Risk of Acute Complications of Diabetes Among People With Schizophrenia in Ontario, Canada

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OBJECTIVE—Diabetes mellitus (DM) is a complex, chronic disease requiring active self-management and coordinated care. This study aimed to evaluate the relationship between schizophrenia and risk of preventable, acute DM complications.

RESEARCH DESIGN AND METHODS—With the use of administrative data, a retrospective study assessed acute DM complications (emergency department [ED] 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. Primary outcome was ED visit or hospitalization for hypo- or hyperglycemia. Secondary outcome was the first of either the primary outcome or hospitalization for infection.

RESULTS—People with schizophrenia had a 74% greater risk of requiring a hospital visit for hypo- or hyperglycemia (hazard ratio [HR] = 1.74, 95% confidence interval 1.42–2.12) compared with those without schizophrenia. 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.

CONCLUSIONS—People with schizophrenia are at greater risk for developing an acute complication of DM. 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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Diabetes mellitus (DM) is a serious chronic condition associated with potentially devastating complications. Chronic poor control of DM can lead to macrovascular and microvascular complications. Suboptimal DM management can result in metabolic decompensation acutely, such as states of extreme hypo- or hyperglycemia and the associated metabolic derangements. Such events have been classified as ambulatory-care sensitive conditions for which hospitalization is thought to be avoidable through interventions and early disease management delivered in an ambulatory care setting. 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 lack of integration between medical services.

Risk factors for poorer DM control and DM complications include nonwhite ethno-racial groups, low socioeconomic status (SES), and certain geographic locations (1–6). 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 with the general population (7–10) and are also less likely to receive adequate care for other medical conditions (11). The relationship between DM and schizophrenia is complex and incorporates a number of factors, including the understanding and management of DM by patients and their mental health care providers and an acute care system not well designed to support patients with comorbid chronic medical and psychiatric illnesses. The coexistence of schizophrenia may increase the inherent social and economic challenges to achieving DM targets, leading to an increase in the occurrence of acute DM complications. Therefore, the current study examines the relationship between acute complications of DM in individuals with and without schizophrenia in a public healthcare system where financial barriers to access should be reduced.

RESEARCH DESIGN AND METHODS

A population-based retrospective matched cohort study was conducted, evaluating the relationship between schizophrenia and acute complications of DM. Individuals with newly diagnosed DM were drawn from the Ontario Diabetes Database, a validated database, derived from administrative data sources, with information on all Ontario residents diagnosed with DM (12). Ontario residents ages 18 to 50 years, diagnosed with DM between April 1, 1996, and March 31, 2005, were included. Older patients were excluded to minimize the impact of other medical comorbidities, which might also contribute to the principal outcome of emergency department (ED) visits. The index date was the date of diagnosis of DM.

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 individuals with DM but free of schizophrenia. Cases of schizophrenia were identified either by having at least two hospitalizations for schizophrenia or by having one hospitalization and one physician service claim in the Ontario Health Insurance Plan (OHIP) database not related to the hospitalization for schizophrenia

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after April 1, 1992 and before the diagnosis of DM. Hospitalizations were identified in the Canadian Institute for Health Information database (CIHI-DAD). A hospitalization was attributed to schizophrenia if the most responsible diagnosis recorded in the discharge abstract was for schizophrenia using ICD-9 CM = 295.0–295.9 or ICD-10 = *F*20.0× to *F*20.9× coding.

Controls were identified as people without medical records for schizophrenia at any time during the observation period (April 1, 1992, through March 31, 2006) and were matched to schizophrenia cases on age (± 2 years), sex, geographic region, and both area and individual-level SES. Ecologic attribution of SES from census data was used to match neighborhood level SES of cases and controls (13). In addition, an individual-level indicator of low SES was used for matching. The Ministry of Health and Long-term Care covers the cost of prescription drugs for people receiving social assistance (welfare or disability support). Coverage thus provides a binary measure of low SES at the patient level. Individuals were considered to have qualified for coverage if they received any reimbursed drug benefits under the Ontario Drug Benefit Program in the year before the index date or within 6 months after the diagnosis of DM. Up to three matched controls were sought for each case of schizophrenia.

