7 displays results of the HR for the primary outcome after adjusting for the following variables: age, gender, income quintile, presence of ODB coverage, RUB at baseline, presence of a chronic unstable medical condition, presence of a usual care provider and number of visits to a primary care physician in the year preceding the diagnosis of diabetes (Figure 5). Presence of schizophrenia had a HR of 1.68 (95% CI 1.4-2.10 P<0.0001) for the primary outcome. Using this model, the individual effect of each variable on the primary outcome is displayed, comparing the effect to that found for each variable in a univariate analysis (Table 7).

The same process was repeated for the secondary outcome (table 8). After adjustment for potential confounding variables, the HR for the secondary outcome was 1.50 (95% CI 1.26-1.78 P<0.0001).

The model used for the composite secondary outcome was repeated, evaluating each component of the secondary outcome (Table 9). The rate ratio was increased for at least one hospital admission for infection (HR=1.497, 95%CI 1.258-1.781). Although there was a trend of increased hazard ratio for people with schizophrenia for each

individual type of infection, only the hazard ratio for pneumonia was statistically significant.

7.7 Linear Hypothesis Testing

The importance of the covariates that represent modifiable characteristics was assessed using the hypothesis that all of the coefficients for these covariates are zero. The process was performed twice, for the primary and secondary outcome respectively. Both assessments indicated that none of the coefficients were significantly different from zero, indicating they should all be included in the final model for each outcome.

8. Discussion

This is the largest study in North America to explore the risk of acute complications of diabetes (DM) among in people with schizophrenia and newly diagnosed DM. This is also the first study evaluating acute DM-related outcomes in people with schizophrenia using a population-based cohort. To date, published literature assessing diabetes care among people with schizophrenia has focused on intermediary endpoints, such as rate of retinal eye screening examinations or glycosylated hemoglobin measures. Previous studies have included cohorts within the Veterans Affairs population, or from private drug benefit claims. These cohorts comprised much smaller sample sizes, and do not represent DM care and outcomes in a universal publicly-funded health care system, and as such did not include all members of the population such as those in lower income groups. Preventable hospital visits in an ambulatory-sensitive medical condition are an important process of care measure. An increase in such hospital visits among people with schizophrenia is an important finding because it reflects the quality of DM care provided to this population. This outcome confers a direct negative impact suffered by the patient, as well as the health care system.

8.1 Major findings

8.1.1 Primary outcome: Rate of hospitalization or emergency department visit for hypo- or hyperglycemia

Among people with newly diagnosed DM in Ontario, those with a pre-existing diagnosis of schizophrenia had a significantly higher rate-ratio of at least one hospitalization or emergency department visit for hypo- or hyperglycemia, compared to

similar people without schizophrenia. This relationship remained significant after adjustment for potential confounding variables (HR =1.68, 95% CI =1.34-2.10, P<0.0001)

8.1.2 Secondary Outcome: Rate of hospitalization or emergency department visit for hypo- or hyperglycemia *or* hospitalization for infection

Assessment of the combined endpoint of the first of either a hospital visit relating to hypo- or hyperglycemia, *or* infection (skin and soft tissue infections, pneumonia, urinary tract infections and bacteremia) among people with newly diagnosed DM in Ontario revealed that schizophrenia was associated with an increased rate ratio of at least one of these outcomes. Again the relationship between schizophrenia and the composite outcome remained significant (HR = 1.50, 95% CI 1.26-1.78, P<0.0001)

The different components of the composite outcome were evaluated individually. As demonstrated in the primary analysis, the hazard ratio for hospital visit for hypo- or hyperglycemia was increased among people with schizophrenia. Similarly, the hazard ratio for infection also was increased (HR = 1.38, 95% CI 1.09-1.73). Each of the four categories of infection was evaluated, and schizophrenia significant increased the risk for each diagnosis except bacteremia.

8.1.3 Secondary Outcome: Mortality Rate

Finally the study evaluated the relationship between schizophrenia and mortality rate among people with newly diagnosed DM in Ontario. Prior to initiating the study, it was assumed that the expected death rate would be low. Considering that the study

population was between 18 and 50 years at diagnosis and the maximum follow-up was 10 years, this was a relatively young cohort. Accordingly, mortality was set as a secondary outcome, assuming there would be a lack of statistical power to detect a difference in mortality rate if indeed there was a difference. However, a statistically significant mortality difference was demonstrated.

8.2 Interpretation:

Not only are people with pre-existing schizophrenia experiencing more acute complications of DM but the time to these adverse events is shorter compared to individuals without schizophrenia. This increase in hospital visits has implications at a number of levels: there is direct suffering for the patient, there is a burden to the healthcare system both in terms of time and financial resources, and acute complications of DM likely reflect a level of DM-control that increases an individual's risk of developing chronic complications.

There are several potential factors that may contribute to the increased risk of acute complications of DM in people with schizophrenia compared to similar people without. These include factors at the patient level and at the level of the health care system (figure 1). With respect to patient factors, both behavioural and clinical factors can make it difficult to effectively self manage DM, thus increasing the risk of avoidable hospital visits. It is conceivable that patients with co-existing schizophrenia and DM may not prioritize DM care if they feel their mental health issues are more important. It may be more difficult to follow through with appointments and instructions regarding medications or lifestyle changes, due to poorly controlled schizophrenia or side effects of

the schizophrenia treatment. If delusions are present, they may be fearful or not trust the medical system. Each of these factors can worsen glycemic control, and thus increase susceptibility to sequelae of poorly controlled DM.

People with schizophrenia have more fragmented social supports than the general population. They decline in several socioeconomic domains and quality of life measures and often are not employed (97). They are commonly unmarried and do not have, or are estranged from relatives. Patients are overrepresented in the homeless population (98). It is common for this population to reside in group homes or shelters. The living environment combined with lack of financial resources make it difficult to access healthy food choices, maintain daily routines and engage in physical activity. DM alone has been associated with reduced quality of life, with co-existing schizophrenia only compounding the problem. Among a cohort of people with mental illness, those with DM were significantly more likely to report lower satisfaction with physical health than those without DM (99), but not with other life domains. This suggests that DM-related reductions in quality of life specifically impacts health-satisfaction in people with both conditions.

Poor DM self-management may result not only from lack of social and financial resources, but from behavioural features of schizophrenia or the medications used to manage the disease. As a chronic psychiatric illness, schizophrenia can manifest as a number of different symptoms. The “positive symptom”, often synonymous with psychosis include hallucinations and delusions (100). When an individual’s sense of reality is disturbed, it is conceivable that he/she may not understand or trust instructions given to him/her for DM-management, let alone follow such instructions. “Negative”

symptoms and affect disturbances result in a general sense of amotivation (101). Patients experience a loss of drive for all forms of engagement, including both social interaction and constructive activity. This can lead to significant self-neglect, again contributing to poor hygiene and poor DM self-management. Symptoms suggestive of hypo- or hyperglycemia, or the onset of infection, which may prompt others to seek intervention, could be ignored in a patient with schizophrenia experiencing negative symptoms. As demonstrated in this study, among the people who suffered an event, there was a significant proportion of people who did not have any physician visits between index and event.

