Antipsychotic Medication and the Incidence of Type II Diabetes among Quebec Welfare Recipients, 1993 – 2004

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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Initial Submission: February 2009

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ACKNOWLEDGMENTS

First and foremost I would like to thank my supervisor Dr. Eric Latimer for his unwavering support, particularly when the end of this project was unfathomable! I greatly benefited from his academic expertise, extensive knowledge in the field, constructive feedback and general optimistic approach. I would also like to thank Dr. Robyn Tamblyn for adding her epidemiological expertise to this project- her critical feedback affirmed everything I learned in epidemiology classes. I very much enjoyed meetings with Dr. Latimer and Dr. Tamblyn, they were an inspiring mix of possibility and practicality!

I would also like to thank Dr. Armel Kelome for lending his statistical experience to this project and for his willingness to not only teach but to discuss solutions. I am indebted to Willy Wynant for his help with data preparation and to Jenn Hutcheon who helped me get over my initial fear of Stata. I would also like to thank Dr. Ridha Joober who generously opened his door and helped me to understand the biology behind this project.

Finally I would like to thank my friends and family, most especially: Vlad, Muffin, my parents, and Savithri, who were there through it all.

ABSTRACT

Objective: To compare the risks of developing type II diabetes after initiation of different antipsychotic drugs.

Methods: Adult welfare recipients in Quebec who filled a prescription for an antipsychotic(s) drug between 1993 and 2004 were included in this study. Exposure was measured across 6 antipsychotic drug groups: clozapine, olanzapine, quetiapine, risperidone, low-potency typical drugs and other typical drugs. Cox proportional hazard models were used to estimate the risk of diabetes after exposure, adjusting for age at study entry, sex, obesity before drug initiation, schizophrenia and entry year.

Results: Risk of diabetes associated with one more standard monthly dose was significantly higher for: clozapine (RR 1.14 (95% C.I.: 1.04, 1.24)); olanzapine (1.09 (1.04, 1.14)) and low potency typicals (1.08 (1.03, 1.13)).

Conclusions: Consistent with many prior studies, clozapine, olanzapine and low potency typical drugs pose a higher risk for diabetes than other antipsychotic drugs. This risk also increases with dosage.

RÉSUMÉ

Objectif: Comparer les risques de developper le diabète de type 2 après l'initiation de différents antipsychotiques.

Méthodes: L'étude inclut les adultes bénéficiares de l'aide sociale au Québec qui ont obtenu une ordonnance pour un antipsychotique entre 1993 et 2004. L'exposition a été mesurée dans 6 groupes d'antipsychotiques: la clozapine, l'olanzapine, la quétiapine, la rispéridone, des médicaments typiques à faible teneur et d'autres médicaments typiques. Des modèles "Cox proportional hazard" ont été employés pour estimer le risque de diabète contrôlant pour l'âge lors de l'entrée à l'étude, le sexe, l'obésité avant l'initiation des médicaments, la schizophrénie et l'année de l'accès.

Résultats: Le risque de diabète associé à un mois supplémentaire à dose standard était plus elévé pour les médicaments suivants: clozapine (RR 1.14 (95% C.I.: 1.04, 1.24)); olanzapine (1.09 (1.04, 1.14)) et les antipsychotiques typiques à faible teneur (1.08 (1.03, 1.13)).

Conclusions: En accord avec plusieurs études antérieures la clozapine, l'olanzapine et les antipsychotiques à faible teneur présentent un risque pour le diabète plus élevé que les autres antipsychotiques. Le risque augmente aussi avec la dose.

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Chapter 1 Introduction

The development of diabetes has been reported after initiation of antipsychotic medications, particularly some of the atypical antipsychotic drugs. However, estimates of the risk associated with different antipsychotic drugs have been discrepant. The purpose of this study is to compare the risks of developing type II diabetes after initiation of different antipsychotics.

This section first discusses antipsychotic drugs: their history, indications (with an emphasis on schizophrenia), mode of action, effectiveness and side effects. Next, diabetes is discussed: basic physiology, criteria, risks, and potential mechanisms of antipsychotic induced diabetes. This section concludes with a review of the existing literature on antipsychotic use and diabetes; particularly large scale database studies that have examined specific antipsychotic drugs and the differential risks that they pose for diabetes.

1.1 Overview of Antipsychotic Drugs

1.1.1 History

The first antipsychotic drug, chlorpromazine, was derived from a drug that was used as an anesthetic for surgery. During the early 1950's, a French surgeon discovered that the anesthetic drug he used on his patients had an effect on patients' central nervous system. The drug was sent for pharmacologic testing and a minor change was made, after which the drug was introduced as an antipsychotic under the name of chlorpromazine. Psychiatrists, notably Delay and Deniker, found that chlorpromazine reduced positive schizophrenia symptoms such as; delusions, hallucinations and disorganized thought and behavior [1]. In Canada, Heinz Lehman, along with psychiatrists around the world, conducted clinical trials of chlorpromazine which provided evidence that chlorpromazine had a therapeutic effect on psychoses. In 1954, chlorpromazine was approved in the US for treatment of psychiatric disorders [2]. Chlorpromazine revolutionized care for the

mentally ill, allowing patients to be discharged from psychiatric facilities once their psychotic behaviors were under control. Chlorpromazine also provided an alternative treatment to invasive procedures such as electroconvulsive shock therapy (ECT) and insulin shock therapy. The benefits of chlorpromazine stimulated the search for other chlorpromazine derivatives. Many other antipsychotic drugs have been introduced since then: from first generation drugs that work similarly to chlorpromazine to newer ones that have different mechanisms of action.

1.1.2 Indications

Antipsychotic drugs are typically used to treat psychoses. However, they can also be prescribed to relieve specific symptoms (see Table 1.1). Antipsychotic drugs are most often prescribed to reduce multiple symptoms that occur in the presence of a psychotic disorder.

Table 1.1 Target symptoms that may respond to antipsychotic drugs[1]

Aggressive-Hyperactive type symptoms	**Positive Symptoms**	**Negative Symptoms**	**Other Symptoms**
Agitation*	Hallucinations*	Insomnia*	Confusion
Irritability*	Delusions*	Negativism*	Defective Judgment
Hyperactivity*	Thought disorganization	Indifference to environment	Delirium
Hostility*	Suspiciousness	Anxiety	Disorientation
Combativeness*	Paranoid ideation	Apathy (emotional flattening)	Catatonic motor behavior
Aggressiveness	Unusual thought content	Poor appetite	Difficulty in relating
Assaultiveness	Feelings of unreality	Poor concentration	Motor retardation
Resistiveness	Lack of insight	Slowed speech	Mannerisms or facial grimaces
Excitement	Bizarre thinking/speech	Social withdrawal	Somatic concern
Grandiosity	Flight of ideas	Deterioration of social habits	Inappropriateness
Elation			Irrelevancy

* Symptoms most likely to improve from antipsychotic drugs

[1] Taken from: Mason G: Clinical handbook of antipsychotic drug therapy. New York, Brunner/Mazel Publishers, 1980

1.1.2.1 Schizophrenia

Schizophrenia is the most common disorder for which treatment with antipsychotic medications is indicated.

1.1.2.1.1 Definition

Schizophrenia is a disabling mental disorder that often leads to a loss of functioning across several domains. Symptoms of schizophrenia are divided into 2 categories: positive and negative symptoms. Positive symptoms include: delusions, hallucinations, disorganized speech and disorganized behavior. Negative symptoms include: flattened affect, poverty of speech (alogia), difficulty beginning and completing tasks (avolition) and an inability to take pleasure in things (anhedonia). A diagnosis of schizophrenia requires that these symptoms cause social or occupational dysfunction for at least six months [3]. Two other psychotic disorders are closely related to schizophrenia: schizophreniform disorder and schizoaffective disorder. Both require fewer symptoms than those necessary for a diagnosis of schizophrenia, indicating a possible continuum of schizophrenia. The majority of first episode psychoses occur in individuals between the ages 15-30 and may occur earlier in individuals who have immediate relatives with the illness. The onset tends to be earlier in males with an average age of onset in males of 18 years and in females of 25 years [4].

The incidence of schizophrenia has been estimated at 0.20 per 1000 per year [3, 5, 6]. Prevalence estimates of schizophrenia are much higher and can be measured either at a point in time (point prevalence) or across a lifetime (lifetime prevalence). Prevalence estimates can vary depending on the underlying age structure of a population (since typical schizophrenia onset is late teens or after, the prevalence of schizophrenia may be lower in populations that have a greater proportion of children and teenagers). Lifetime prevalence estimates of schizophrenia typically vary between 0.5% -1.0 % worldwide [7].

1.1.2.1.2 Risks and Critical Periods

The most well known risk factor for schizophrenia is a family history of schizophrenia. Meta analyses of familial studies estimating the risk of schizophrenia in first-degree relatives compared to age and gender matched controls have yielded an Odds Ratio (OR) of 9.77 [6]. A meta-analysis of twin studies found a high heritability of schizophrenia[2] estimated at 81% and a much smaller albeit statistically significant environmental effect (shared environmental influences) estimated at 11% [8]. Late life risk factors for schizophrenia include social stress and substance abuse. Social adversity can induce problems with the dopamine system, relevant to the pathology of schizophrenia. An animal study induced social stress by housing a bully mouse with a less dominant mouse, after which, the less dominant mouse showed changes in brain structure and dopamine functioning relevant to the pathophysiology of schizophrenia [9]. Also, studies have found that past and current cannabis use is more common in persons with schizophrenia. Cannabis use has been found to precipitate a psychotic episode that may lead to schizophrenia [10].

Abnormal brain development at different stages in life has been implicated in the development, onset and course of schizophrenia. The early developmental model points to factors during the second half of gestation that may lead to a lesion which can interfere with later brain functioning. Prenatal exposure to maternal infection and inflammation (which may occur more in urban areas), maternal malnutrition and maternal stress can all lead to brain abnormalities in the developing fetus that may be related to the development of schizophrenia [11-13]. The late developmental model posits that normal changes that occur in the adolescent brain in areas such as: delta sleep, membrane synthesis, gray matter volume and prefrontal metabolism are exaggerated in patients with schizophrenia as compared to healthy controls. The post-illness progression model seeks to account for deterioration in patients with schizophrenia; adverse structural changes in the brain may increase after first episode psychoses by way of neurochemical sensitization which can occur after persistent exposure to neurochemical stressors [6, 14].

[2] A measure of genetic variance that explains how much the characteristics of the offspring are dependent on the parent

1.1.2.1.3 Progression

Although schizophrenia is not typically diagnosed in childhood, evidence has shown that *some* children who later develop schizophrenia differ in terms of cognitive and behavior measures compared to children who do not develop schizophrenia. A1946 British cohort study found that persons who developed schizophrenia, compared to healthy age matched controls: learned to walk at later ages, had more speech problems, had lower education scores between ages 8-16, and had greater solitary play preferences between 4-6 years [15]. Furthermore, adolescent males aged 16-17, who were later hospitalized for schizophrenia had significantly lower social functioning, organizational and intellectual abilities compared to age matched males who were not later hospitalized for schizophrenia [16]. However, not all patients who develop schizophrenia display early signs; these patients may have a better prognosis.

Early symptoms that may indicate the onset of schizophrenia, known as prodromal symptoms, can occur anywhere from weeks to years before the first episode of psychosis. Prodromal symptoms include: suspicious thoughts, ideas of reference (intrusive thoughts that are known not to be real), auditory hallucinations, increased distractibility and attention problems [3]. Progression of symptoms causes severe impairment of social and occupational functioning. Negative symptoms may cause the most impairment and are also the most resistant to treatment [7]. Patients may be divided into categories with many falling into the category of cyclic episodes and recoveries, other patients showing a stable, chronic course with poor prognosis and still others showing a steady course of illness with consistent good outcome [17].

Patients with schizophrenia have mortality rates that are two to three times higher than the general population, which may be a result of increased suicide rates and common co-morbidities which may result from the interaction between poor diet, medications, low rates of physical activity and substance abuse [18].

1.1.2.2 Other Indications

Although schizophrenia is the most common psychiatric disorder for which antipsychotic medications are prescribed, antipsychotic medications can be used to treat a variety of psychotic disorders (as part of a treatment regimen or as stand alone treatment). Table 1.2 outlines various psychotic disorders from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) that may be treated with antipsychotic medications.

1.1.2.2.1 Children

Antipsychotic drugs can also be prescribed to children for some of the above conditions such as schizophrenia (early onset) and mood disorder with psychotic features. However, antipsychotics may also be prescribed as part of a treatment regimen for disorders that occur in youth such as autism and developmental disorders (defined by impairments in social interaction and communication as well as stereotyped behavior) (DSM-IV). Additionally, antipsychotic medications may be prescribed for Tourette's disorder (motor or verbal tics), disruptive behavior disorders in youth and anorexia nervosa (refusal to maintain a healthy body weight).

1.1.2.2.2 Elderly

Antipsychotic medications are often prescribed to elderly persons in nursing homes or in the hospital [19, 20]. Antipsychotic medications are most frequently prescribed to elderly persons for disorders such as chronic schizophrenia, paranoid disorder and degenerative dementia. However medications may also be prescribed off label, particularly in the elderly to help control non-psychotic behavioral and psychological symptoms associated with dementia, depression and bipolar disorder [21].