The primary outcome was the first occurrence of an acute complication of DM, defined by a hospitalization or ED visit for hyperglycemia or hypoglycemia. Secondary outcomes included the first occurrence of either hospitalization or ED visit for hyper- or hypoglycemia or hospital admission for any of the following infections: skin and soft tissue infection, bacteremia, pneumonia, or urinary tract infection, and death from any cause.

Before 2002, ED visit records were not available apart from physician service (OHIP) claims. Diagnostic information on these claims was inadequate to distinguish hyperglycemia from hypoglycemia. ED visits were included in the outcome if the OHIP claim had a diagnosis code 250 or 251. From April 1, 2002, onward, eligible ED visits were identified in the National Ambulatory Care Reporting System record, by diagnosis codes in any position and contained the following (E10–E14)0.0 or (E10–E14)0.1. 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 or from April 1, 2002, onward, records in which the most responsible diagnosis was (E10-E14)0.0 or (E10-E14)0.1.

The secondary outcomes were identified by the first date that an individual developed either the primary outcome or had a hospital admission with one of the listed infections as the most responsible diagnosis (Supplementary Table 1).

Outcomes were measured from the index date until the end of the observation period (March 31, 2006). Individuals were censored at death, migration out of province, or development of the outcome of interest.

Baseline covariates at index were recorded. A usual care provider was identified if in the 2 years before the index date there were more than two physician visits and at least 50% of these visits were to the same physician. Comorbidity was estimated using the Johns Hopkins Collapsed Aggregated Diagnosis Groups (CADGs) (14). In this study, CADG category 5 was used (chronic unstable medical disease). Resource Utilization Band (RUB), a predictor of healthcare expenditure for a given individual, was also used as a measure of comorbidity. The annualized numbers of physician visits for primary care physicians, psychiatrists, and internal medicine specialists between the index date and both the first primary and secondary outcome event were used as a measure of healthcare utilization.

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

Overall proportions or means, medians, ranges, and 95% confidence intervals were calculated for the covariates by study group. Comparisons were made between the groups accounting for strata, since the groups were matched in a ratio of 1:3.

Frequency of a first hospital visit for hypo- or hyperglycemia by schizophrenia status was described. Survival analysis using a Cox proportional hazard model was estimated using time from index to the first outcome. A series of univariate Cox models were fit to assess the individual effects of each of the covariates (including schizophrenia) on the outcome. A multivariable Cox model was then fit to determine the hazard ratio (HR) associated with coexistence of schizophrenia after adjustment for potential confounders. A similar analysis was repeated for the secondary composite.

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

Before study initiation, ethics approval was obtained from the Institutional Review Board at Sunnybrook Health Sciences Centre (Toronto, ON, Canada).

RESULTS—There were 1,262 newly diagnosed cases of DM among people with pre-existing schizophrenia in Ontario between 1996 and 2005 and 3,771 matched controls. People with schizophrenia (99.13%) matched to three people in the comparison group without schizophrenia, with the remainder matched to one or two controls. The final analysis included 5,033 individuals.

Baseline data for the groups are compared in Table 1. The mean age at index was 38.8 years. The groups were well matched on the indicated variables. Compared with people without schizophrenia, those with schizophrenia were more likely to have seen a primary care provider preceding the diagnosis of diabetes but less likely to have a usual care provider. They were significantly more likely to be placed in a higher RUB. There was no difference in the proportion of people with a chronic unstable medical illness.

Among people with schizophrenia, over 12% required at least one hospital visit for hypo- or hyperglycemia, compared with about 7% in the group without schizophrenia (Table 2). There were a significantly higher proportion of individuals with the composite secondary outcome in the group with schizophrenia. Analysis of the infection rates revealed the greatest difference in the hospital admission rate for pneumonia (Table 2). Individuals with schizophrenia had an almost twofold increased death rate ($P < 0.0001$).

Among the people who had developed an outcome, 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 (data not presented), 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.

Table 1—*Baseline characteristics by presence of schizophrenia*

Variable	Schizophrenia (*N* = 1,262)	No schizophrenia (*N* = 3,771)
Age at diagnosis (years)	38.78 (7.62)	38.90 (7.62)
Women (%)	46.99	47.10
Income quintile (%)		
1	39.26	39.33
2	24.02	24.06
3	15.49	15.46
4	12.62	12.53
5	8.61	8.62
ODB coverage (%)	78.37	78.28
Number of visits to PC provider within year before DM diagnosis	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
3	41.52	56.85
4	35.66	24.16
5	22.35	8.96

Data are means ± SD, median (range), and percent. ODB, Ontario Drug Benefit Program. PC, primary care.