Similarly, second-generation antipsychotic (SGA) medications have side effects that can pose challenges in DM self-management. The most common adverse effect is weight gain and insulin resistance. There is a well documented relationship between obesity and DM (102). Independent of lifestyle factors, weight loss is more difficult with all of the SGAs but particularly with Olanzapine and Clozapine. The widespread use of these agents already was occurring during the observation window in this study.

Another issue which may contribute to quality of care and outcomes in DM is access to care (44) or access to appropriate care. As seen in the Kaplan-Meier curves, there is a depression in the curve for the primary and secondary event rate immediately for both groups. Although participants were excluded from the analysis if the diagnosis of DM and the event occurred on the same day, it is conceivable that the initial management at the time of DM diagnosis did not allow time to establish effective management of DM, leading to an ED visit. After the first few days from DM diagnosis, the curves begin to separate. It is possible that individuals with schizophrenia may have reduced access to

care. However, this study was consistent with previous literature, indicating that people with schizophrenia actually had a greater number of physician visits. Despite having more frequent outpatient physician visits, people with schizophrenia still were more likely to suffer an acute complication of DM. Therefore these encounters may not be effectively addressing DM-related care, suggesting that when individuals with schizophrenia do seek and receive medical care, it is substandard. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study evaluated treatment rates among schizophrenia patients who had been screened for metabolic disorders (diabetes, hypertension, and dyslipidemia) (103). Their data indicated a significant non-treatment rate for these conditions. At study entry non-treatment rates were 30.2 percent for DM, 62.4 percent for hypertension and 88 percent of individuals with hypertension were not receiving treatment. In this study, there was a high likelihood of not seeing any physician among the people who suffered an event. This is especially important among the group with schizophrenia, as the majority of them received ODB coverage. Thus, if they were taking SGAs, they would require a prescription renewal each month. This likely means that they were not taking antipsychotic medication as prescribed, and certainly their glucose levels were not being monitored, nor were other metabolic risk factors being addressed. All of these factors increase the risk of repeat acute complications, as well as the risk of long-term complications.

At the provider level, it is possible that physicians and other healthcare providers are addressing other patient needs, such as social issues. In 2008, an expert consensus panel published a summary of evidence concluding that in general, somatic health is often neglected in people with severe mental illnesses such as schizophrenia and bipolar

disorder (104). The result is poorer physical health, and a shorter life expectancy, primarily due to premature cardiovascular disease.

Several factors likely contribute to such a disparity in medical care and outcomes in people with schizophrenia. Provider factors include challenges faced by both primary care physicians and mental health providers. There may be a lack of training of health care professionals to care for both medical issues and mental health issues. Providers may be distracted by the patients' mental illness, resulting in challenges in obtaining pertinent patient history and other aspects of communication. Furthermore, psychiatrists and primary care physicians generally work under great time constraints, limiting their availability to provide additional services (105). Stigmatization of psychiatric conditions not only impacts social interactions, but also discriminates against mentally ill individuals in provision of healthcare. Health care providers may misinterpret patient reports or behaviours, if there is a history of psychotic illness or antipsychotic medication (89).

Health care professionals may not be convinced that health and wellness are feasible in a population with schizophrenia, providing differential DM care compared to people without mental illness. Data suggests that people with serious mental illness are as able as the general population to achieve adherence to dietary recommendations and weight loss, suggesting that the presence of mental illness itself is not sufficient to prevent patients from achieving specific health goals (90, 106, 107). Despite the challenges faced by people with mental illness, studies indicate that people with schizophrenia and other types of serious mental illness can recover from addiction (108, 109) (110), stop smoking (111), prevent or reverse weight gain (109, 110) and develop healthier eating and exercise habits (107, 112).

This data suggests that simply increasing the number of physician encounters does not improve DM-related outcomes in individuals with schizophrenia. Perhaps it is the content of the visits, or the lack of integration with other health care professionals and social resources. Current models of DM care may not be appropriate in this population. Common care paths including group education and the *type* of visits may require change. The current increase in visit frequency among the majority of people with schizophrenia suggests that physician visits for people with schizophrenia may not be equitable with respect to quality of DM care. Although it is necessary for individuals with schizophrenia to visit physicians regularly, it may be that the frequency is unnecessarily elevated, as these people are not receiving the care that they require.

While acute complications of DM may be reversible, they may predispose individuals with DM to chronic and more severe complications. Specifically with respect to foot infections, there is an increased risk of chronic complication and limb amputation. People with schizophrenia may not have the luxury of a living environment in which they can maintain personal hygiene. Poor hygiene may predispose to infection. When signs or symptoms of infection develop, they may not recognize and seek treatment in a timely fashion for the multiple reasons outlined above. Furthermore, it has been demonstrated both *in vitro* and *in vivo*, that hyperglycemia is associated with increased infection risk. In a sense, infection may be considered a predisposing factor to the end-organ damage caused by long-term hyperglycemia.

With respect to the increased mortality rate demonstrated in people with schizophrenia, the cause-specific mortality was unknown. It is known that cardiovascular and respiratory disease represent the leading cause of death among people with

schizophrenia. It also has been demonstrated that DM significantly increases the risk of cardiovascular disease and cardiovascular death. Therefore among people with both DM and schizophrenia the risk of cardiovascular disease would be increased further. There are likely patient factors, including metabolic and behavioural, as well as system factors that elevate this risk. As outlined above, memory, cognition and mood issues certainly can play a role in patient self-care. Compared to the general population, people with psychotic disorders have higher rates of smoking and substance abuse (62, 110, 113). Despite a considerable reduction in tobacco use in the general population over the last few decades, there has been almost no reduction among smokers with psychiatric illness (110). These behaviours, coupled with the difficulties in following a healthy diet and exercise plan certainly can increase the risk of cardiovascular burden.

However, health system limitations also contribute to substandard quality of medical care which increases this risk in people with mental illness. Among patients 65 and older with chronic medical conditions (including psychotic illness), unrelated disorders are relatively neglected and under-treated (15). As described previously in the CATIE study, even when metabolic conditions are identified in the high-risk population with schizophrenia, they are largely under-treated (103). A study by Kreyenbuhl et al demonstrated that when cardiovascular risk factors were being addressed (lipid and blood pressure lowering), patients with *both* DM and serious mental illness were treated less aggressively for cardiovascular risk than individuals with either condition alone (72). A Canadian study conducted in Nova Scotia evaluated the association between mental illness and circulatory disease patterns of care and outcomes (114). Not only were psychiatric patients more likely to die from circulatory disease (hazard ratio =1.31, 95%

confidence interval 1.25-1.36), they were no more likely to undergo a number of relevant procedures than the general population. This suggests that even in a Canadian universal health care system, mental illness still limits type of health care received. Interestingly, it has been shown that in patients treated for schizophrenia and DM and/or hypertension, medication adherence differed across medications (115). Specifically patients were more likely to demonstrate poor adherence to hypoglycemic or antihypertensive medications than antipsychotic medications. This highlights the interaction between patient and system factors. Perhaps different strategies are required to address adherence to DM and other medical treatments in this population.