1.2 Typical Antipsychotic Drugs

There are a number of different typical antipsychotic drugs (also known as first generation drugs) that are chemically related. These drugs are classed together because of the similar therapeutic effects that they have on positive symptoms as well the mechanism by which they work.

Table 1.2 Psychotic disorders that can be treated with antipsychotic drugs[3]

Disorder	Symptoms	Duration	Types
Schizophreniform Disorder	Delusions, hallucinations, disorganized speech/behavior, negative symptoms	1-6 months	Rapid onset, confusion at height of psychotic episode
Brief Psychotic Disorder	Delusions, hallucinations, disorganized speech or behavior not consistent with cultural norms	1 day or less than a month	With marked stressors, without marked stressors, postpartum onset
Delusional Disorder	Non-bizarre delusions (plausible but incorrect belief)	At least 1 month	Erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
Shared Single Psychotic Disorder	Delusion developing in context of close relationship with another person(s) who has an already established delusion; delusion is similar to the other person's	-	-
Psychotic Condition Due to a General Medical Condition	Prominent hallucinations or delusions; with evidence from history or physical findings that they are the direct physiological consequence of a medical condition	-	With delusions, with hallucinations
Substance-Induced Psychotic Disorder	Prominent hallucinations or delusions without insight in context of substance intoxication or withdrawal, or with evidence that medication use is etiologically related to the disturbance	-	Onset during intoxication, Onset during withdrawal
Mood Disorder with Psychotic Features	Presence of either delusions or hallucinations in context of major depressive episode or manic episode	-	Mood congruent, Mood incongruent
Delirium	Disturbance of consciousness with attentional impairments, change in cognition or development of perceptual disturbance such as hallucinations, with evidence that it is a direct physiological consequence of a general medical condition	Short period of time and fluctuates during the course of a day	
Dementia	Development of multiple cognitive deficits; presentation depends on type of dementia	Sudden onset or chronic	Delusions can be prominent hallucinations

[3] Taken from: Leonard BE: Atypical antipsychotics- from bench to bedside. New York, Marcel Dekker Inc., 2004

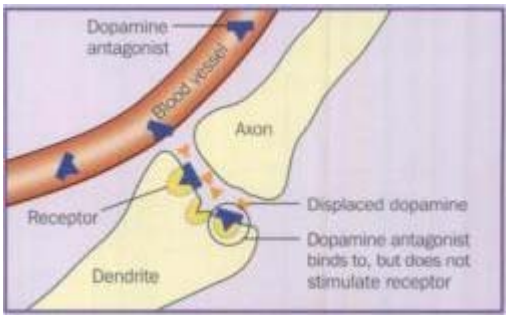
1.2.1 Mode of Action

Typical antipsychotic drugs inhibit dopamine function in the brain. Specifically, these drugs block post-synaptic dopamine receptors in the brain, in areas such as the frontal cortical region and limbic region. Figure 1.1 illustrates antipsychotic binding to dopamine receptors. An excess of dopamine is associated with positive schizophrenia symptoms such as hallucinations and paranoia [22]. Typical antipsychotics also block histamine H_1 receptors, adrenergic $alpha_1$ receptors and muscarinic cholinergic receptors. Blockage of the latter receptors can be associated with antipsychotic side effects [6]. Blockage of dopamine receptors is related to both therapeutic and negative side effects. Specifically, blockage of D_2 receptors in the basal ganglia is related to negative side effects, while blockage of D_2 receptors in areas such as the cerebral cortex may be related to therapeutic effects [23].

1.2.2 Effectiveness

Typical antipsychotic medications have been found to: lessen the intensity of positive symptoms such as hallucinations, delusions and disorganized behaviors; shorten psychotic episodes and weaken the risk of relapse. Elkes and Elkes used a case cross-over design in which patients with chronic schizophrenia served as their own control to illustrate the effectiveness of chlorpromazine compared to no medication [24]. The U.S. National Institute of Mental Health published a study in 1964 showing that 60% of psychotic patients who used antipsychotic medication had complete remission of positive symptoms in a 6-week period as compared to 20% of psychotic patients in the placebo group [25]. A 1968 study found antipsychotic medication alone superior to: psychoanalysis alone, psychoanalysis and medication, ECT or combination therapies (not including antipsychotics) in patients with schizophrenia [6]. Hogarty and Goldberg found that in patients discharged from the hospital and randomized to take either chlorpromazine or placebo, the placebo group was more likely to have a relapse after 12 months of follow-up [26]. While typical antipsychotic drugs reduce positive symptoms, there has been no such evidence that these drugs reduce negative symptoms, and it is even possible that typical antipsychotic drugs may exacerbate some negative symptoms such as blunted affect and emotional withdrawal at high doses (7).

Figure 1.1 Antipsychotic binding to dopamine receptors[4]



1.2.3 Side Effects

The most common side effects of typical antipsychotic drugs are extrapyramidal side effects (EPS). EPS include: a distressing feeling of restlessness and resulting movements referred to as akathisia; symptom clusters such as tremor, muscle rigidity, cognitive slowing and apathy referred to as drug-induced parkinsonism; muscular spasms, abnormal neck positioning and problematic swallowing referred to as dystonia; neuroleptic malignant syndrome defined by symptoms such as rigidity and hyperthermia; and tardive dyskinesia defined by involuntary, repetitive movements of the face and extremities[7]. EPS can occur after acute or chronic long term use of antipsychotic drugs[27]. EPS is observed more in patients who use high potency typical drugs such as haloperidol at high doses. A 1960 study found the prevalence of EPS in patients using antipsychotic medication to be 40%, indicating a large burden on patients [1]. EPS may be reduced by lowering antipsychotic dose, or by administering drugs such as beta-blockers, anticholinergic agents or benzodiazepines.

Another possible side effect of typical antipsychotic drugs is weight gain. Studies have found thioridazine, chlorpromazine, haloperidol, fluphenazine and molindone to be associated with significant weight gain [28]. Cases of diabetes have also been reported with the use of typical drugs (although the occurrence of diabetes has most often been studied in conjunction with atypical antipsychotics). Other side effects that may occur

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[4] Taken from: Cardwell M, Flanagan, C.: *Psychology A2: the complete companion*, Nelson ThornesThomas? Indicate city too. , 2003, page 220

after use of typical antipsychotic drugs include: elevated levels of cholesterol and increased prolactin which can result in sexual problems such as decreased libido and anorgasmia. Additionally, neuroleptic dysphoria may occur, an unpleasant subjective change in arousal, mood, thinking and motivation which occurs in response to antipsychotic medication [7]. Side effects may eventually lead to non-compliance with medication, especially when severe side-effects such as drug-induced parkinsonism are present. Compliance with medication regimens has been shown to result in reduced hospitalizations and rates of death due to suicide [29].

1.3 Atypical Antipsychotic Drugs

Lack of efficacy on negative symptoms and severe side effects from typical antipsychotic drugs motivated the search for new antipsychotic drugs that could target these problems. During the late 1950's, German psychiatrists formulated clozapine, the prototype for the 'atypical antipsychotic drugs' [1]. The label of 'atypical antipsychotic' came from these drugs' ability to block neurotransmitter receptors other than dopamine, which allows the reduction of negative symptoms and EPS.

Clozapine was officially released in Europe during the 1970s. However, reports of agranulocytosis, a rare but severe condition, resulted in the withdrawal of the drug from the market in 1975 [2]. A key study in 1988 demonstrated clozapine's superiority to chlorpromazine in treatment resistant patients [30]; clozapine was eventually marketed in Canada in 1991 with strict guidelines to monitor patient white blood cell counts. During the 1990s several other atypical drugs were introduced in Canada: risperidone was marketed in 1993, olanzapine in 1996 and quetiapine in 1998 [31].

1.3.1 Mode of Action

The atypical antipsychotic drugs work as mixed receptor antagonists[5]. In addition to blocking dopamine receptors (D_2) as do the typical drugs, the atypical drugs can also block serotonin 2A ($5\text{-}HT_{2A}$) receptors. Atypical drugs block can bind more loosely to D_2

[5] An antagonist blocks an action

receptors than the typical antipsychotic drugs, which may help reduce EPS and negative symptoms [23].

1.3.2 Effectiveness

1.3.2.1 Between Class Comparison

Atypical antipsychotic drugs have generally been found to be *at least as effective as*, or more effective than typical drugs in terms of reducing both positive and negative symptoms [7]. Recent evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) did not find atypical drugs quetiapine or risperidone *superior* to the typical antipsychotic drug perphenazine, in terms of time to discontinuation[6] [32]. Furthermore, the British Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS) found that patients randomly switched to an atypical drug other than clozapine compared to patients randomly switched to a typical drug did not experience any benefits in terms of quality of life, positive and negative symptoms or associated costs following 1 year of treatment [33].

Risperidone has been shown to be at least as effective as typical antipsychotic drugs in reducing schizophrenia symptoms and superior to some specific typical agents such as haloperidol. Risperidone has a longer time to all cause discontinuation and lower rehospitalization rates compared to haloperidol [34]. Olanzapine has been shown to be at least as effective as first generation antipsychotics in symptom reduction and some controlled trials have also found olanzapine to be superior to haloperidol in decreasing total psychopathology and negative symptoms [35]. Meta analyses have found quetiapine to be of similar efficacy to haloperidol [36]. A double blind study by Kane and colleagues found that in treatment resistant patents (defined by failing to respond to 3 previous treatments, low functioning and lack of response to haloperidol), 30% of patients receiving clozapine responded to treatment, showing a reduction in symptomology, as compared with 4% of the chlorpromazine group in a 6 week study [30]. Another study found that in a sample of 51 treatment resistant patients, 60% had a reduction in their

[6] Time to discontinuation is a clinically meaning outcome measure that measures the amount of time before a patient discontinues medication.

Brief Psychotic Rating Scale after initiation of clozapine treatment [37]. Although atypical agents are generally superior to haloperidol in terms of symptom reduction, haloperidol works more quickly to control positive symptoms.

1.3.2.2 Within Class Comparison

The relative effectiveness amongst the atypical antipsychotic drugs has been examined, particularly in the CATIE trial [38]. Phase II of the CATIE trial found time to treatment discontinuation as follows: risperidone (median: 7 months), olanzapine (6.3 months), quetiapine (4.0 months) and ziprasidone (2.8 months). A greater time to treatment discontinuation is desirable; if a patient discontinues drug treatment this can indicate the drug does not provide adequate symptom relief or the drug may cause undesirable side effects. Phase I of the CATIE trial found olanzapine superior to both quetiapine and risperidone in terms of time to discontinuation. Reasons for discontinuation differed between the drugs with olanzapine mostly discontinued due to adverse events such as weight gain and metabolic effects while quetiapine and risperidone were often discontinued due to lack of efficacy [32]. In patients with schizophrenia, clozapine has been found to be superior to other atypical drugs in terms of: symptom reduction, time to discontinuation, reduction of suicide attempts, and costs of rehospitalizations [37-40]

1.3.3 Side Effects

All atypical drugs have been found to increase the risk of weight gain (to varying degrees), with clozapine and olanzapine associated with the greatest amount of weight gain [41]. Other general side effects that may occur with use of atypical drugs include: glucose and lipid abnormalities, EPS, hypotension and tachycardia (increased heart rate) (32). In terms of side effects specific to atypical drugs: risperidone (at high doses) increases the risk of EPS and serum prolactin elevation, olanzapine can induce excessive sedation, and quetiapine can cause sedation and hypotension. In rare cases clozapine can cause agranulocytosis, seizures, and myocarditis (inflammation of the heart) [7]. Although decreasing medication dosage can help lessen the risk of severe side effects, due to the number and severity of potential side effects from clozapine use, clozapine has

been relegated to third line treatment and is only recommended for use in patients who have failed to respond to another antipsychotic drug [42].

There is growing concern about the risks of weight gain, metabolic problems and diabetes induced by atypical antipsychotic agents. A number of case reports, chart studies and large scale studies have provided evidence of antipsychotic induced diabetes. All drugs do not appear equal in terms of their risks of diabetes, however. [43-47].

1.4 Type II Diabetes

1.4.1 Physiology

In a healthy individual, glucose is absorbed from sweet, starchy foods after the foods have been digested. The glucose is then utilized by cells to produce energy or convert excess glucose into fat for storage. The absorption of glucose into cells is controlled by the hormone insulin, which is produced in the pancreas by beta cells of the islets of Langerhans. A rise in blood glucose will stimulate insulin secretion and when the blood glucose is low enough, insulin secretion is inhibited by negative feedback [48]. This cycle is illustrated in Figure 1.2.

Diabetes occurs when the body cannot properly utilize glucose as a result of insulin resistance[7] or when there an insufficient amount of insulin. Insulin resistance or insufficient insulin results in the inability of glucose to move into the cells which leads to glucose accumulation in the blood, eventually causing hyperglycemia (elevated blood glucose). Acute hyperglycemia can lead to life threatening complications such as ketoacidosis.