In a univariate Cox proportional hazards analysis comparing the rate ratio of developing the primary outcome, presence of schizophrenia was associated with an unadjusted HR of 1.74 (Fig. 1). Schizophrenia was associated with a HR of 1.62 for the secondary outcome (Fig. 1). After testing for collinearity was done, none of the proposed variables were highly correlated. Therefore, multivariate analyses adjusted for variables that may influence the association between schizophrenia and each outcome (Table 3). Presence of schizophrenia yielded an adjusted HR of 1.68 for the primary outcome and 1.50 for the composite secondary outcome.

CONCLUSIONS—Among people with newly diagnosed DM in Ontario, those with a pre-existing diagnosis of schizophrenia had a significantly higher rate of hospital visits for hypo- or hyperglycemia, compared with similar people without schizophrenia. Schizophrenia was also associated with a significantly increased risk of hospitalization for infection. Finally, there was an almost twofold higher mortality rate among individuals with schizophrenia.

Table 2—*Outcomes by presence of schizophrenia*

Outcome	Schizophrenia (*N* = 1,262)	No schizophrenia (*N* = 3,771)
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 (years)		
Primary event	4.032	4.406
Secondary event	3.770	4.216

*Either hyperglycemia or hypoglycemia. **Either hyperglycemia, hypoglycemia, or infection (see Supplementary Data for diagnostic codes for infection).

DM is a complex condition that is challenging to manage. Coexisting schizophrenia poses additional difficulty in achieving DM targets and minimizing adverse outcomes. This study has demonstrated that individuals with both newly diagnosed DM and schizophrenia are vulnerable, suffering an increased rate of acute complications of DM compared with similar people without schizophrenia. Furthermore, the increase in adverse outcomes was not because of financial barriers to access, since this study was conducted in a universal publicly funded system. Indeed, it appears that these outcomes occurred despite an increased frequency of outpatient visits among the group with schizophrenia. This finding indicates that access to outpatient visits is not the issue but that physician visits for individuals with schizophrenia may not be providing the appropriate components of DM care.

Although patient level factors, such as the effects of cognitive and behavioral disturbances and medications, make the management of DM in individuals with schizophrenia more complex, provider level factors may also be important. It is possible that healthcare providers focus on other patient needs, neglecting somatic health (15). Individual physicians may feel ill-equipped to address both mental health and physical health. Both psychiatrists and primary care physicians work under great time constraints, limiting their availability to provide additional services (16). Stigmatization of psychiatric conditions can impact provision of healthcare, since providers may not be convinced that health and wellness are feasible among individuals with schizophrenia. However, data suggest that people with serious mental illness are as able as the general population to achieve adherence to dietary recommendations and weight loss (17–19).

The Ontario medical system is not unique with respect to the lack of integration leading to fragmented care of people with medical and mental health issues. There are several types of separation between the two systems that care for medical health and mental health: geographic, organizational, cultural, and financial (20,21). In contrast, in a system such as the Veteran's Affairs system, which is highly integrated, there is less of a discrepancy in DM care (22). In fact, it has been suggested that people with DM and serious mental illness may indeed fare better, perhaps due to a more integrated team of healthcare

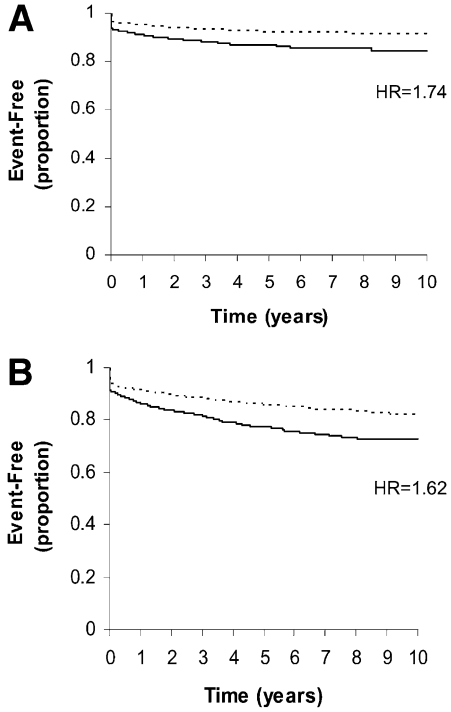

Figure 1—*Event rates.*

professionals involved in their care and well-being (22). These studies combined with the current results suggest that an increased number of physician visits in a system where there is no financial cost to the patient may not be the solution. Rather, the focus may require a shift to altering the content of physician encounters and improving coordination of care with a more holistic approach.