There is lack of consensus as to which health care professionals are responsible for assuring that both physical and mental health issues are being addressed. Overall, there is a lack of integration within the Ontario medical system, thus fragmenting the care of medical issues and mental health. Thus it difficult to extrapolate the results from the VA studies described above, as there is considerable integration of medical services and patient records within the VA system. Furthermore, there may be selection bias within the populations evaluated in those studies. For example, if people with schizophrenia do not have a fixed address or social support to access the care provided within the VA system, they may have worse DM outcomes but will not be included in such studies.

There are several types of separation between the two systems that care for medical health and mental health: geographic, organizational, cultural and financial (116, 117). It is not uncommon for mental health and medical facilities to be separated geographically, necessitating multiple visits for patients. To that end, the medical records from the various practitioners involved for a particular patient also are separated, limiting

communication between clinicians. Often physicians are not aware of prescription changes, diagnostic testing results or management goals made by other physicians. The lack of shared information between practitioners is complicated by patient privacy policies. Culturally, providers of particular conditions are comfortable with providing care for particular patient conditions (ie. psychiatric or medical), rather than seeing themselves as a care provider for the whole person with these conditions. Lastly funding is often targeted to a specific area of health, adding additional challenges to integrating the two systems.

8.3 Limitations

This study has limitations. Although using administrative databases allows for analysis of a large population-based cohort, the databases lack clinical, social and laboratory data. Although the Ontario Diabetes Database has a high specificity to correctly identify people with DM, it does not provide information about the type of DM. However, given that the majority of people with schizophrenia who develop DM have type 2 DM, there were likely a higher percentage of people in the group without schizophrenia to have a diagnosis of type 1 DM. Type 1 DM necessarily requires treatment with insulin, and innately is associated with more frequent episodes of both hypo- and hyperglycemia, specifically diabetic ketoacidosis. If type 1 DM is more common in the group without schizophrenia, and there is a recognized increased risk of metabolic decompensation associated with this type of DM, then this subgroup of people contribute to the event rate predominantly in the non-schizophrenic group. Thus, the

current study design possibly represents a more conservative estimate of the risk of schizophrenia on these events, and biases the study toward the null.

There was not sufficient data available regarding which medications people were taking. This is relevant for both psychiatric and DM medications. Since atypical antipsychotic agents, a mainstay therapy for schizophrenia, have been implicated in weight gain and insulin resistance, they likely are contributing directly to the outcome. Knowing this information would help assess the extent to which these medications play a role. It is also unknown which DM therapies were being taken. Lack of necessary therapy may also contribute to acute complications of DM. Among people with DM, people in a lower SES bracket were less likely to take prescribed medications, despite the fact that they were not less likely to receive the prescription. Thus, prescribing the appropriate therapies may not be enough.

Schizophrenia is a dynamic disease, with significant variation in symptoms. How well the psychiatric illness was controlled, or how this impacted the hospital visit for a given outcome was unknown. Certainly, it is possible that people with poorer control of their psychiatric illness are at a higher risk of developing an acute complication of DM. However, this study was designed to assess the *overall* relationship between schizophrenia and complications, regardless of the mechanism through which schizophrenia impacts DM management. On average, people with schizophrenia were more likely to visit primary care physicians, psychiatrists and internal medicine specialists. However, such databases do not reveal what happened at each visit. Additionally, there is only information on frequency of physician visits, but not interactions with other allied health professionals. Perhaps participation from other

health professionals is an area which can provide the greatest benefit to improving such outcomes. This is certainly an area which can be evaluated in future studies.

Along that line, if people with schizophrenia may have a lower threshold for seeking healthcare, it is possible that they were screened for DM more regularly than the matched population, leading to an ascertainment bias. If this is the case, then the group with schizophrenia would be at an earlier stage in the course of DM, which would be protective against acute complications.

Another limitation is that the data do not have a measure of individual SES. This was estimated using neighbourhood level income quintiles, as well as the presence of ODB coverage. Although people with and without schizophrenia were matched on these variables, there still may have been residual confounding despite adjustment. For example, there were a large proportion of people in the lowest income quintile. However, this quintile represents a range and there may have been differential distribution of the two groups, such that those with schizophrenia were clustered toward the lower end of the income range. Furthermore, neighbourhood income level is an average measure. In reality, within most neighbourhoods there is a variation in individual income level among inhabitants. Thus the use of neighbourhood level data as a measure of individual income is associated with an element of inaccuracy. Additionally, ODB coverage was considered if an individual received drug reimbursement under the ODB. Therefore if people are not prescribed medications, or do not use medications (not uncommon in people with schizophrenia) they may be misclassified as not requiring financial assistance for drug reimbursement. They may be misclassified as non-poor.

Details of patients' social circumstances (education level, social supports, and language barriers), history of smoking and substance use, as well as anthropometric measures also were not captured. There are several distinct measures of the construct of socioeconomic status (SES), and a fuller knowledge of these factors (eg. social support, personal income etc) would allow for a better definition of the contribution of SES, and to control for it in the analysis. Assessment of these factors also should be explored in future research.

Previous studies have evaluated laboratory measures such as glycosylated hemoglobin (HbA1c), as a measure of glucose control and long-term DM prognosis. Although this information is lacking in the current study, an elevated HbA1c is an intermediary marker in the causal pathway between DM and acute complications. However, it does not represent a negative outcome by itself, but rather a marker. The goal of this study was to evaluate the relationship between schizophrenia and acute complications of DM, as an outcome. The outcomes measured in this study were not merely markers but rather meaningful events which have a direct negative impact to the patient as well as the health care system. Evaluating the contributing factors or potential markers of such factors will help healthcare providers to understand where to target changes in care in the future.

This study measured hospital visits for hypo- and hyperglycemia or infections more common among people with DM, as acute complications of DM. What is unknown is whether these outcomes are indeed *complications* of DM. The study design relied on chart coding to capture these outcomes in people with DM. Furthermore, OHIP system coding used for the ED visits did not provide enough detail to describe the exact nature of

the medical reason for the visit. It merely used one code (250) to explain DM as the reason for hospital visit. There is a potential for misclassification, as this the coding system used in this study has not been validated. If indeed there is misclassification, it is likely that more people in the group with co-existing schizophrenia would be miscoded, as the psychiatric illness is often the focus for the physicians. However, it is very unlikely that there would be a reason other than DM which would be associated with hypo- or hyperglycemia severe enough that it required an emergency department visit or hospital admission. Therefore, the coding used is likely biases toward the null for a difference in hypo- or hyperglycemia. Given the biologic plausibility of hyperglycemia increasing susceptibility to infection, and the previous literature supporting the increase risk of the stated infections in people with DM, it was felt a reasonable argument to evaluate this outcome as an acute DM complication. However, infections have not been validated as an acute complication of DM. Furthermore, it is possible that physicians may have a lower threshold to admit an individual to hospital if there is co-existing schizophrenia, rather than arranging outpatient management. Regardless these events are considered preventable, and are associated with unnecessary morbidity and perhaps financial cost. Furthermore these events occurred more frequently and more rapidly among individuals with schizophrenia.