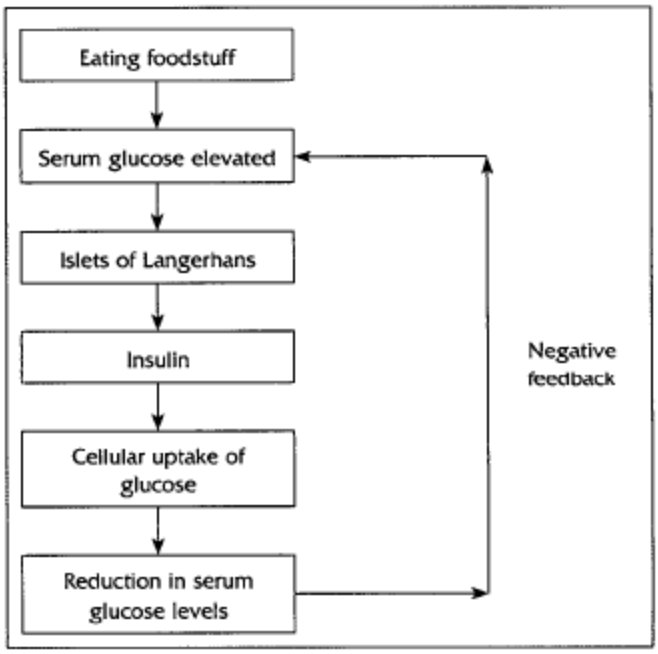
1.4.2 Criteria

One of the defining features of diabetes is chronic hyperglycemia. The WHO criteria for diabetes requires a fasting blood glucose level above 126 mg/dL, or a 2 hour post load glucose above 200 mg/dL. Common symptoms of diabetes include increased thirst, weight loss, fatigue, blurred vision and slow bruise healing. Type II diabetes has an

[7] Insulin resistance occurs when adequate amounts of insulin are present but glucose is not taken up by cells.

estimated prevalence of 4.5 % in the general population and 16%- 25% in patients with schizophrenia [49, 50].

Figure 1.2 Negative feedback of insulin control[8]



1.4.3 Risks

Metabolic syndrome represents a group of risk factors for type II diabetes. Metabolic syndrome is diagnosed when 3 or more of the following are present: increased weight around the waist, high levels of triglycerides, low levels of high-density lipoproteins cholesterol, high blood pressure, and high fasting blood glucose levels [51]. Another well known risk factor for diabetes is obesity. Mokdad found that severely overweight men had an OR of 7.4 for diabetes compared to age-matched men with a healthy weight [52]. Age is another major risk factor for diabetes; rates of diabetes are much higher in older populations [53]. Family history of diabetes and ethnicity are also risk factors for the development of type II diabetes [7]. Additionally, a diagnosis of schizophrenia may increase the risk for diabetes. Untreated patients with schizophrenia have been shown to

[8] Taken from: Nair M: Diabetes mellitus, part 1: physiology and complications. British Journal of Nursing 16: 2007, page 184

have more glucose abnormalities including insulin resistance compared to healthy controls [54].

1.4.4 Mechanisms of Antipsychotic- Induced Diabetes

One mechanism of antipsychotic-induced diabetes is through direct effects of antipsychotic drugs on insulin resistance. Antipsychotic drugs may have a direct effect on insulin-sensitive target tissues [55]. It is possible that antipsychotic drugs can directly impair the glucose transporter function in the absence of weight gain.

Another plausible mechanism of antipsychotic-induced diabetes is via weight gain, which can lead to insulin resistance and hyperglycemia. Several antipsychotic drugs have been linked to weight gain; atypical antipsychotic drugs such as olanzapine and clozapine are associated with the greatest amount of weight gain with patients gaining as much as 10% of their original weight within a year of treatment initiation compared to patients who receive no medication [41]. Significant weight gain is also observed with typical antipsychotic drugs, especially low-potency drugs such as chlorpromazine and thioridazine [41].

Weight gain is dependent on both energy intake and energy expenditure. A positive net energy leads to weight gain. This can occur through increased food intake, decreased exercise or a combination of both factors. The primary effect of antipsychotic medication on weight gain is through appetite stimulation and increased food intake (in the absence of compensatory increase in energy expenditure) [7]. The hypothalamus is the site in the brain responsible for weight regulation. Dopamine and serotonin are involved in messaging satiety to the hypothalamus. Antagonism of serotonin may increase appetite and lead to weight gain [56]. The specific receptor 5-HT_{2c} is a possible candidate for weight gain in atypical antipsychotic drugs (56). Atypical antipsychotic drugs can act as agonists[9] for this receptor which may lead to weight gain [28]. Histamine can also signal an anti-obesity message to the hypothalamus. Antipsychotic affinity for histamine receptors may interfere with signaling to hypothalamus and may be related to weight gain

[9] A drug that binds to a receptor of a cell and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance (from www.medterms.com)

[57]. An increase in prolactin levels, caused mainly by typical antipsychotic drugs may also lead to weight gain (56). Atypical antipsychotic drugs may possibly enhance a brain chemical function (gamma aminobutyric acid) which may cause weight gain (56). Levels of the hormone leptin are increased in patients treated with atypical antipsychotic drugs who have gained weight and have been found to decrease after medication cessation (29). Additionally, sedative effects of antipsychotic drugs can lead to physical inactivity, thereby contributing to weight gain (7).

1.5 Antipsychotic Drugs and Diabetes

Several studies have examined the risk of antipsychotic drugs on the development of diabetes. This section provides a brief overview of these studies.

A Medline search was conducted using the following search terms: antipsychotic (clozapine, risperidone, olanzapine, quetiapine, first generation, typical, second generation, atypical) and diabetes. Studies had to meet the following criteria to be included:

1) Studies had to analytic in nature, which included many cohort, case-control, and nested-case control studies (we did not find any relevant randomized trials); descriptive studies such as case reports and small chart studies were not included in the following review but are discussed later.

2) *Differential* risks of antipsychotic exposure and diabetes had to be assessed; of interest is the risk an antipsychotic drug poses relative to the risk of another antipsychotic drug within a particular study; it may be difficult to compare risks of drugs *between* different studies since each study generally has its own unique methodology that can directly affect the risk estimate.

3) Studies had to assess the effect of antipsychotic exposure on the outcome of diabetes.

Eleven studies met these criteria and are summarized below.

1) *Leslie & Rosenheck (2004) [58]*

Patient Source: VA database, patients with schizophrenia, n=56,649; Study Design: Retrospective Cohort Design; Exposure: measured as any consistent 3 month antipsychotic regime; Outcome: Diabetes measured by outpatient claims for diabetes; Funding: VA, NIMH, Bristol-Meyers Squibb.[10]

Main Findings: Clozapine and olanzapine both posed a significantly increased risk of diabetes compared to use of a typical agent; clozapine (HR=1.57 (95 % CI=1.31, 1.89)), olanzapine (HR= 1.15 (CI=1.07, 1.24)). Neither quetiapine nor risperidone posed a significant risk for diabetes compared to a typical agent.

Strengths: (1) Large sample size (allowing sufficient power to detect differences in risks amongst the antipsychotic drugs); (2) A homogenous patient population from VA with a diagnosis of schizophrenia; (3) Inclusion of several relevant factors: race, income, co-morbid mental health diagnoses, levels of service use, degree of VA service-connected disability.

Limitations: (1) a short follow-up that may not have detected cases of diabetes that took longer than a year to develop; (2) failure to control for antipsychotic switching and polytherapy outside of the 3 month interval; (3) assuming equal risk for all typical antipsychotic drugs.

2) *Lambert et al. (2005) [59]*

Patient Source: California Medicaid claims, n=18,186; Study Design: Matched case-control study; Exposure: antipsychotic medication measured 12 weeks prior to diabetes; Outcome: Diabetes measured by ICD-9 codes or prescription of an antidiabetic agent; Funding: Bristol-Myers Squibb.

Main Findings: Clozapine and olanzapine both pose a significantly increased risk of diabetes compared to use of typical antipsychotic drugs: clozapine (OR=1.36 (CI=1.16, 1.55)), olanzapine (OR=1.34 (CI=1.20, 1.53)). Risks for olanazpine increased with dosage. Risperidone and quetiapine did not pose significant risks of diabetes.

[10] Manufactures antipsychotic aripiprazole

Strengths: (1) Large sample size; (2) measurement of a dose response relationship (dose was measured in quartiles), which may be more relevant to development of diabetes; (3) inclusion of covariates race and use drugs that have been found to increase the risk of diabetes.
Limitations: (1) Inclusion of prevalent antipsychotic users, who may have used multiple drugs and or switched drugs during study period; (2) A short window of antipsychotic exposure (12 weeks prior to diabetes).

3) Sernyak et al. (2002) [60]

Patient Source: VA database, patients with schizophrenia, n=38,632; Study Design: Retrospective Cohort; Exposure: antipsychotic medication measured in a 4 month period; Outcome: Diabetes measured by ICD-9 codes in database; Funding: VA Mental Illness Research.

Main Findings: Clozapine, olanzapine and quetiapine pose significant risks for diabetes compared to typical antipsychotic drugs: clozapine (OR=1.25 (CI=1.07, 1.46)), olanzapine (OR=1.11 (CI=1.04, 1.18)), quetiapine (OR=1.31 (CI=1.11, 1.55)). Risperidone did not pose a significant risk of diabetes.
Strengths: (1) Large sample size, particularly in the clozapine group (n= 1,207); (2) Stratification by age helping to equalize patients in terms of baseline risk factors for diabetes; (3) Including covariates: race, income, distance to nearest hospital and days hospitalized in a psychiatric facility.
Limitations: (1) Short follow-up time; (2) Inclusion of patients who may have switched antipsychotic drugs or used more than one antipsychotic drug; (3) Lack of data on weight; (4) Grouping of all typical drugs together.

4) Kornegay et al. (2002) [61]

Patient Source: United Kingdom General Practice Research Database, patients with schizophrenia, n=3,147; Study Design: Nested Case Control; Exposure: Antipsychotic medication measured in a 3 month period prior to diabetes; Outcome: Diabetes measured by ICD-9 codes in database; Funding: Bristol-Meyers Squibb.

Main Findings: Use of olanzapine posed a significant risk for diabetes compared to use of typical antipsychotic drugs (OR=5.8 (CI=1.5, 10.9)). Risperidone did not pose a significant risk of diabetes. Clozapine and quetiapine were not included due to small sample size.
Strengths: (1) Stratification by age; (2) Several factors were controlled for: index year, duration of follow-up and use of medications known to increase the risk of diabetes
Limitations: (1) Short follow-up to detect diabetes; (2) Inclusion of patients who may have switched antipsychotic drugs or used more than one antipsychotic drug; (3) Lack of data on weight; (4) Grouping of all typical drugs together.

5) Barner et al. (2004) [62]

Patient Source: Veterans Healthcare Texas, n=6,735; Study Design: Retrospective Cohort; Exposure: index antipsychotic used, 1 year of follow-up; Outcome: Diabetes measured by ICD-9 codes in database or prescription of an antidiabetic agent; Funding: Eli Lilly.[11]

Main Findings: Use of olanzapine, risperidone or quetiapine did not significantly increase the risk of diabetes compared to use of a typical antipsychotic. Clozapine was not included in the study.
Strengths: (1) Inclusion of several factors including: body mass index, hyperlipidemia, hypertension, race and mental health comorbidity.
Limitations: (1) Small sample size (especially for individual atypical drugs); (2) Antipsychotic exposure measured by index drug; (3) Failure to account for antipsychotic switching or polytherapy; (4) Typical antipsychotic drugs were grouped together.

6) Citrome et al. (2004) [63]

Patient Source: New York mental health database, n=1,629; Study Design: Case-control study; Exposure: Antipsychotic used up to 6 months before diabetes; Outcome: Diabetes

[11] Manufactures olanzapine

measured by prescription of an antidiabetic agent; Funding: Eli Lilly, Janssen[12] Research and Pfizer Inc.

Main Findings: Use of clozapine and quetiapine significantly increased the risk of diabetes compared to use of a typical antipsychotic; clozapine (OR=2.06 (CI=1.07, 3.99)), quetiapine (OR=3.09 (CI=1.59, 6.03)). Use of olanzapine or risperidone did not significantly increase the risk of diabetes compared to use of a typical antipsychotic.
Strengths: (1) Assessing whether certain antipsychotic drug users were monitored more for diabetes.
Limitations: (1) Small sample size; (2) failure to account for antipsychotic switching or polytherapy; (3) Diabetes measured by prescription for antidiabetic drug alone (which can be prescribed prophylactically, in the absence of diabetes); (4) Typical antipsychotic drugs were grouped together.

7) *Buse et al. (2003) [64]*

Patient Source: Advance PCS, n=58,751; Study Design: Retrospective Cohort; Exposure: Antipsychotic drugs used during a 1 year period; Outcome: Diabetes measured by prescription of an antidiabetic agent; Funding: Eli Lilly.

Main Findings: Use of any antipsychotic drug significantly increased the risk of diabetes compared to a general patient population: low potency typical (HR=4.2 (CI=3.2, 5.5)), risperidone (HR=3.4 (CI=3.1, 3.8)), clozapine (HR=3.3 (CI=1.4, 8.0)), other typical (HR=3.1 (CI=2.6, 3.7), olanzapine (HR=3.0 (CI=2.6, 3.5)), quetiapine (HR=1.7 (CI=1.2, 2.4)). Use of risperidone and not any other atypical antipsychotic increased the risk of diabetes compared to haloperidol users. A positive-dose response relationship was observed with low-potency drugs alone.
Strengths: (1) Very large sample size; (2) Measurement of exposure to specific typical antipsychotic drugs; (3) Measuring antipsychotic dose (quartiles of dose).