This study has limitations. Although the use of administrative databases allows for analysis of a large population-based cohort, the databases lack comprehensive clinical and laboratory data or medications. It is important to know the extent to which antipsychotics play a role in DM complications, as well as what therapies are being used to treat DM. Schizophrenia is a dynamic disease, with significant variation in symptoms. 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.

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.

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. There is a potential for misclassification, since this coding system used in this study has not been validated. If indeed there was misclassification, it is likely that more people in the group with coexisting schizophrenia would be miscoded, since 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 ED visit or hospital admission. Therefore, the coding used is likely biased toward the null for a difference in hypo- or hyperglycemia. Given the biologic plausibility of hyperglycemia increasing susceptibility to infection, and previous literature supporting the increased risk of the stated infections in people with DM, it was thought that a reasonable argument to evaluate this outcome as an acute DM complication. However, infections have not been validated as an acute complication of DM. Regardless, hospitalization for these infections is considered preventable and may be associated with unnecessary morbidity and financial cost. Furthermore, these events occurred more frequently and more rapidly among individuals with schizophrenia.

This is the first study to evaluate these acute adverse events in people with coexisting 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

Table 3—*HR of schizophrenia*

	HR (95% CI)			
	Primary outcome		Secondary composite outcome	
Variable	Univariate	Adjusted model*	Univariate	Adjusted model*
Schizophrenia	1.74 (1.42–2.12)	1.68 (1.34–2.10)	1.62 (1.39–1.89)	1.45 (1.26–1.78)
Age	0.93 (0.84–1.02)	0.94 (0.85–1.05)	0.96 (0.89–1.03)	0.96 (0.88–1.03)
Sex	—	—	—	—
RUB category (%)				
3	0.64 (0.51–0.79)	0.58 (0.38–0.88)	0.55 (0.46–0.65)	0.62 (0.45–0.87)
4	0.95 (0.74–1.22)	0.57 (0.35–0.92)	1.02 (0.85–1.23)	0.68 (0.47–1.00)
5	2.32 (1.71–3.16)	1.01 (0.55–1.83)	2.77 (2.23–3.45)	1.25 (0.80–1.95)
Unstable condition	1.35 (1.06–1.70)	1.12 (0.83–1.51)	1.83 (1.54–2.17)	1.40 (1.12–1.74)
Income quintile	—	—	—	—
ODB coverage	—	—	—	—
Usual care provider	0.60 (0.47–0.76)	0.68 (0.53–0.88)	0.63 (0.53–0.76)	0.75 (0.62–0.90)
PC visits				
Number	1.01 (1.00–1.02)	1.00 (0.99–1.01)	1.01 (1.01–1.02)	1.00 (1.00–1.01)
Annual	1.03 (1.02–1.04)		1.03 (1.03–1.04)	
Annual internist visits	1.03 (1.01–1.04)		1.01 (1.00–1.01)	

*Model adjusted for age; sex; RUB categories 3, 4, and 5; presence of a chronic unstable condition (unstable condition); income quintile; ODB (Ontario Drug Benefit Program) coverage; presence of a usual care provider; and number of visits to a PC (primary care) physician in the year preceding diabetes diagnosis (number of PC visits).

medical care to the entire population. However, these results raise the question of whether DM care is indeed equitable when access is not the issue. These results underscore the importance of addressing the needs of subpopulations with DM, particularly those that may be vulnerable to adverse outcomes. Future studies are warranted to explore further factors that contribute to acute DM complications in people with schizophrenia and to evaluate delivery models, which could mitigate such outcomes.

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T.B. researched data, performed statistical analysis, and wrote the article. J.H. contributed to discussion and reviewed and edited the article.

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