This study only assessed the rate of the first occurrence of such hospital visits, censoring patients at the time of first visit. Since these events should be prevented for the most part through effective ambulatory care, even one such event is too many. In reality, there are likely individuals for whom there are several repeat outcomes. Therefore it is likely that the relationship between schizophrenia and acute complications of DM has not

been fully characterized by this study, as multiple visits in a given individual were not evaluated.

Lastly, this study aimed to capture all Ontario residents with schizophrenia and newly diagnosed DM in the specified age range and time frame. The schizophrenia case definition algorithm has good face validity but has not yet been subjected to vigorous validation. However, the chosen case identification method has high specificity, implying that the number of false positives has been minimized, perhaps at the expense of missing some true positive cases. Therefore some cases of individuals with schizophrenia and DM may not have been captured in this population. In addition, the methods used rely on individuals having a valid OHIP card and stable address. It is conceivable that people with schizophrenia do not fit these criteria, due to an increase in homelessness or having identification cards lost or stolen. However, if this is the case, it would suggest that the results of this study are biased in a conservative direction, underestimating the relationship.

8.4 Clinical implications and future strategies

The results of this study are important because they are not only novel, but they indicate people with pre-existing schizophrenia who subsequently develop DM are at higher risk for acute complications of DM compared to similar people without schizophrenia. These complications, including both hospital visits for hypo- or hyperglycemia, or infection should be preventable with effective outpatient medical care. Not only do such events have a direct negative impact suffered by patients and an already overburdened health care system, but they suggest that current models of DM care in

Ontario may not be appropriate in this population. Current guidelines in DM care do not target different models of care for different subpopulations of people with DM.

Shifting the focus of care to a more holistic and integrated approach could lead to improved communication and coordination of medical, mental, and social issues. Combined clinics including a multidisciplinary approach could help coordinate care of different illnesses and issues. This includes increasing the role of nurses, nurse practitioners, case workers and social workers. Such an approach has been demonstrated to be beneficial in a handful of studies from the US. A randomized trial within the Veterans Administration (VA) mental health clinic found that people with serious psychiatric illness randomized to receive onsite primary care were more likely to have improved physical health compared to those with “usual” care (71). Similar approaches have demonstrated promising results in subpopulations of people with mental health issues including alcoholism (118), addiction (109, 119), and depression (120). In 2008 a 3-year pilot program to integrate primary care and behavioural care was initiated in Missouri in seven partnerships (121). Recently, a review of the lessons learned in the first year was published. To date, six sites were involved, representing both urban and rural areas. One of the most successful aspects of successfully implementing and monitoring the program was the inclusion of a project management team. The study is still in its infancy, but is the largest example of changing a system approach, and hopefully will provide information on process and outcomes. A more coordinated model of care may improve communication and patient follow-up, making it easier for patients to attend fewer appointments; and ultimately reduce acute (and chronic) complications of DM.

In addition to coordinating care to create a more holistic approach, strategies to improve patient self-care and empowerment may be effective. Currently, DM care relies on patients making contact with the health care system (eg. they must attend appointments, fill and refill prescriptions, and follow medical instructions). The above approach relies on change mainly from healthcare providers. Training and educating patients to improve self-management of medical issues and/or lifestyle changes requires far less input from health providers. Obesity, sedentary lifestyle and poor nutrition are common among people with schizophrenia and DM and can contribute to poorer DM outcomes. As demonstrated by previous studies (103) when there is treatment for DM, it primarily focuses on glycemic control, but clearly a broader approach to cardiovascular and morbidity risk reduction is warranted. Studies in assessing strategies to improve empowerment and modify lifestyle behaviours have demonstrated considerable potential to reduce smoking and obesity in people with schizophrenia (122-124).

DM education mainly occurs in a predominantly “medical” environment, such as a hospital, medical clinic or DM education center; and takes place in a group setting. Perhaps education models which occur in the home or in the community, with a more individualized approach would be more effective in this population. Although it did not focus on mental illness, a systematic review of interventions to improve DM care in socially disadvantaged populations reported success for several strategies (92). Specifically approaches that included cultural tailoring of interventions, community educators or lay people leading interventions and individualized assessments and reassessments were associated with positive effects, including DM complications and patient-reported quality of life.

Lastly, perhaps an entirely different approach may be necessary which does not reduce hospital visits. The concept of “ambulatory-sensitive” conditions and prevention quality indicators predominantly reflects illness in the general population, but may not extend to the subpopulation of people with schizophrenia. Perhaps individuals with schizophrenia and DM fare better when cared for in hospital, in terms of preventing recurrence or prolongation of these events (eg. infection). The current study did not assess event recurrence but this should be evaluated in future research.

Future studies are warranted to evaluate further more specific factors that contribute to acute complications of DM in a Canadian population with schizophrenia, the effect of modifying these factors on reducing such complications, and whether different models and goals of care improve both patient outcomes and cost to the healthcare system. Newer models will need to be tested in the Ontario system, as the approach of adding physician visits is clearly not the answer. Such strategies would need to be assessed in terms of patient satisfaction and clinical outcomes, as well as cost-effectiveness.

8.5 Conclusions

Compared to similar people without schizophrenia, those with pre-existing schizophrenia and newly diagnosed DM in Ontario suffered a significant increase in hospitalizations and emergency department visits for hypo- or hyperglycemia, and an increase in hospitalizations for infection, and mortality. These findings are novel, in that they not only evaluate intermediary indicators of DM care, but demonstrate a direct negative short-term outcome. This is important as the adverse outcome is suffered at the

patient level, as well as at the health care system level. It is also the first study to evaluate these acute adverse events in people with co-existing schizophrenia and DM, in a provincially funded medical system, and may relate to quality of DM care. The intention of such a system is to provide equal medical care to the entire population. However, these results raise the question as to whether the DM care is indeed equitable. These results underscore the importance of addressing the needs of subpopulations with DM, particularly those which may be vulnerable to negative outcomes. It was beyond the scope of this study to evaluate solutions to improve outcome, or factors which explain this relationship. Future studies are warranted to explore further factors which contribute to acute DM complications in people with schizophrenia, and interventions to prevent such outcomes.