[12] Manufactures risperidone

Limitations: (1) Failure to account for antipsychotic switching or polytherapy; (2) Diabetes measured by prescription for antidiabetic drug alone; (3) Failure to measure any psychiatric diagnoses; (4) Short follow-up time period.

8) Carlson et al. (2005) [65]

Patient Source: United Kingdom General Practice Research Database, n=68,142; Study Design: Retrospective Cohort; Exposure: Number of days on drug from index date to study end, between 1994-2001; Outcome: Diabetes measured by patient records or prescription of an antidiabetic agent; Funding: Eli Lilly.

Main Findings: Use of risperidone, olanzapine or thiordazine, a low-potency typical significantly increased the risk of diabetes compared to no use of an antipsychotic drug; risperidone (HR=2.5 (CI=1.4-4.5)), olanzapine (HR=3.9 (CI=1.9-8.1)), thiordazine (HR=1.7 (CI=1.1-2.5)). Clozapine and quetiapine were not included in the study.
Strengths: (1) Long follow-up period; (2) Included individual typical antipsychotic drugs; (3) Controlled for obesity and use of drugs associated with diabetes; (4) Considered cumulative antipsychotic exposure.
Limitations: (1) Sample size was small for atypical drugs; (2) Reference population (persons in the UK database not using antipsychotic medications) were significantly older than antipsychotic users; (3) Psychiatric diagnoses were not controlled for in this study.

9) Gianfrancesco et al. (2002) [66]

Patient Source: Managed care health plan from the US, n=7,933; Study Design: Retrospective Cohort; Exposure: Treatment episodes of antipsychotic drugs between 1996-1997; Outcome: Diabetes measured by patient records or prescription of an antidiabetic agent; Funding: Janssen.

Main Findings: Use of clozapine, olanzapine, high potency typicals and low potency typicals significantly increased the risk of diabetes compared to no use of an antipsychotic: clozapine (OR=7.4 (CI=0.6, 34.8)), olanzapine (OR=3.1 (1.6, 5.9)), high potency typicals (OR=2.1 (1.1, 4.1)), low potency typicals (OR=3.5 (CI=1.5, 7.8)). Use

of risperidone did not increase the risk of diabetes compared to the general population. Quetiapine was not available at the time of this study.
Strengths: (1) Individual typical drugs assessed; (2) Measurement of antipsychotic treatment duration and dosage (in risperidone equivalent units); (3) Control for several factors including use of drugs associated with diabetes, type of health care coverage, psychiatric diagnoses.
Limitations: (1) Failure to measure weight or BMI, known risk factors for diabetes; (2) failure to account for antipsychotic switching and polytherapy.

10) Guo et al. (2006) [67]

Patient Source: Managed care health plan from the US, patients with Bipolar Disorder, n=6,178; Study Design: Case-control study; Exposure: 3 month exposure period before diabetes; Outcome: Diabetes measured by patient records or prescription of an antidiabetic agent; Funding: Bristol-Meyers Squibb.

Main Findings: Use of clozapine, olanzapine, risperidone or quetiapine significantly increased the risk of diabetes compared to use of typical antipsychotics: clozapine (HR=7.0 (CI=1.7, 28.9)), olanzapine (HR=3.2 (2.7, 3.8)), risperidone (HR=3.4 (2.8, 4.2)), quetiapine (HR=1.8 (1.4, 2.4)).
Strengths: (1) Controlled for several factors including use of drugs associated with diabetes, type of health care coverage, psychiatric diagnoses.
Limitations: (1) Small sample size; (2) Failure to account for antipsychotic switching or polytherapy; (3) Short window of antipsychotic exposure.

11) Ostbye et al. (2005) [68]

Patient Source: Advance PCS in the US, n=14,872; Study Design: Retrospective Cohort design; Exposure: Antipsychotic exposure measured during an 18 month period; Outcome: Diabetes measured by prescription of an antidiabetic agent; Funding: Eli Lilly.

Main Findings: Use of clozapine, olanzapine, risperidone or quetiapine did not significantly increase the risk of diabetes compared to use of typical antipsychotic drugs.

Strengths: (1) Assessment of individual typical drugs; (2) Inclusion of chronic disease score, which is associated with diabetes.
Limitations: (1) Failure to measure weight or BMI; (2) Failure to account for antipsychotic switching or polytherapy; (3) Small sample size for individual atypical drugs.

Overall, clozapine and olanzapine appear to increase the risk of diabetes compared to use of typical antipsychotic drugs and no use of an antipsychotic drug. Furthermore, the few studies that have estimated the risk of diabetes in specific typical antipsychotic drugs have found low-potency typical drugs to pose an increased risk of diabetes compared to no use of an antipsychotic. The risks for risperidone, quetiapine and typical drugs (other than low-potency drugs) appear discrepant in terms of risks relative to other antipsychotic drugs.

Limitations common to the majority of studies include: short follow up time (usually less than a year) which may not allow adequate time to detect diagnoses of diabetes, a short window of antipsychotic exposure that cannot account for antipsychotic switching or polytherapy, and a small sample size of users of particular atypical antipsychotics.

1.6 Study Objectives

Similar to the above-mentioned studies, this study seeks to assess the differential risks that antipsychotic drugs pose for diabetes. However, this study seeks to improve upon some of the fore-mentioned limitations of previous studies. Specifically, this study: 1) spans many years (1993-2004), allowing a long follow-up period to detect cases of diabetes; 2) measures antipsychotic exposure across entire time in study; 3) Includes a sensitivity analysis that restricts analysis to single drug users; 4) includes incident drug users; and 5) has a relatively large sample of atypical drug users.

This study seeks to add evidence of a causal relationship between antipsychotic exposure and diabetes by assessing a dose-response relationship between antipsychotic drugs and diabetes. Demonstrating a dose-response relationship between two variables can help

establish causation according to the Austin Bradford Hill criteria (69). To our knowledge, this is the first study that uses a standardized dose that accumulates across time. The few studies that have examined a dose-response relationship have used antipsychotic quartiles that are driven by specific data; an increase in a specific drug from quartile 1 to quartile 2 may not be equivalent to an increase from quartile 3 to quartile 4 of that same drug. An increase in quartile may not correspond to a clinically meaningful increase of an antipsychotic drug dose.

Chapter 2 Methods

2.1 Study Design

The present study relied on data from a larger study, as yet unpublished, that examined antipsychotic prescribing practices amongst general practitioners and psychiatrists and evaluated the impact of cost sharing and its removal on antipsychotic use. The present study is a longitudinal observational study in which individuals are followed throughout time. This study employed a retrospective cohort design.

2.2 Data Sources

The data was provided by the Regie de l'assurance maladie du Quebec (RAMQ) and by the Ministry of Health and Social Services (MSSS) with approval from the Commission d'Accès à l'Information and the Douglas Hospital Research Ethics Board. Data on persons who filled at least one prescription for an antipsychotic drug between January 1993 and December 2004 while on welfare in Quebec were extracted from RAMQ and Med-Echo databases[13]. Data provided by the RAMQ include: Pharmaceutical Data (including all prescriptions filled between 1993-2004, Drug Identification Number (DIN), dose, duration, date prescription filled, patient identifier, prescribing physician identifier, etc); Physician Services Data (including data on type of medical service, diagnosis, date of service, patient identifier, physician identifier, etc). RAMQ also provided demographic patient information including sex and age, as well as insurance status which can change over time. Dates of death were also provided. The MSSS provided Med-Echo data on hospitalizations that occurred between 1993 and 2004 including; primary and secondary diagnoses, admission and discharge dates, patient identifier, hospital identifier, physician identifier etc. The patient identifier contained in all datasets allowed the linking of a given patients' prescription, medical and hospital records in order to identify all prescriptions filled and diagnoses during 1993-2004. Data on hospitalizations and physician services contain no interruptions as long as an individual remains in the province of Quebec. Data on physician services may omit some services not provided on

[13] As this study relied on previous data from the above mentioned study, only persons on welfare were included. The criterion of welfare use captured a large group of antipsychotic users of varying ages, including elderly persons.

a fee-for-service basis. Prescription records may be interrupted if, for example, a patient is hospitalized, or is no longer covered by welfare.

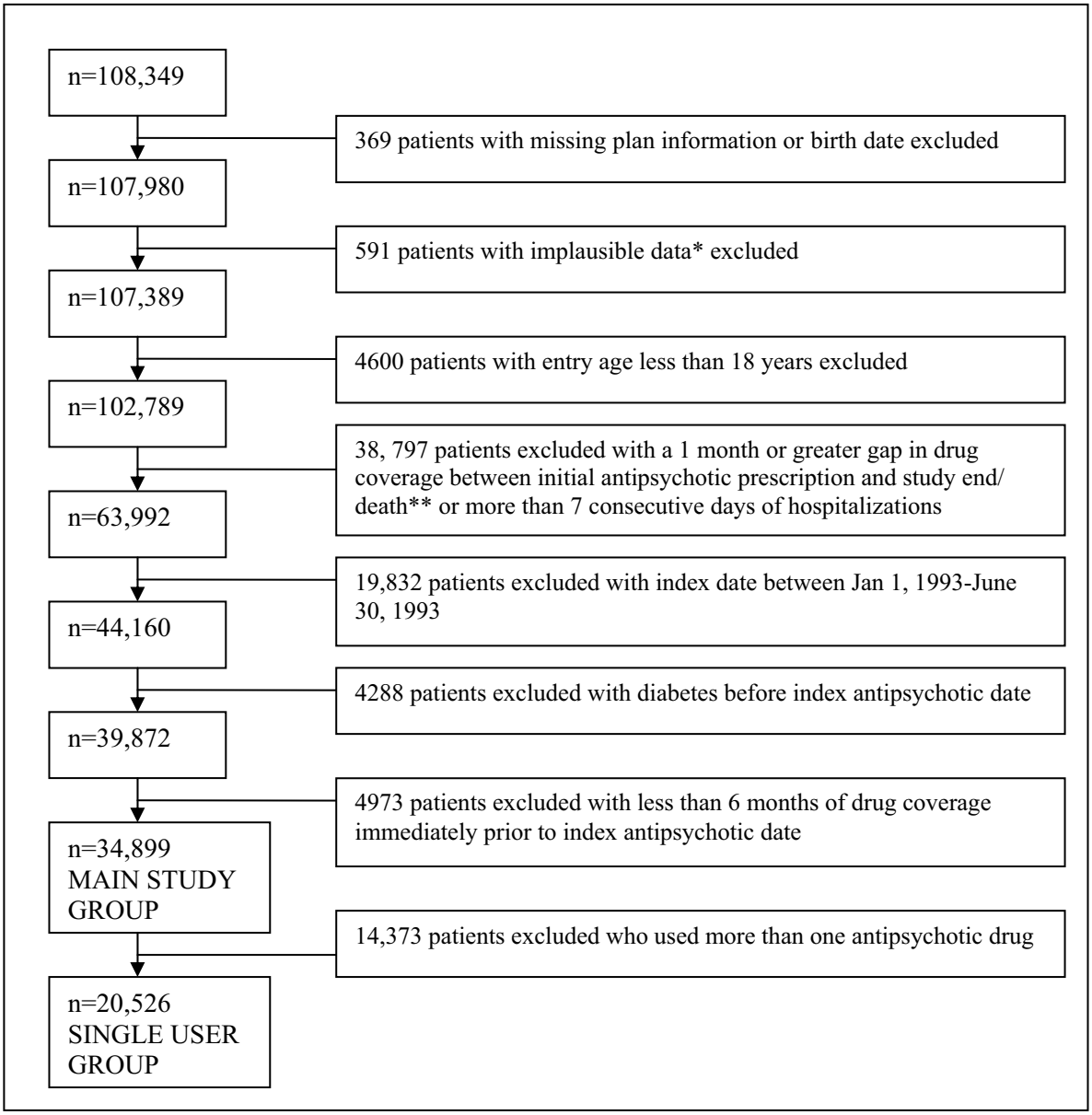
2.3 Sample Selection

The initial cohort consisted of 108,349 patients who filled at least one prescription for an antipsychotic drug between January 1993 and December 2004 with welfare coverage in Quebec. The final main study group consisted of 34,899 patients.

A small number of individuals were excluded from the study with missing information or implausible data for one or more prescriptions. Since the number of individuals with implausible data was small (and their removal would not significantly affect the sample size), this study did not attempt to keep these persons in the study by making imputations for their missing values. A small percentage of individuals were less than 18 years of age at index antipsychotic date and were excluded from the main study group in order to help equalize the population in terms of risk for diabetes and indication for antipsychotic. A large number of individuals were excluded from the study due to incomplete information on prescription drug coverage during the study period. If a patient was not on welfare for 1 month or more, then their exposure status could not be ascertained that month (and possibly additional months) which could bias their overall exposure status downwards. Also, if a patient was hospitalized for 7 consecutive days or more, their exposure status could not be ascertained during this period which could bias exposure specifically in the cumulative dose model. In addition, in order to include only incident antipsychotic users, six months of welfare coverage was required prior to first antipsychotic prescription (in order to be sure that initial antipsychotic was the first prescribed antipsychotic). Finally 4,288 individuals were excluded from the study due to a medical diagnosis of diabetes prior to initial antipsychotic prescription. This study was concerned with incident diabetes that developed at some point after initial antipsychotic exposure and not prevalent cases of diabetes. After all exclusions 34,899 individuals formed the main study group. Another 14,373 individuals, who used more than one antipsychotic drug, were excluded from the study to form what will be called the single user group

(n=20,526). Figure 2.1 summarizes the exclusions made to the initial cohort to form the study groups.

Figure 2.1 Exclusion of patients in formation of main study group and single user group



* Implausible data, such as such as a prescription duration equal to 0 days or greater than 270 days or a prescription that appears to be filled outside of the drug plan coverage dates as indicated by RAMQ data.
**Individuals who died before the study end date but who had complete drug coverage from index antipsychotic date till date of death were included in the study.

2.4 Outcome Measures

The outcome in this study is type II diabetes. A patient was identified as having diabetes if their medical or hospital records contained an International Classification of Diseases, Ninth Revision (ICD-9) code of 250.X0 or 250.X2. If a patient had multiple diagnoses of diabetes, the first date at which a diagnosis was observed served as the index date of diabetes. A small number of individuals (less than 1%) received a prescription for an antidiabetic drug (RAMQ code 68:20 Hormone and Synthetic Substitutes) in the absence of a medical diagnosis of diabetes. Patients who filled a prescription for an antidiabetic drug without a medical diagnosis of diabetes were not considered to have diabetes since anti-diabetic medications can sometimes be used as a prophylactic (82).

2.5 Antipsychotic Exposure

Antipsychotic exposure was assessed, first, by identifying all prescriptions with a RAMQ class code of 28:16:08 (Central Nervous Systems Agents: Psychotropic: Antipsychotic Agents). Each prescription contained a unique DIN that could be looked up in the RAMQ list of medications to find the correct drug name and active quantity in mg (for drugs in pill form) or in mg/mL (for drugs in non-pill form). Table 2.2 contains a list of all the antipsychotic medications used in this particular cohort, listed by year introduced (if after 1993, the beginning of our observation period) and by typical/atypical categorization.

2.5.1 Antipsychotic Classification

The first level of antipsychotic classification used in this study was by typical or atypical class. Several studies of this kind have looked at atypical antipsychotic drugs individually while grouping the typical antipsychotic drugs together. However, this study did not assume a homogenous risk amongst all typical drugs and further classified typical drugs by their potency[14] in light of evidence that low-potency antipsychotic drugs cause more weight gain than other typical drugs. This classification is warranted considering the weight gain pathway to diabetes described in the previous chapter. The low potency

[14] The benchmark low-potency antipsychotic is chlorpromazine. Antipsychotics with a potency equivalent to or less than chlorpromazine are categorized as low-potency. Low-potency antipsychotics require high doses to effectively block dopamine, relative to other antipsychotics such as haloperidol, a classic high potency antipsychotic (Leucht, 2003).

drugs used in this study were: chloropromazine, mesoridazine and thioridazine (7). All other typical antipsychotic drugs in the study were classified as “Other Typical Drugs”, each having a potency higher than chlorpromazine.

Table 2.1 Antipsychotic drugs included in this study

Antipsychotic agent	
Typical	Atypical
Chlorpromazine	Clozapine (1991)
Perphenazine	Risperidone (1993)
Fluphenazine	Olanzapine (1996)
Haloperidol	Quetiapine (1998)
Loxapine	
Flupenthixol	
Fluspirilene	
Mesoridazine	
Pimozide	
Pipotiazine	
Prochlorperazine	
Pericyazine	
Thioproperazine	
Thioridazine	
Thiothixene	
Trifluoperazine	
Zuclopenthixol	

2.5.2 Division of Time

This study considered antipsychotic exposure as a time-varying covariate. Antipsychotic exposure was evaluated at each month, according to study time (and not calendar time). The date the index antipsychotic prescription was filled was considered day 1 for that patient and the first month was considered as the first 30.5 days after the index prescription was filled. Each prescription was assigned a specific month by using the date the prescription was filled as a proxy for the date the medication was taken. A month was assigned for each drug by taking the difference between the date the prescription was

filled and the index date and divided by 30.5. Months took on integer values between 1 and 138.

This method of approximation may allow for a small amount of error: if the duration of a prescription extended beyond the end of the 30.5 day interval, the total dose contained in that prescription was attributed to that 30.5 day period which could result in an unusually high dosage for that month. Such an error would, however, be cancelled out by a corresponding underestimate the following month. (This simplification should have little effect on the results as about 97% of prescriptions were for 30 days or less and only 0.10% of prescriptions were for more than 90 days.)

The index prescription for each patient was defined as their first prescription of drug class 28:16:08. Prescriptions for a given patient with the same DIN were summed across each 30.5 day interval based on the date the prescription was filled. For example, if a patient filled two prescriptions for the same drug within the same 30.5 day interval, these drug doses would be combined to form a monthly dose for each unique antipsychotic drug.

2.5.3 Antipsychotic Dosage

Each prescription contained a DIN that corresponded to an active quantity field in mg for drugs prescribed in pill form or in mg/mL for drugs prescribed in long acting injectable form (known as depot). About 98% of prescriptions for antipsychotic drugs were in oral pill form and the remaining 2 % of prescriptions were prescribed as depot. A raw dosage score was formed by multiplying the physical quantity of a drug by the active drug quantity. For example: DIN= 17698 corresponds to the typical drug haloperidol with an active quantity of 5mg per pill. The most common physical quantity of a drug is 30 pills (for one month). In this case, a raw dosage score would be formed by multiplying 5mg*30 pills= 150mg. A DIN= 2130300 corresponds to the typical drug haloperidol depot form with an active quantity of 100 mg/mL. A common physical quantity of 2mL (for one month) would give a raw dosage of 2mL*100mg/mL= 200mg. Dosages for drugs prescribed in depot form tended to be higher than dosages for pills.

2.5.4 On/Off model

In the on/off model, the raw dosage was converted into a binary measure, with 1 indicating a non-zero dosage for a specific drug during a particular month, and 0 indicating a 0 dosage. This measure was calculated separately for clozapine, olanzapine, risperidone, quetiapine, low-potency typical drugs and other typical drugs. The model captures the risk associated with current use of an antipsychotic drug at the time of diabetes detection. This model does not allow the risk associated with certain drugs to accumulate across time, but rather considers the risk associated with a drug at an instant in time.

2.5.5 Cumulative Dose Model

The cumulative dose model takes both antipsychotic treatment duration and antipsychotic dosage into account. This is likely the more biologically plausible model, allowing for the diabetic effect of antipsychotic medications to increase with both length and average dosage of antipsychotic treatment [66]. Exposure is time varying, as with the on/off model. WHO standard dosages for each individual drug were used to generate a ratio of study dosage to WHO standard dosage[15]. In order to compute this ratio, a standard table with WHO recommended daily doses for each antipsychotic drug was used. The WHO daily doses were then converted into a monthly dose, as this study considered antipsychotic dose at the month level. Each dosage calculated from the study was then divided by the WHO standard dose to generate a ratio that would equal 1 if a patient took the WHO recommended dose for a specific antipsychotic drug and less than 1 if a patient used less than the recommended dose by WHO and greater than 1 if a patient used a dosage above that recommended by the WHO. Dosage ratios took on values between 0 and10. For example, a 30 day prescription of haloperidol in pill form could have a raw dosage of 150mg (as outlined above); the standard WHO dose of haloperidol is 8mg/day or 240 mg/month in pill form. In this example, the standardized dose would be 0.625 (150/240). The dosage was then accumulated over time, either remaining constant for a

[15] Taken from WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atcddd/) Anatomical Therapeutic Chemical (ATC)/ Defined Daily Dose (DDD) classification

month with no exposure to a drug or increasing with each month of a non-zero dosage. It should be noted that in contrast to the on/off model, this measure is not affected by the timing of exposure. For example, if Patient 1 uses clozapine in year one and then changes to olanzapine in year two and Patient 2 uses olanzapine in year one and then changes to clozapine in year two, the drug exposures for these patients would be considered the same.

2.6 Other Covariates

Known risk factors for the outcome (diabetes) that could have been associated with exposure (antipsychotic medication) were identified and controlled for in this study. The following covariates were controlled for as possible confounders:

Schizophrenia has been found to be associated with an increased risk of diabetes independent of antipsychotic exposure. Studies of first-episode untreated patients have found these patients to have abnormally high glucose levels [7].

Schizophrenia was identified in this study through medical and hospital records with an ICD-9 code of 295.xx. A patient who began antipsychotic treatment and was later diagnosed with schizophrenia was considered to have schizophrenia for their entire period of observation in the study, as it was assumed that the doctor who first prescribed an antipsychotic simply did not record the diagnosis on the claim form. Unlike antidiabetics, antipsychotics are not normally administered prophylactically due to their serious side-effects. A diagnosis of schizophrenia was treated as a constant covariate in this study and coded as a binary variable.

Obesity is a well established risk factor for diabetes and we attempted to control for it this study. Obesity was detected through hospital and medical records with an ICD-9 code of 278.0X. Obesity was coded as a binary variable, set equal to 1 if a patient had a diagnosis of obesity *before* their index antipsychotic date. A diagnosis of obesity after antipsychotic exposure could have resulted from weight gain after antipsychotic initiation and may have been along the causal pathway of antipsychotic induced diabetes.

Increasing age is associated with an increased risk of type II diabetes. The prevalence of diabetes has been found to be up to 3 times as high in persons over 65 compared to adults between 34-64 (Stats Canada). Month and year of birth was provided in the pharmacy records for each patient (date was estimated as the 15th of each month) and entry age was calculated by subtracting a patient's date of birth from the date that their index antipsychotic prescription was filled and then dividing the difference by 365.25. Age at study entry was expressed as a continuous variable. The relationship between entry age and diabetes is not linear (see Appendix), therefore entry age was modelled as a quadratic term in the main analyses.

Males have been found to have increased risks of type II diabetes (Public Health Agency of Canada). This finding could be explained *if*, for example, males in a population are older, more obese, or of ethnic descent, all known risk factors for diabetes. Male sex has not generally been cited as a risk factor for diabetes. However, this study still controlled for sex.

Year of entry in the study may to be associated with diabetes, with a greater year of entry associated with an increased risk of diabetes. The rates of diabetes have increased with time; the prevalence of diabetes has increased by 24% between 2000 and 2004 in Canada after adjusting for differences in age distribution (Public Health Agency of Canada). This study considered year of entry in the study as a fixed value for a given individual, which could take on integer values ranging from 1993 to 2004. Year of entry was considered as a linear term in the analyses. Evidence of a linear relationship between year of entry and diabetes is documented in the Appendix.

2.7 Statistical Analysis

Descriptive statistics were computed to assess differences between the initial population, the main study group and the single user group. Additional descriptive statistics also showed differences across various antipsychotic groups in their baseline risk factors for diabetes as well as the raw risk of diabetes across different drug groups.

Cox proportional-hazards regression was used to estimate the risk of antipsychotic use on the development of diabetes while controlling for potential confounding variables. The `stcox` command was used in Stata v 9.0. This particular method of survival analysis was chosen in order to take into account: the cohort design of this study, censored data (right hand censoring due to death or study end), and time-varying exposure measures [69]. Both time-varying and static covariates were included in the analysis. Antipsychotic exposure was measured both as a binary variable as in the on/off model and as a continuous variable as in the cumulative exposure; in both cases, 6 separate variables were constructed for 4 atypical antipsychotics and the two groups of typical antipsychotics: clozapine, olanzapine, risperidone, quetiapine, low-potency typical, other typical drugs. In this analysis, the referent group for any given drug was considered as the heterogeneous group not on Drug X. In the On/Off model this could result in the referent group containing patients with past but not current use of Drug X. In the Cumulative Dose Model, the referent group not on Drug X at time t had exposure to another drug in the study, but not to Drug X – at least, had not taken drug X between January 1993 and time t.

The following model was used:

$$\ln[h(t)/h_0(t)] = \beta_1 x_1 + \beta_2 x_2 + \ldots. \beta_k x_k$$

The x values represent the covariates, β values are model parameters, h(t) represents the hazard at a point in time *t*, and $h_0(t)$ represents the hazard at baseline (the hazard for an individual when all the covariates are set equal to 0). The interpretation of the hazard ratios for covariates (and antipsychotic exposure) depends on whether the variable is continuous or binary.

The Cox proportional-hazards regression assumes that if use of a specific drug increases the risk of diabetes by a factor of X at month 1, use of the same drug at any month during the study would also increase the risk of diabetes by a factor of X. This proportional hazards assumption was tested using the `linktest` command in Stata.

Chapter 3 Results

This chapter includes: descriptive statistics, main analyses and sensitivity analyses. Descriptive statistics begin by comparing three populations: the initial cohort provided by RAMQ, the subset of the initial cohort that forms the main study group and a subset of the main study group who use only one antipsychotic drug (single user group). These three groups are compared in terms of values of the covariates and the outcome of diabetes. Descriptive statistics are then given for the main study group alone focusing on antipsychotic exposure (types of drugs used, number of drugs used, frequency of drug use). Covariates, study end points and the outcome are then compared across the different antipsychotic exposure groups. Next, the main analyses, Cox proportional hazard models, are presented: an on/off model and a cumulative dose model. Finally sensitivity analyses are carried out to assess the robustness of the findings to key assumptions.

3.1 Descriptive Statistics

Statistics describing the outcome and covariates are first presented separately for the main study group and the single user group. Descriptive statistics are then presented in the main study group and broken down by exposure group (antipsychotic drug group).