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Table 1: Baseline Characteristics by Presence of Schizophrenia

Variable	Schizophrenia N=1262	No Schizophrenia N=3771
Age at diagnosis (mean +/- SD)	38.78 (7.62)	38.90 (7.62)
Female (%)	46.99%	47.10%
Income quintile 1	39.26%	39.33%
Income quintile 2	24.02%	24.06%
Income quintile 3	15.49%	15.46%
Income quintile 4	12.62%	12.53%
Income quintile 5	8.61%	8.62%
ODB coverage (%)	78.37%	78.28%
Number of visits to primary care provider within year prior to DM diagnosis (median , range)	11 (0-179)	7 (0-151)
Presence of a usual care provider (%)	37.64%	42.03%
CADG5 (chronic medical unstable)	29.48%	29.70%
RUB category 0, 1, or 2	0.48%	10.03%
RUB category 3	41.52%	56.85%
RUB category 4	35.66%	24.16%
RUB category 5	22.35%	8.96%

Table 2: Outcomes by presence of schizophrenia

Outcome	Schizophrenia N=1262	No Schizophrenia N=3771
Primary Outcome (%)*	158 (12.52%)	277 (7.35%)
Secondary Outcome (%) **	268 (21.24%)	513 (13.60%)
• Infection	152 (12.04%)	295 (7.82%)
• Skin/ soft tissue infection	48 (3.80%)	98 (2.60%)
• bacteremia	28 (2.22%)	68 (1.80%)
• Pneumonia	36 (2.85%)	61 (1.62%)
• urinary tract infection	48 (3.80%)	101 (2.68%)
Death	48 (3.80%)	75 (1.99%)
Mean duration of follow-up for analysis to primary event (yr)	4.032	4.406
Mean duration of follow-up for analysis to secondary event (yr)	3.770	4.216

*either hyperglycemia or hypoglycemia

**either hyperglycemia, hypoglycemia or infection (see appendix 2 for diagnostic codes for infection)

† Between diagnosis of DM primary outcome

‡ Between diagnosis of DM and secondary outcome

Table 3: Number of physician visits among people who had an event

Visits measured among those with the primary event	Schizophrenia N=158	No Schizophrenia N=277
Annualized number of visits to a primary care physician (mean)†	6.38	2.83
Annualized number of visits to a psychiatrist (mean)†	2.06	0.04
Annualized number of visits to an internist (mean)†	1.72	0.83
Visits measured among those with the secondary event	Schizophrenia N=268	No Schizophrenia N=513
Annualized number of visits to a primary care physician (mean)‡	8.27	4.23
Annualized number of visits to a psychiatrist (mean)‡	3.58	0.10
Annualized number of visits to an internist (mean) ‡	1.75	0.89

† Between diagnosis of DM primary outcome

‡ Between diagnosis of DM and secondary outcome

Table 4: Percentage of people with at least one physician visit prior to event among people who had an event

Visits measured among those with the primary event	Schizophrenia N=158	No Schizophrenia N=277
Number of people with ≥ 1 visit to a primary care physician †	93 (58.86%)	163 (58.85%)
Number of people with ≥ 1 visit to a psychiatrist †	62 (39.24%)	26 (9.39%)
Number of people with ≥ 1 visit to an internist †	27 (17.09%)	60 (21.66%)
Visits measured among those with the secondary event	Schizophrenia N=268	No Schizophrenia N=513
Number of people with ≥ 1 visit to a primary care physician ‡	175 (65.30%)	317 (61.79%)
Number of people with ≥ 1 visit to a psychiatrist ‡	132 (49.25%)	62 (12.09%)
Number of people with ≥ 1 visit to an internist ‡	45 (16.79%)	96 (18.71%)

Table 5: Significance of predictor variables for primary outcome using univariate analysis

Predictor variable	Hazard Ratio (95% CI)	P-value
Schizophrenia	1.74 (1.42 - 2.12)	<0.0001
Age	0.93 (0.84 - 1.01)	0.107
CACG5 category “chronic medical unstable”	1.35 (1.06 - 1.70)	0.014
RUB 0,1 or 2	1.33 (0.88 - 1.96)	0.179
RUB 3	0.64 (0.51 - 0.79)	<0.0001
RUB 4	0.95 (0.74 - 1.22)	0.666
RUB 5	2.32 (1.71 - 3.16)	<0.0001
Usual care provider	0.60 (0.47 - 0.76)	<0.0001
Number of primary care visits prior to index	1.01 (1.00 - 1.02)	0.004
Number of annual visits to a primary care physician	1.03 (1.02 - 1.04)	<0.0001
Number of annual visits to a psychiatrist	1.03 (1.01 - 1.04)	0.0004
Number of annual visits to an internist	1.01 (1.01 - 1.01)	<0.0001

CI = Confidence Interval

Table 6: Significance of predictor variables for secondary outcome using univariate analysis

Predictor variable	Hazard Ratio (95% CI)	P-value
Schizophrenia	1.62 (1.39 - 1.89)	<0.0001
Age	0.96 (0.89 - 1.03)	0.2134
CACG5 category “chronic medical unstable”	1.83 (1.54 - 2.17)	<0.0001
RUB 0,1 or 2	1.05 (0.77 - 1.42)	0.7789
RUB 3	0.55 (0.46 - 0.65)	<0.0001
RUB 4	1.02 (0.85 - 1.23)	0.8490
RUB 5	2.77 (2.23 - 3.45)	<0.0001
Usual care provider	0.63 (0.53 - 0.76)	<0.0001
Number of primary care visits prior to index	1.01 (1.01 - 1.02)	<0.0001
Number of annual visits to a primary care physician	1.03 (1.03 - 1.04)	<0.0001
Number of annual visits to a psychiatrist	1.06 (1.04 - 1.07)	<0.0001
Number of annual visits to an internist	1.01 (1.00 - 1.01)	<0.0001

Table 7: Hazard Ratio of schizophrenia for the primary outcome

Variable	HAZARD RATIO (95% CI)	
	Univariate Analyses	Adjusted Model*
Schizophrenia	1.74 (1.42 - 2.12)	1.68 (1.34 - 2.10)
Age	0.93 (0.84 - 1.02)	0.94 (0.85 - 1.05)
Gender	--	--
RUB category 3	0.64 (0.51 - 0.79)	0.58 (0.38 - 0.88)
RUB category 4	0.95 (0.74 - 1.22)	0.57 (0.35 - 0.92)
RUB category 5	2.32 (1.71 - 3.16)	1.01 (0.55 - 1.83)
Unstable condition	1.35 (1.06 - 1.70)	1.12 (0.83 - 1.51)
Income quintile	--	--
ODB coverage	--	--
Usual care provider	0.60 (0.47 - 0.76)	0.68 (0.53 - 0.88)
Number pc visits	1.01 (1.00 - 1.02)	1.00 (0.99 - 1.01)
Annual pc visits	1.03 (1.02 - 1.04)	
Annual internist visits	1.03 (1.01- 1.04)	

* model adjusted for age, gender, RUB category 3, RUB category 4, RUB category 5, Presence of a chronic unstable condition (= unstable condition), income quintile, ODB coverage, presence of a usual care provider, and number of visits to a primary care physician in the year preceding diabetes diagnosis (=number pc visits)