3.1.1 Covariates across Study Groups

In order to address potential confounding, it is necessary to measure variables that are associated with both exposure to antipsychotic drugs, and with the outcome, diabetes. Several variables were identified as potential confounders that are associated with diabetes onset and that vary by exposure group: schizophrenia, sex, obesity (prior to first antipsychotic use), entry age, and year of entry into study. Table 3.1 shows how these variables differ between the initial cohort, the main study group and a subset of the main study group, single antipsychotic users.

3.1.1.1 Main Study Group versus Initial Cohort

In general, the main study group should be representative of the initial population. A comparison of relevant covariates can indicate whether the proportions are similar

between main study groups and the initial cohort. In this study, the main study group differed from the initial cohort after application of exclusion criteria to the initial cohort.

Table 3.1 Covariates in initial cohort, main study group and single user group

	Initial Cohort * (n=108,349)	Main study group** (n=34,899)	Single user group*** (n=20,526)
Schizophrenia (%)	38.0	27.0	13.1
Male (%)	51.0	45.0	43.0
Obese (%)	3.6	4.2	4.7
Entry Age Mean(SD)	40.2(13.6)	42.9(12.5)	45.1(12.4)
Index Year Mean (SD)	1998 (3.9)	1999 (3.4)	1999 (3.5)

***** Initial cohort as provided by RAMQ
****** Main study group is a subset of the initial cohort who met the eligibility requirements for the study (see previous chapter).
***Subset of main study group who have used only one antipsychotic drug

Fewer than half of the initial cohort of antipsychotic users have a diagnosis of schizophrenia. An even smaller proportion of the main study group have a diagnosis of schizophrenia. Table 3.2 shows disorders identified from patient hospital and medical records for which treatment with antipsychotic medication may have been recommended. Schizophrenia is one of the main indications for antipsychotic drugs; given the low rates of schizophrenia in this study, it is possible that schizophrenia was underestimated in this study.

The exclusion of patients who filled an antipsychotic prescription between January and June of 1993 resulted in the loss of many persons with schizophrenia. Prevalent antipsychotic users (who were already using an antipsychotic drug when the study began) are likely to be long term antipsychotic users; long term antipsychotic users are more likely to have schizophrenia. Also, many persons who were excluded from the main study group as a result of discontinuous drug coverage in the six months prior to their index date had a diagnosis of schizophrenia. Persons with schizophrenia have high rates

of homelessness [70] and may therefore not have continuous welfare coverage. These exclusions in the main study group help account for the smaller percentage of individuals with schizophrenia in the main study group.

Table 3.2 Possible indications for antipsychotic based on hospital and medical claims

	Initial Cohort	Main study group	Single antipsychotic users
Schizophrenic Disorders*	38.0	27.0	13.1
Other**	41.9	38.3	33.7
Undetermined	20.1	34.7	53.2

* Schizophrenia, Schizophreniform Disorder, Latent Schizophrenia, Residual Type, Schizoaffective Disorder, Other Specified types of Schizophrenia, Unspecified Schizophrenia
** Acute Psychoses, Bipolar Disorders, Delirium, Dementia, Delusional Disorder, Tourette Syndrome, Obsessive Compulsive Disorder, Panic Disorder

The proportion of males is approximately half in the initial cohort and less than half in the main study group. The smaller percentage of males in the main study group is the result of losing a disproportionate number of males with study exclusion criteria of discontinuous welfare coverage or fewer than 6 months of drug coverage prior to index antipsychotic date. Data from the Government of Canada indicate that there is a higher proportion of homeless men than women [71]. Men may therefore be more likely to have discontinuous welfare coverage when they are living on the street.

Although the overall percentage of obesity detected in this study was low, as obesity was only detected through ICD-9 codes, the percentage of obesity is greater in the main study group than in the initial cohort. This is at least partially the result of the exclusion of persons less than 18 in the main study group, as these persons had disproportionately lower rates of obesity. Also the exclusion of prevalent antipsychotic users with an index antipsychotic date between January and June 1993 resulted in the loss of persons with very low apparent rates of obesity. It is possible that prevalent antipsychotic users had diagnoses of obesity prior to 1993 that were not captured in this study.

The average entry age is higher in the main study group. Approximately 3% of the initial cohort were less than 18 years old, whereas the main study group is comprised of persons 18 years or older, which can explain the higher average entry age in the main study group.

The index year, the year during which a patient filled their first antipsychotic prescription between 1993 and 2004, is higher in the main study group compared to the initial cohort. The exclusion of patients who entered the study during the first 6 months of 1993 helps to explain the increase in average index year in the main study group.

3.1.1.2 Single Antipsychotic Users versus Main Study Group

The single user group differs from the main study group on most covariates as shown in Table 4.1. The only exclusion criteria applied to the single antipsychotic user group is that they use only one antipsychotic drug. The group of single antipsychotic users appear to differ systematically from the main study group. The higher average entry age, higher proportion obese and much smaller proportion with schizophrenia indicate that this group is older, and are more likely to be prescribed antipsychotic medications for conditions other than schizophrenia, such as dementia or delirium. Studies have found that patients over 50 years are most likely to be prescribed antipsychotic medications off-label as a tranquilizer or anxiolytic [21, 42].

3.1.2 Diabetes across Study Groups

A greater proportion of individuals have a diagnosis of diabetes in the initial cohort than in the main study group and single user group. This is largely the result of excluding persons who have a diagnosis of diabetes prior to their index antipsychotic date in the main study group and single user group. Table 3.3 shows the percentage of diabetes in the initial cohort, main study group and single user group as well as the proportion of persons who have a medical diagnosis of diabetes and a prescription for an antidiabetic medication.

Table 3.3 Diabetes in initial cohort, main study group and single user group*

	Initial Cohort (n=108,349)	Main study group (n=34,899)	Single User Group (n=20,526)
%			
Diagnosis Alone	6.2	4.3	3.8
Diagnosis & Antidiabetic	9.4	5.0	5.5
Total Number	15.6	9.3	9.3

* Diabetes after filling a prescription for an antipsychotic drug(s)

More than half of the patients identified with diabetes are also identified as having filled a prescription for an antidiabetic agent. However, a significant portion of patients with diabetes do not fill a prescription for an antidiabetic medication during the study period. Patients who use antidiabetic medications may be unable to control their diabetes through diet and exercise alone which could indicate a more severe form of diabetes.

3.1.3 Covariates by Diabetes Status

Patients who developed diabetes differed on all covariate measures. Table 3.4 illustrates how covariates for persons with diabetes differ from covariates for persons without diabetes.

3.1.4 Antipsychotic Exposure in Main Study Group

3.1.4.1 Types of Drugs

As shown in Table 3.5, of the 34,899 persons in the main study group, comparable numbers use exclusively typical antipsychotic drugs and exclusively atypical drugs, while a smaller portion use both classes of drugs.

Table 3.4 Covariates in patients with and without diabetes in the main study group and single user group

	Main study group (n=34,899)		Single User Group (n=20,526)	
	Diabetes (n=3,240)	No Diabetes (n=31,659)	Diabetes (n=1,910)	No Diabetes (n=18,616)
Schizophrenia %	32.0	26.0	18.0	12.6
Male %	39.0	45.2	37.0	43.9
Obese %	7.6	3.9	8.2	4.4
Entry Age mean(SD)	45.7 (11.4)	42.6 (12.6)	48.1 (11.2)	44.8 (12.5)
Index Year mean(SD)	1997 (2.9)	1999 (3.5)	1997 (3.1)	1999 (3.5)

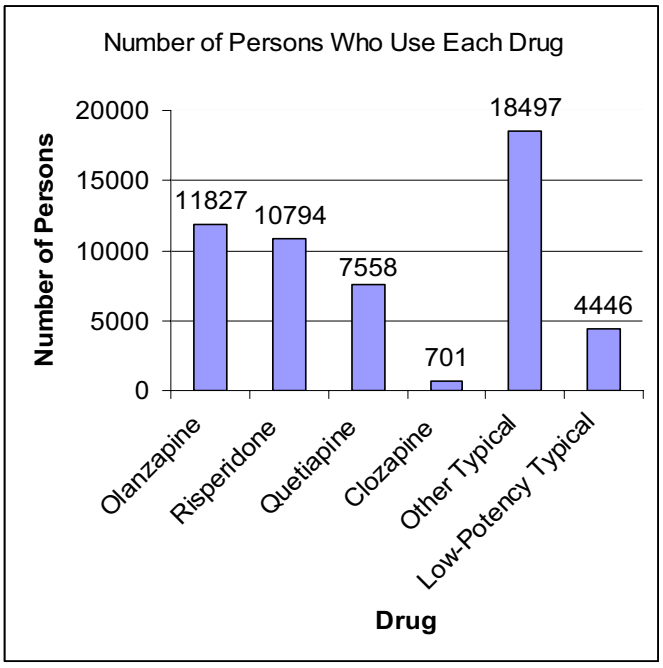
Table 3.5 Frequency of antipsychotic drug class

Antipsychotic Drug Class	**Number who Used**
Typical	13, 483*
Atypical	12, 491*
Mixed	8,925**
	34,899

*Patients who used only one or multiple drugs of this class only
** Patients who have used at least one typical drug and one atypical drug

Olanzapine is the most used atypical antipsychotic in our data set, while clozapine is the least used. As explained in the section on methods, the typical drugs were classified into two groups, low-potency typicals and other typicals. The other typical group has the most users, which reflects the large number of drugs that were grouped together in the other typical group compared to the small number of antipsychotic drugs grouped into the low-potency typical group. Figure 3.1 shows the number of persons who use each drug group in the main study group.

Figure 3.1 Frequency of drug use in the main study group *



*It is possible for a person to belong to more than one drug group- therefore the sum of persons using each drug exceeds the number in the main study group

Within the other typical group, the most commonly used drugs are haloperidol (n=7,054) and prochlorperazine (6,535)[16]. The most commonly used low-potency typical drug is chlorpromazine (n=2,894).

3.1.4.2 Numbers of Drugs

Over half of the persons in the study population use only one drug during the study period (59%). Of those who use more than one antipsychotic drug, clozapine users fill more prescriptions for other antipsychotic drugs (median=3 drugs) compared to all the other individual drugs group users (median= 1 other antipsychotic drug). Patients who use multiple drugs may use 2 or more drugs simultaneously (polytherapy) and/or are switched from one drug to another. When a patient is switched from one antipsychotic medication to another, treatment with the old antipsychotic may overlap with new

[16] Very few persons who took this drug had a diagnosis of schizophrenia. A main indication for this drug is to treat nausea, especially in patients receiving chemotherapy. We included it in the study because it is also used as an antipsychotic.

treatment for a short period in order to help reduce withdrawal symptoms [72]. A patient may be prescribed a combination of antipsychotic drugs, especially if that patient does not respond to treatment with a single antipsychotic drug [73]. Our analysis does not distinguish between switching and polytherapy.

3.1.4.3 Proportion of Time on an Antipsychotic Drug

It is possible for a patient to contribute person-time to the study on a zero dose at some point after their index month (which by design had to have a non-zero dose). This could occur if a patient was continuously covered by welfare, was not hospitalized for more than seven days[17] and still did not fill a prescription for an antipsychotic drug within a given month (30.5 day interval).

Approximately one fifth of the cohort contribute most of their time in the study on a 0 dose of antipsychotic drug. Approximately one fifth of the cohort spend all of their time in the study on a non-zero dose. Figure 3.2 shows the distribution of time on an antipsychotic drug in the main study group. Table 3.6 shows the proportion of study time on an antipsychotic drug and the total number of months of follow-up.

[17] If a patient was hospitalized for more than 7 days they were excluded from the study as we would be unable to see prescriptions given in the hospital which could result in underestimating antipsychotic exposure.

Figure 3.2 Proportion of study time on an antipsychotic drug in main study group

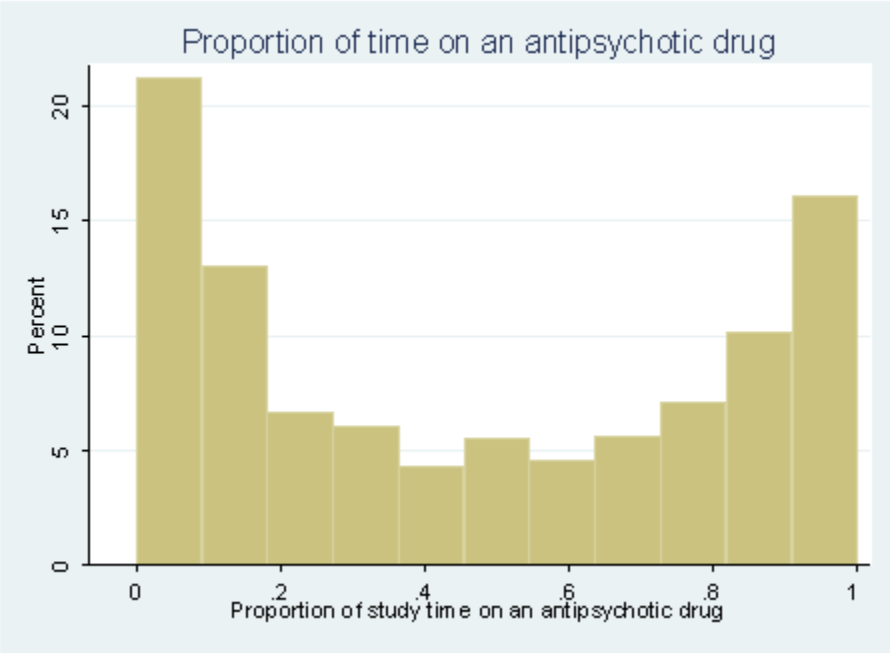


Table 3.6 Proportion of study time on antipsychotic and total months of follow-up

Proportion of Study Time on Drug	Total Follow-Up (in months) (50^{th} percentile)	25^{th} percentile-75^{th} percentile
0	73	41-107
0.1	38	16-80
0.2	39	14-82
0.3	28	8-71
0.4	49	18-91
0.5	36	6-84
0.6	52	20-96
0.7	52	16-99
0.8	52	17-95
0.9	60	27-97
1.0	32	4-79

3.1.4.4 Covariates by Drug Group

The covariates included in this study varied by exposure group. Table 3.7 shows the distribution of covariates, by exposure category in the main study group.