CI = Confidence Interval

Table 8: Hazard Ratio of schizophrenia for the secondary outcome

Variable	HAZARD RATIO (95% CI)	
	Univariate	Adjusted Model*
Schizophrenia	1.62 (1.39 - 1.89)	1.45 (1.26 - 1.78)
Age	0.96 (0.89 - 1.03)	0.96 (0.88 - 1.03)
Gender	--	--
RUB category 3	0.55 (0.46 - 0.65)	0.62 (0.45 - 0.87)
RUB category 4	1.02 (0.85 - 1.23)	0.68 (0.47 - 1.00)
RUB category 5	2.77 (2.23 - 3.45)	1.25 (0.80 - 1.95)
Unstable condition	1.83 (1.54 - 2.17)	1.40 (1.12 - 1.74)
Income quintile	--	--
ODB coverage	--	--
Usual care provider	0.63 (0.53 - 0.76)	0.75 (0.62 - 0.90)
Number pc visits	1.01 (1.01 - 1.02)	1.00 (1.00 - 1.01)
Annual pc visits	1.03 (1.03 - 1.04)	
Annual internist visits	1.01 (1.00 - 1.01)	

* model adjusted for age, gender, RUB category 3, RUB category 4, RUB category 5, Presence of a chronic unstable condition (= unstable condition), income quintile, ODB coverage, presence of a usual care provider, and number of visits to a primary care physician in the year preceding diabetes diagnosis (=number pc visits)

CI = Confidence Interval

Table 9: Hazard Ratio of Schizophrenia for Each Component of the Composite Secondary outcome

Outcome	Hazard Ratio (95% CI)
Secondary Outcome	1.50 (1.26 - 1.78)
• Infection	1.38 (1.09 - 1.73)
• Skin/ soft tissue infection	1.31 (0.88 - 1.93)
• bacteremia	1.27 (0.72 - 2.22)
• Pneumonia	1.82 (1.05 - 3.16)
• urinary tract infection	1.19 (0.78 - 1.80)

CI = Confidence Interval

Figure 1: Relationship Between Schizophrenia and Acute Complications of DM

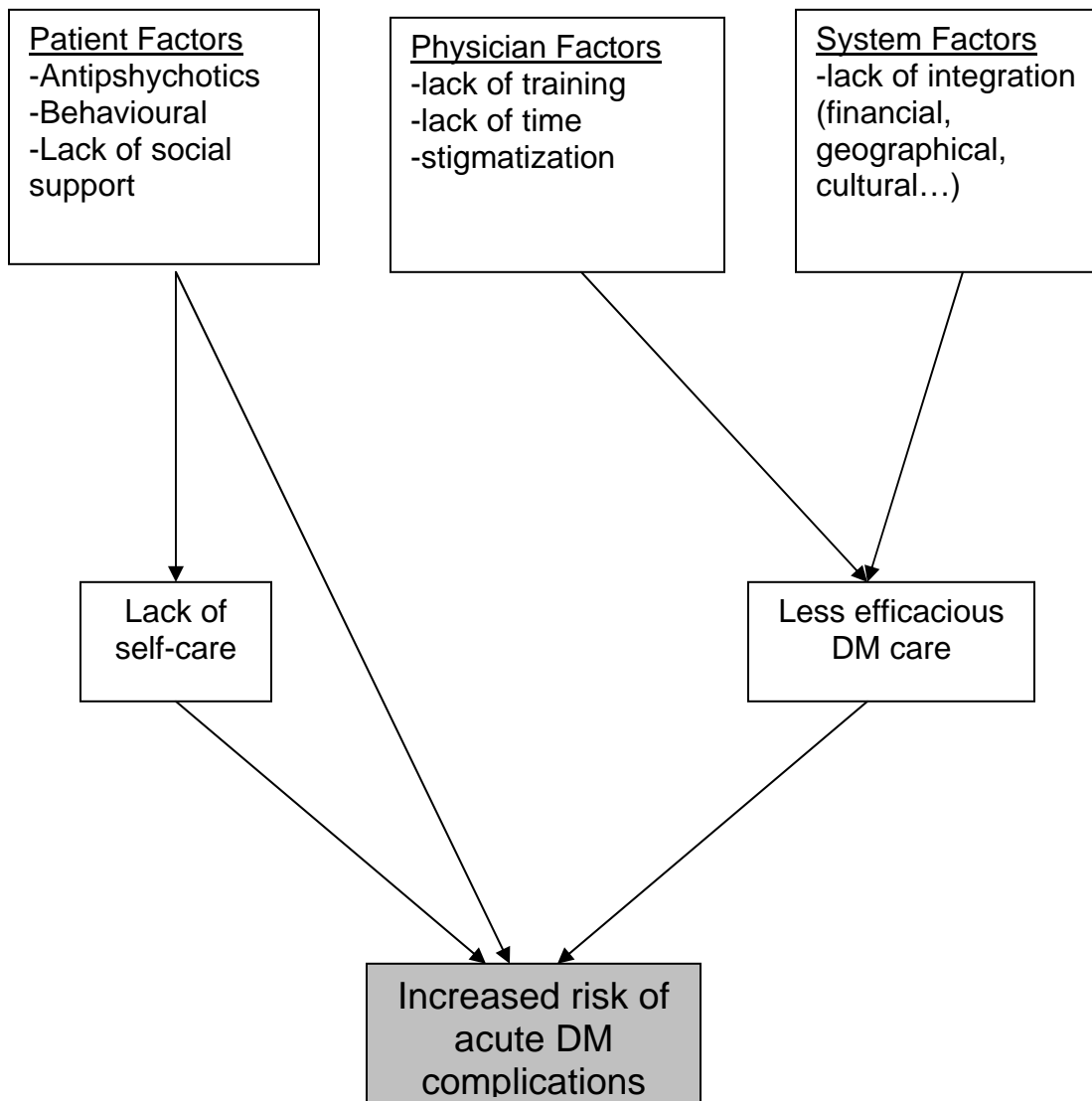


Figure 2: Summary of studies evaluating quality of DM care in people with schizophrenia

REFERENCE	FINDINGS	LIMITATIONS
Desai et al. Am J Psychiatry. 2002	<p>Assessed process of care indicators</p> <ul style="list-style-type: none"> -Among people with a wide range of mental disorders (major affective, psychotic, posttraumatic stress disorders, substance abuse), there was inconsistent evidence of difference in quality of DM care compared to people without mental illness 	<ul style="list-style-type: none"> -studied people within a VA population (American) -prevalence of schizophrenia only 4.3% -89% of cohort were male -cross sectional -varied duration of DM
Jones et al. Medical Care. 2004	<p>Assessed process of care indicators</p> <ul style="list-style-type: none"> -People with DM and serious mental disorders received more services than people without mental disorders but were less likely to receive HbA1c and cholesterol testing -frequency of retinal eye examination and urine protein testing was similar in both groups -they had a greater number of DM-related visits compared to people without mental illness 	<ul style="list-style-type: none"> -American population -only included people with private medical insurance -unclear proportion of people with schizophrenia -focused on people in Iowa with private insurance <ul style="list-style-type: none"> a) racially homogenous population b) accuracy of coding is unknown in these claims databases

REFERENCE	FINDINGS	LIMITATIONS
Frayne et al. Arch Intern Med. 2005	<p>Assessed process of care indicators</p> <ul style="list-style-type: none"> -people with DM and mental health conditions were less likely to meet DM performance measures (HbA1c testing, retinal eye examination and cholesterol testing) than those without mental health conditions -the percentage not meeting DM care standards increased with increasing number of mental health conditions -those with mental illness were more likely to evidence poor glycemic and lipemic control 	<ul style="list-style-type: none"> -studied people within a VA population (American) -observational study -97% male -varied duration of DM
Krein et al. Psychiatric Services. 2006	<p>Assessed process of care indicators</p> <ul style="list-style-type: none"> -People with DM and serious mental illness appear as likely to receive recommended performance measures than people without mental illness (HbA1c, LDL and cholesterol measurements) -they had more outpatient visits, both primary and specialty care and were more likely to receive to attend multi-service visits 	<ul style="list-style-type: none"> -studied people within a VA population (American) -observational study -unclear proportion of people with schizophrenia -varied duration of DM

REFERENCE	FINDINGS	LIMITATIONS
<p>Dixon et al. Psychiatric Services. 2004</p> <p>Goldberg et al. Psychiatric Services. 2007</p>	<p>Assessed process of care indicators</p> <p>-people with serious mental illness were less likely to receive the full set of performance measures (HbA_{1c}, eye and foot examination, blood pressure check, urine and lipid profile) compared to people without serious mental illness</p> <p>-patients with serious mental illness were less likely to receive DM education</p>	<p>-small sample size (300 people) in an American population</p> <p>-retrospective chart review</p> <p>-relied on patient self-report for education cues</p> <p>-1/3 had schizophrenia and 1/3 had major mood disorder</p> <p>-patients were all recruited from mental health clinics</p> <p>-varied duration of DM</p>

VA =Department of Veterans Affairs

Quality of care indicators =HbA_{1c} measurement, eye and foot examinations, blood pressure check, urine and lipid profiles

HbA_{1c} =glycosylated hemoglobin

LDL =low density lipoprotein

Figure 3: Frequency of Primary Care Visits in the Year Prior to the Diagnosis of DM by Schizophrenia

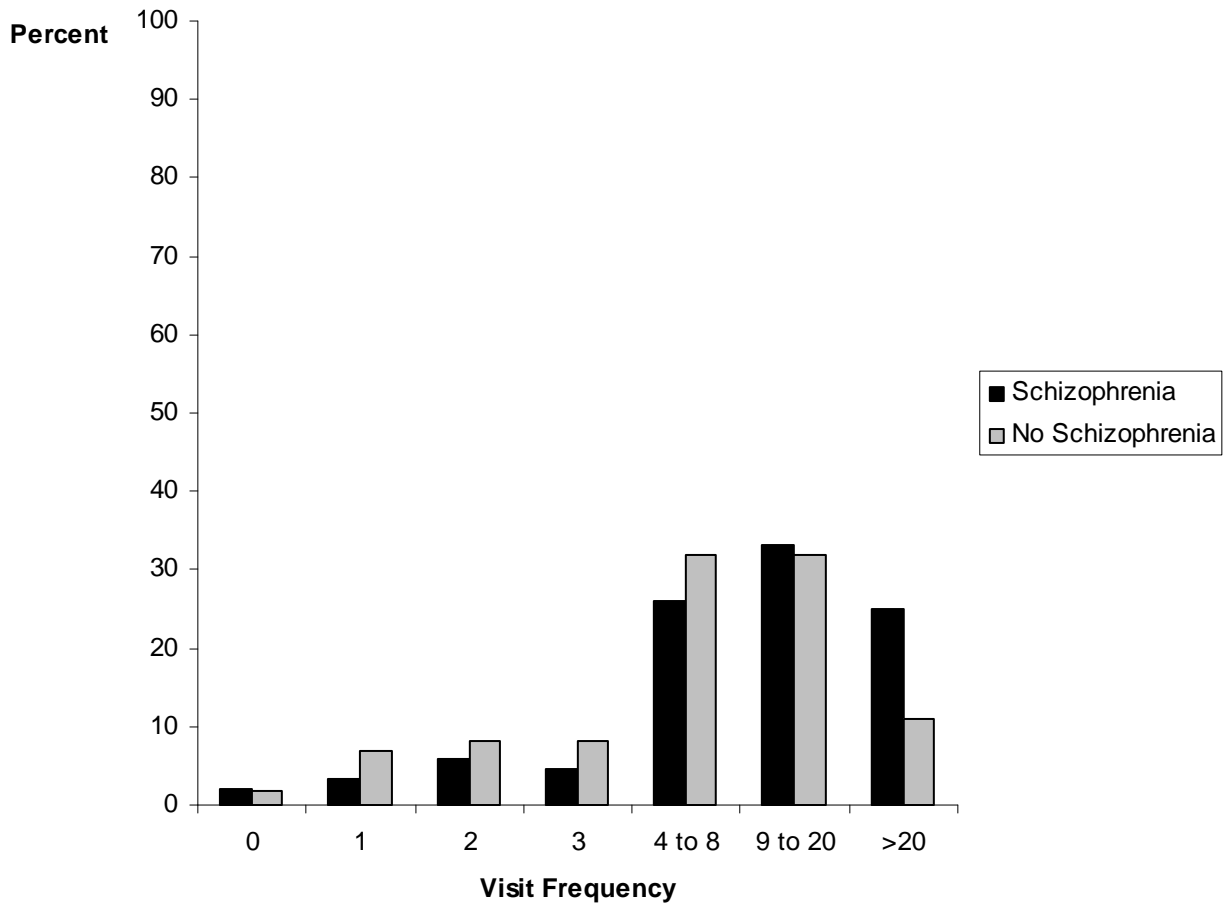
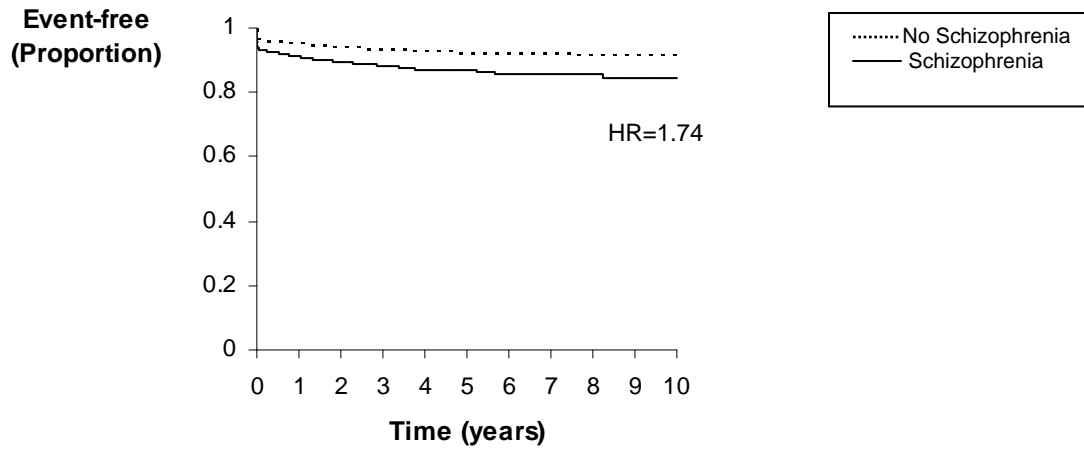