3.1.4.5 Study End Points by Drug Group

Patients can contribute between 1 and 138 study months. Table 3.8 shows the average number of months each group of drug users contribute to the study.

Table 3.7 Distribution of covariates by drug group in the main study group

	Clozapine Users (n=701)	Olanzapine Users (n=11,827)	Quetiapine Users (n=7,558)	Risperidone Users (n=10,794)	Users of low-potency typicals (n=4,446)	Users of other Typicals (n=18,497)
Schizo-phrenia (%)	94.6	43.2	31.6	43.0	31.8	33.0
Male (%)	62.3	47.3	40.2	45.6	53.8	44.9
Obese (%)	2.6	3.6	5.4	4.3	3.0	3.5
Index Year Mean (SD)	1998.8 (2.4)	1998.9 (3.3)	2000.0 (3.4)	1998.8 (3.2)	1995.8 (2.3)	1997.0 (3.1)
Entry Age Mean (SD)	33.9 (10.5)	40.0 (12.09)	39.2 (11.8)	40.1 (12.6)	40.0 (11.7)	43.6 (12.5)

Table 3.8 Total months in study, by drug group in main study group

Drug Group	Total Follow-up (in months) (50th percentile)	25th percentile-75th percentile
Clozapine	96	71-113
Olanzapine	61	30-94
Quetiapine	43	19-84
Risperidone	62	34-96
Low potency typicals	97	61-120
Other typicals	75	25-110

Clozapine users and low-potency typical users have the longest average follow-up. Patients in this study are censored either by death or by study end (December 31st 2004).

The remaining patients exit the study upon a diagnosis of diabetes. Table 3.9 shows the study exit reason broken down by drug group.

Table 3.9 Study exit reason, by drug group in main study group

	Cloza-pine n=701	Olanza-pine n=11,827	Quetia-pine n=7,558	Risperi-done n=10,794	Low potency typicals n=4,446	Other Typicals n=18,497
Exit Reason	%					
Death	2.1	5.1	2.7	5.2	15.5	24.3
Study End	87.6	87.2	92.0	87.2	71.3	64.4
Outcome	10.3	7.7	5.3	7.6	13.2	11.3

A relatively large proportion of persons who use the typical antipsychotic drugs (both the low-potency and other typical antipsychotic drugs) leave the study as result of death. This finding is likely the result of the typical drug users having a higher average entry age compared to other drug users.

3.1.4.6 Diabetes by Drug Group

The percentage of persons who develop diabetes varies by drug group. Additionally, the time to diabetes varies by drug group. Table 3.10 shows the fraction of persons who develop diabetes over the number of persons still present in the study, for the first four years in study, broken down by drug group.

Clozapine users and typical drug users are the most likely to develop diabetes. This finding could be the result of these particular drug users having the longest amount of follow-up time. Within each drug group, the fraction of persons with diabetes over the number of persons in the study increases with each successive year for almost all drugs. The longer a person is followed, the more likely diabetes is to be detected.

There is a sharp increase in the fraction of clozapine users who develop diabetes across time. This finding could indicate that clozapine users are the most consistent users, as their risk continues to rise sharply across time; users of other drugs may only intermittently use a drug and their risk of diabetes may not rise as much across time.

Clozapine users usually have a diagnosis of schizophrenia, and follow a stable regimen of medication, much more so than with other antipsychotic drugs. However, the small sample size of clozapine users precludes any conclusions.

Table 3.10 Occurrence of diabetes according to number of years from first use of an antipsychotic, by drug group in the main study group*

	Clozapine Users (n=701)	Olanzapine Users (n=11,827)	Quetiapine Users (n=7,558)	Risperidone Users (n=10,794)	Users of Low-Potency Typical Drugs (n=4,446)	Users of Other Typical Drugs (n=18,497)
Percent Who Develop Diabetes	10.3	7.7	5.3	7.6	13.2	11.3
Number of persons with diabetes / Number of persons still in study at year X (proportion)						
1 year	1/695 (0.14)	97/10755 (0.90)	58/6350 (0.91)	75/9921 (0.76)	35/4172 (0.84)	265/15454 (1.71)
2 year	4/679 (0.59)	118/9470 (1.24)	52/5199 (1.00)	87/8932 (0.97)	63/3980 (1.58)	225/14011 (1.61)
3 year	6/660 (0.91)	111/8270 (1.34)	44/4264 (1.03)	102/7907 (1.29)	58/3793 (1.53)	219/12902 (1.70)
4 year	12/616 (1.94)	103/7130 (1.44)	37/3520 (1.13)	107/6757 (1.58)	65/3597 (1.81)	257/11793 (2.18)

* Patients could be counted in more than one column

3.2 Cox Proportional Hazard Models

We model the risk of diabetes as dependent on two types of factors: antipsychotic exposure and a set of potential confounders that are related to antipsychotic exposure and diabetes. Antipsychotic exposure is measured across 6 drug groups: clozapine, olanzapine, risperidone, quetiapine, low potency typical drugs and other typical drugs. Antipsychotic exposure is measured each month, where a month is measured by each 30.5 day interval a patient contributes to the study from their index date. Two models are estimated: antipsychotic exposure is represented either as a time-varying on/off measure or as a cumulative exposure measure. In both cases, potential confounding variables are measured as static - fixed measurements that remain constant throughout the study. Five

covariates are included in the models: schizophrenia, male, obese, entry age, and index year.

3.2.1 On/Off Model

For each of the 6 drug variables in the study, a value of 1 or 0 is assigned; with a 1 indicating that a patient is exposed to a non-zero dose of a particular drug in a given month or a 0 indicating that a patient is not exposed to that drug during the month. Table 3.11 shows the exposure hazard ratios for incident diabetes in patients using different antipsychotics in the On/Off model.

All static covariates are significant in the on/off model. The covariates: schizophrenia, male and obese are all binary variables, and thus their respective HRs have a similar interpretation: the risk as a result of having condition X compared to not having condition X, where the values of all other covariates in the model are the same. In this model the HRs are greater than 1 for obese and schizophrenia indicating that these are both risk factors for diabetes. The hazard ratio for obese is the largest. Male sex is protective, as the hazard ratio is less than 1.

Entry age and year of entry being continuous variables, their hazard ratios can be interpreted as follows: for each one year increase, the hazard increases/decreases by a factor of X. For example, each one year increase in entry year decreases the hazard ratio by a factor of 0.847.

In this model, antipsychotic exposure is binary and the hazard ratios can be interpreted as the risk for diabetes in a group of individuals currently using drug X compared to a group of individuals who are not taking drug X, where the values of all other covariates in the model are the same. Filling a prescription for clozapine, olanzapine, risperidone or a low-potency typical drug during a month is associated with a significantly increased risk of being diagnosed with diabetes that month compared to not being clozapine, olanzapine, risperidone or a low-potency typical (respectively) with all over covariates in the model equal . The risk is largest for clozapine and smallest for other typical drugs (note the CIs

do not overlap for clozapine and other typical drugs indicating that the difference between these drugs is statistically significant).

Table 3.11 Hazard ratios in the on/off model for the main study group

	On/Off Model (N=34899)
Static	HR (95% CI)
Obese before	2.165 (1.894, 2.469)*
Entry Age	1.047 (1.023,1.065)*
Entry Age^2	0.999 (0.999, 0.999)*
Schizophrenia	1.260 (1.157, 1.372) *
Male	0.801 (0.736, 0.855) *
Year of Entry	0.845 (0.833, 0.860) *
Time Varying	
Clozapine	2.071 (1.389, 3.092) *
Olanzapine	1.550 (1.284, 1.895) *
Quetiapine	1.130 (0.893, 1.500)
Risperidone	1.321 (1.083, 1.611) *
Low potency typicals	1.227 (1.020, 1.476) *
Other typicals	1.091 (0.902, 1.318)
Log Likelihood	-31,189.27
AIC	62,402.54

* $\alpha < 0.05$ (two-sided)

3.2.2 Cumulative Dose Model

For each of the 6 drug variables in the cumulative dose model, a continuous value is assigned that represents a standardized dose value (outlined in the Methods section). Standardized dose values for each drug are then cumulated across each month in study. Table 3.12 shows the exposure hazard ratios for incident diabetes using the cumulative dose model in the main study group.

All static covariates are significant in the cumulative dose model and are similar to those in the on/off model.

Table 3.12 Hazard ratios in the cumulative dose model in the main study group

	Cumulative Dose Model (N=34,899)
Static	HR (95% CI)
Obese before	2.143 (1.870, 2.446)*
Entry Age	1.051 (1.045, 1.061)*
Entry Age^2	0.998 (0.998, 0.999)*
Schizophenia	1.238 (1.139, 1.350)*
Male	0.792 (0.737, 0.850)*
Year of Entry	0.842 (0.832, 0.853)*
Time Varying	
Clozapine	1.134 (1.038, 1.239)*
Olanzapine	1.091 (1.041, 1.143)*
Quetiapine	1.013 (0.814, 1.263)
Risperidone	1.057 (0.990,1.132)
Low potency typicals	1.077 (1.026, 1.127)*
Other typicals	1.019 (1.007, 1.030)*
Log Likelihood	-33,187.43
AIC	66,398.86

* $\alpha < 0.05$ (two-sided)

In this model, antipsychotic exposure is continuous and the HRs can be interpreted as the risk of diabetes for being on one additional month of a standard dose of drug X, controlling for cumulative doses of the other drugs (where the values of all other covariates in the model are the same). Clozapine, olanzapine, low-potency typicals and other typical drugs all pose a significant increased risk for diabetes. The risk is largest for clozapine and smallest for other typical drugs (the CIs do not overlap for these drugs indicating that the difference between these two drugs is significant).

It is possible to rank competing models using the Akaike Information Criterion (AIC), where a model with a lower AIC better fits the data [74]. The AIC is slightly lower in the cumulative dose model compared to the on/off model indicating that the cumulative dose model may be the better model.

3.3 Sensitivity Analyses

A sensitivity analysis can strengthen the conclusions of an analysis. In this study, sensitivity analyses are performed in order to confirm results in a smaller sample of patients who: 1) had varying amounts of follow-up time, and 2) used only one antipsychotic drug.

3.3.1 Altered follow-up time

In order to maximize sample size and achieve statistically significant results, this study only required one month of follow-up. Given case reports of clozapine induced diabetes in an extremely short period of time this criterion was thought to allow the maximum number of patients and cases of diabetes to appear in the data [55, 75]. However, descriptive results indicate that persons with a longer follow-up period are more likely to be diagnosed with diabetes. Year of entry was measured as a covariate in order to help control for the bias arising from persons with a longer follow-up period being more likely to be detected with diabetes. Requiring persons to have a certain amount of follow-up time can also help reduce the potential biases of including persons with very short follow-up time who are unlikely to be detected with diabetes. Table 3.13 shows the analyses performed using the cumulative dose model with varying amounts of follow-up time.

The hazard ratios for the static covariates did not show any clear trend with the possible exception of obesity (before index date). Obesity appears to show a slight decreasing trend which could be explained if requiring greater follow-up time excludes persons who enter the study at later times, since persons who enter the study later have more pre-screening time (as we have all data on all diagnoses and prescriptions since 1993) and therefore more time to detect diagnoses of obesity prior to index antipsychotic prescription. Also, all confidence intervals increase with increasing follow-up time requirements indicating that the estimates are less precise in the smaller samples.

The hazard ratios for the time varying exposure variables show a clear trend: hazard ratios decrease with increasing follow-up time requirements (and smaller sample sizes). This finding could be the result of losing a number of persons with the outcome, which

could attenuate the hazard ratio. As with the static covariates, confidence intervals increase with increasing follow-up time requirements (and consequent declining sample size).