Figure 4: Event Rates

4a. Time to Primary Event



4b. Time to Secondary Event

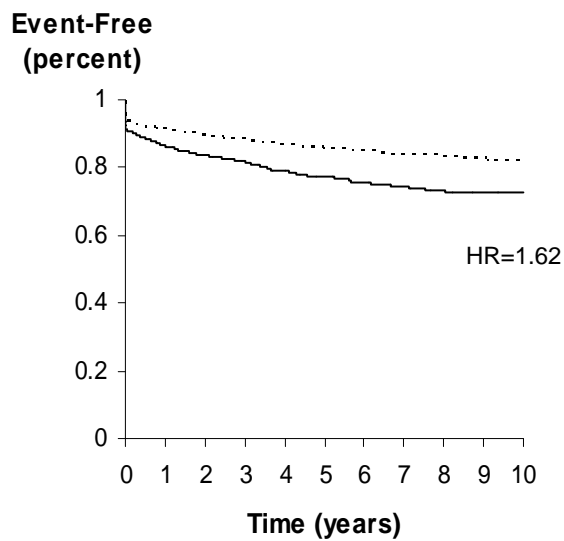
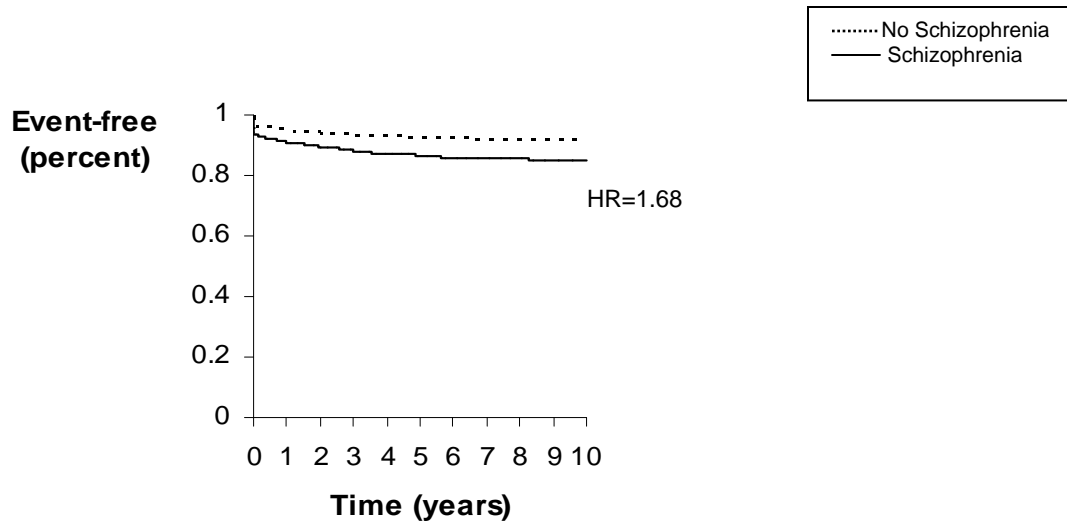
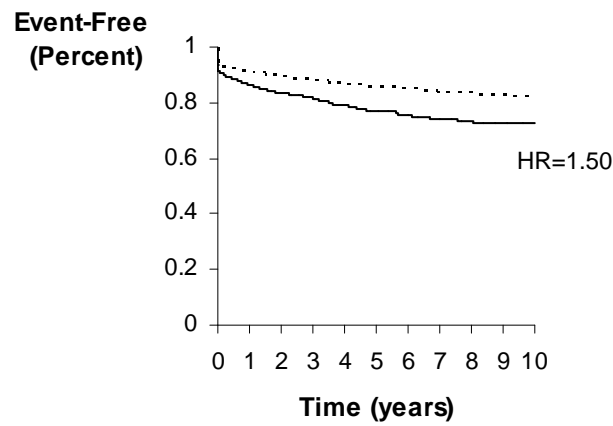


Figure 5: Adjusted Event Rates

5a. Time to Primary Event (Adjusted)



5b. Time to Secondary Event (Adjusted)



Appendix 1: Codes used to define presence of psychotic disorder other than schizophrenia

Code	Definition
ICD9_297.X	Delusional disorders
ICD9_298.X	Other nonorganic psychoses
ICD9_299.X	Pervasive developmental disorders
ICD10_F21.X	Schizotypal disorder
ICD10_F22.X	Persistent delusional disorders
ICD10_F23.X	Acute and transient psychotic disorders
ICD10_F24.X	Induced delusional disorder
ICD10_F25.X	Schizoaffective disorders
ICD10_F28.X	Other nonorganic psychotic disorders
ICD10_F29.X	Unspecified nonorganic psychosis
OHIP_297	Paranoid states
OHIP_298	Other psychoses
OHIP_299	Childhood psychoses (eg. Autism)

Appendix 2: Codes used to define hypoglycemia or hyperglycemia

Code	Definition
OHIP 250	Diabetes Mellitus (DM)
ICD9 250.0	DM without mention of complication
ICD9 250.1	DM with ketoacidosis
ICD9 250.2	DM with hyperosmolarity
ICD9 250.3	DM with other coma
ICD10 E10.0	Insulin-dependent DM with coma
ICD10 E11.0	Non-insulin-dependent DM with coma
ICD10 E12.0	Malnutrition-related DM with coma
ICD10 E13.0	Other specified DM with coma
ICD10 E14.0	Unspecified DM with coma
ICD10 E10.1	Insulin-dependent DM with ketoacidosis
ICD10 E11.1	Non-insulin-dependent DM with ketoacidosis
ICD10 E12.1	Malnutrition-related DM with ketoacidosis
ICD10 E13.1	Other specified DM with ketoacidosis
ICD10 E14.1	Unspecified DM with ketoacidosis

Appendix 3: ICD9, ICD10 and OHIP codes used to define hospital visit for infection

Infection	ICD9 codes	ICD10 codes	OHIP
Urinary tract infections	590.01-590.9, 595	595.0 N300, N308, N309 590.01-590.9 N10, N12 599.0 N390	590, 595
Pneumonia and upper respiratory tract infections	481, 482.0-482.4, 482.8-482.9, 483, 486, 460-466, 382.0-382.9, 380.1	481,482.0-482.4,482.8-482.9,483-486 J110, J12, J13, J14, J15, J16, J17	486 460, 461, 463, 464, 466
Bacteremia/Septicemia	036.2, 038.0, 038.1, 038.2, 038.3, 038.40-49	003.1,036.2, 038.0-038.3, 038.40-038.49,038.8-038.9 A40, A41, A499, A394	36, 38
Skin, soft tissue and bone infection	680.0-680.9, 681.01-681.9, 682.1-682.9, 684, 685.0-685.1, 686.0-686.9 730.2, 711	680.0-680.9, 681.01-681.9, 682.1-682.9, 683, 684, 685.0-685.1, 686.0-686.9, 729.4, 785.4, 040.0 L01, L02, L03, L04, L05, L08, A480, E1051, E1151, E1351, E1451, R02	689, 682, 684, 685, 686 730, 711
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