Table 3.13 Cumulative dose model with various follow-up times

	At least one month (n=34,899)	At least 6 months (n=31,482)	At least 12 months (n=28,581)	At least 18 months (n=26,326)	At least 24 months (n=24,318)
Static	HR (95% CI)				
Obese	2.144* (1.870, 2.445)	2.193* (1.893, 2.538)	2.178* (1.858, 2.547)	1.998* (1.675, 2.378)	1.985* (1.646, 2.388)
Entry age	1.018* (1.015, 1.021)	1.019* (1.014, 1.020)	1.018* (1.013, 1.020)	1.017* (1.012, 1.020)	1.018* (1.014, 1.021)
Schizophrenia	1.243* (1.143, 1.353)	1.236* (1.134, 1.348)	1.253* (1.148, 1.371)	1.268* (1.158, 1.389)	1.299* (1.184, 1.427)
Male	0.790* (0.735, 0.849)	0.788* (0.730, 0.849)	0.797* (0.737, 0.863)	0.780* (0.718, 0.849)	0.782* (0.717, 0.855)
Time Varying	HR (95% CI)				
Clozapine	1.136* (1.041, 1.240)	1.129* (1.038, 1.241)	1.126* (1.035, 1.244)	1.123* (1.033, 1.248)	1.121* (1.031, 1.250)
Olanzapine	1.091* (1.042, 1.142)	1.086* (1.040, 1.142)	1.083* (1.038, 1.142)	1.080* (1.037, 1.143)	1.079* (1.034, 1.141)
Risperidone	1.058 (0.990, 1.131)	1.054 (0.985, 1.129)	1.052 (0.983, 1.132)	1.051 (0.980, 1.134)	1.050 (0.979, 1.135)
Quetiapine	1.015 (0.817, 1.261)	1.012 (0.815, 1.261)	1.008 (0.814, 1.263)	1.007 (0.812, 1.262)	1.003 (0.811, 1.264)
Low Potency Typicals	1.076* (1.027, 1.128)	1.070* (1.022, 1.125)	1.069* (1.020, 1.126)	1.067* (1.019, 1.127)	1.066* (1.017, 1.128)
Other Typicals	1.019* (1.008, 1.030)	1.017* (1.007, 1.030)	1.014* (1.006, 1.029)	1.013* (1.005, 1.029)	1.011* (1.004, 1.030)

* $\alpha < 0.05$ (two-sided)

Note : This analysis is primarily intended to examine the relationship between the time-varying covariates and the length of follow-up time, the exclusion of the quadratic age term does not affect this analysis

3.3.2 Single User group

Restricting the sample to single drug users can help alleviate the problem of assigning one specific drug as the main causal agent of an outcome. The main analyses in this study allowed multiple antipsychotic users into the study in order to maximize the sample size. A further analysis with single antipsychotic users was carried out and the results are shown in Table 3.14 (using the cumulative dose model).

The static covariates show similar trends: obesity, entry age and schizophrenia also pose an increased risk for diabetes, while male sex and year of entry show protective effects. All static covariates are still significant.

Table 3.14 Cumulative dose model in single user group

	Cumulative Dose Model (N=20,526)
Static	HR (95% CI)
Obese before	2.098 (1.778, 2.476)*
Entry Age	1.020 (1.016, 1.024)*
Schizophrenia	1.341 (1.183, 1.520) *
Male	0.767 (0.698, 0.843) *
Year of Entry	0.838 (0.823, 0.854) *
Time Varying	
Clozapine	1.340 (0.959,1.873)
Olanzapine	1.326 (1.137, 1.546) *
Quetiapine	1.113 (0.901, 1.375)
Risperidone	1.213 (1.035, 1.420) *
Low potency typicals	1.125 (1.002, 1.264) *
Other typicals	0.975 (0.897,1.059)
Log Likelihood	-18,498.417
AIC	37,018.83

* $\alpha < 0.05$ (two-sided)
Note : This analysis is primarily intended to examine time varying covariates in single antipsychotic users, the exclusion of the quadratic age term does not affect this analysis

The time varying exposure variables differ in the single user group and the main study group. Only olanzapine, risperidone and low-potency typicals pose significant risks for

diabetes. Clozapine has a high hazard ratio but is not significant, this is likely the result of only a very small number of clozapine users being included in the single user drug group (since this study primarily captured first time antipsychotic users and clozapine is generally not prescribed as a first time antipsychotic drug and the number of clozapine is expected to be very low). Risperidone poses a significant risk for diabetes in the cumulative model in the single user group but not in the main study group.

Chapter 4 Discussion

4.1 Main Findings

This retrospective cohort study examined the risk of taking antipsychotic medications on the development of type II diabetes, controlling for age, sex, schizophrenia, year of entry into the study and obesity prior to study entry. The analysis was based on a unique population of all adult Quebec welfare recipients with continuous coverage who took antipsychotic medications between 1993 and 2004. The reference group was the heterogeneous group of adult antipsychotic users who had previously/ or were currently using another antipsychotic agent. Two methods were used to measure exposure: a binary measure of exposure to each antipsychotic drug group for each month in study and a cumulative dose measure that accumulated each month for each antipsychotic drug group.

To our knowledge, this is the first study of this type to compare results from two different models of antipsychotic exposure on the risk of diabetes while using a reference group of heterogeneous antipsychotic users. This study found that current use of, in addition to cumulative exposure to clozapine, olanzapine or low potency typical drugs significantly increased the risk of diabetes. The risks associated with clozapine were higher than the risks for other typical drugs (the confidence intervals for these two drug groups did not overlap). Current but not cumulative exposure to risperidone was associated with an increased risk of diabetes. Cumulative past exposure to, but not current exposure to, other typical drugs was also associated with an increased risk of diabetes. Differences in risks between clozapine, olanzapine, and low-potency typical drugs were not statistically significant.

A diagnosis of obesity prior to antipsychotic initiation posed a greater risk for diabetes than a diagnosis of schizophrenia (the CIs did not overlap, indicating a significant difference). Entry age also posed a significant risk for diabetes. In this study, both male gender and later year of entry to the study appeared to be protective against diabetes.

4.2 Static Covariates Across Different Drug Groups

The percentage of persons with schizophrenia is much higher in the clozapine group than in the other drug groups. This finding is consistent with treatment guidelines that recommend that clozapine be used only on treatment-resistant patients with schizophrenia, which is not the case for the other antipsychotic drugs.

The proportion of males is close to half in most drug groups except for clozapine and quetiapine. The proportion of males is higher in the clozapine group. It is possible that factors such as a milder course of schizophrenia in women, a higher incidence of side effects from clozapine in women compared to men, combined with a greater level of distress from clozapine induced weight gain in women [32] may result in clozapine being more often prescribed to males. A study by Mhaolain et al. also found a higher proportion of males who use clozapine [40]. In contrast, we find that quetiapine users tend to be women. A research group from Brown University in the US found that quetiapine was frequently prescribed for depression [76]. If this is the case in the province of Québec as well, this could explain the higher use in women, as depression affects more women than men [77].

The proportion of persons with a diagnosis of obesity (prior to antipsychotic exposure) varied slightly by drug group. Persons who use clozapine and low-potency typical drugs appear to have lower rates of obesity prior to drug consumption. This finding could be explained if a physician knows that clozapine and low-potency typical drugs pose a relatively greater risk of weight gain compared to other antipsychotic drugs, which in turn leads them to prescribe another antipsychotic drug with less risk of weight gain.

The average index year is lower for users of typical drugs and higher for those of atypical drugs. This finding reflects the later introduction of the atypical drugs into the market. Quetiapine users have the highest average entry year, which can be explained by the relatively late introduction of this drug.

Average entry age is comparable across drug groups, with the exception of clozapine. Clozapine users enter the study at a much lower age than other drug users. This finding could be the result of almost all clozapine users having a diagnosis of schizophrenia, where schizophrenia has a much earlier onset than the other disorders that antipsychotics may be prescribed for such as delirium and dementia. In this study, patients with increased age are less likely to have a diagnosis of schizophrenia (OR=0.96 (CI=0.96, 0.97)).

Patients with a diagnosis of schizophrenia tend to have higher values for the proportion of study time on a drug (OR=5.7 (CI=5.3, 6.1)) meaning that these patients are more frequent antipsychotic users. This indicates that infrequent antipsychotic users (who spend less of their study time on an antipsychotic drug) are likely to be using antipsychotic drugs for off-label conditions.

4.3 Static Covariates and Occurrence of Diabetes

The prevalence of schizophrenia is higher among people who developed diabetes during the study period in both the main study group and single user group. In this study, only cases of diabetes that occurred after first antipsychotic use were considered. It may be that persons with schizophrenia have greater exposure to antipsychotic medications which increases their risk of diabetes. It is also possible that something about the disease process of schizophrenia poses an increased risk for diabetes, even in the absence of antipsychotic medication [54].

The prevalence of obesity is higher among people who have developed diabetes during the study period in both the main study group and the single antipsychotic user subset. Recall that only diagnoses of obesity that preceded the diagnosis of diabetes were included. Obesity and higher BMI are commonly listed as risk factors for diabetes [52].

Persons who developed diabetes have a higher average entry age in both the main study group and in the single antipsychotic user group. Increased age is a risk factor for diabetes (though the risk may level off for very advanced ages) [78].

Patients who developed diabetes entered the study earlier than those who did not in both the main study group and single user group. This finding could reflect the fact that those with a smaller index year have a greater amount of follow-up time and are therefore more likely to be detected with diabetes (given a certain lag between symptoms and diagnosis).

A greater proportion of persons who developed diabetes are female in both the main study group and the single antipsychotic user subset. Female sex is not a known risk factor for diabetes, however, in this study univariate logistic regression revealed that females are more likely to be obese (OR=3.1 (CI=3.02, 3.14)) and older (OR= 1.02 (CI=1.020, 1.022); obesity and age are both known risk factors for diabetes.

4.4 Main Findings Compared to Previous Studies

4.4.1 Clozapine

This study found that current use of as well as past cumulative exposure to clozapine increased the risk for diabetes. In the on/off model, the increased risk of diabetes in clozapine users is specifically with reference to patients who were not currently using clozapine *that* month: patients may have used clozapine at a previous time but were not currently using that drug, or patients may have been currently using another antipsychotic drug, or had used another antipsychotic drug in the past. In the cumulative dose model, the increased risk of diabetes in clozapine users is with reference to patients who had accumulated exposure to antipsychotic drug(s) other than clozapine.

Buse et al. [64] and Gianfrancesco et al.[66] both found that patients who used clozapine had an increased risk of diabetes relative to both: a general patient population, and a population with psychoses not using antipsychotic medications. Both studies examined dose-response relationships and neither found a significant dose effect for clozapine. Although both studies found clozapine to increase the risk of diabetes, neither reported clozapine as posing the highest risk for diabetes relative to other antipsychotic drugs.

Several other studies have compared the risk of diabetes in clozapine users compared to users of typical antipsychotic medications. Guo et al.[67] found clozapine to pose a significantly higher risk for diabetes compared to all atypical antipsychotic drugs in a population of patients with Bipolar Disorder. Similarly, Leslie & Rosenheck [58] found clozapine to pose a significantly higher risk for diabetes than other atypical drugs in patients with schizophrenia. Citrome et al.[63], Lambert et al.[59], and Serynak et al. [60] also found clozapine to pose a significant risk for diabetes compared to use of a typical drug, however, none of these studies found clozapine to pose the highest risk amongst the atypical antipsychotic drugs.

Ostbye et al. [68] found that patients using clozapine did not have an increased risk of diabetes compared to patients using typical antipsychotic drugs, however this study only controlled for age and sex. No adjustments were made for obesity, diagnosis of psychoses/ schizophrenia or length of follow-up. Failure to control for these variables could have interfered with the detection of a significant association for diabetes.

Overall, our study adds to the other studies that have found clozapine to increase the risk of diabetes compared to both patients who are not using an antipsychotic medication and patients who are using a typical antipsychotic drug. The findings of this study are similar to those of Guo et al. and Leslie & Rosenheck: clozapine appears to pose the highest magnitude of risk. However, it must be noted that an association between clozapine and diabetes does not imply causation. Although our study and many others have clearly found an association between clozapine and diabetes, it may be other factors associated with clozapine use that increase the risk for diabetes. In this study clozapine users almost exclusively have a diagnosis of schizophrenia, which is not found in any of the other antipsychotic drug groups. Schizophrenia itself is a risk factor for diabetes and although we do control for a diagnosis of schizophrenia, our measure may be imperfect (a diagnosis may not always be recorded) which could partially account for an increased risk. This study found that clozapine users tended to use more antipsychotic drugs compared to users of other antipsychotic drugs (4 drugs on average compared to 2 or 3 drugs for the other drug groups).

This makes it difficult to interpret hazard ratios for clozapine: is the risk due to the clozapine, or due to another drug that a patient used prior to clozapine? It is possible that the risks associated with use of clozapine are overestimated. In addition, treatment refractory patients, a subgroup of patents that typically use clozapine, may be at a greater risk of diabetes due to factors associated with treatment resistance, such as overall poorer health which could lead to more sedentary life styles thus causing weight gain.

In order to demonstrate causation and not just an association between antipsychotic exposure and diabetes, the Austin Bradford Hill criteria can be considered, which if met, may help show causation: strength of association, consistency of results, temporality (the exposure precedes the disease), biological gradient (increased dose leads to increased risk) amongst others [79].

Large scale database studies have consistently found clozapine to be associated with an increased risk of diabetes and these risks tend to be relatively large in magnitude. Furthermore, an analysis of 384 case reports of clozapine-induced diabetes found cases of diabetes that developed within days, or weeks of clozapine therapy. Hyperglycemia (central to a diagnosis of diabetes) was reversed or decreased with withdrawal or reduction of clozapine dose [80]. These findings lend weight to a biological gradient. Furthermore, there is a clear biological mechanism of clozapine induced diabetes: clozapine has been found to lead to significant weight gain, which in turn can lead to the development of diabetes.

4.4.2 Olanzapine

This study found that current use of, or past cumulative use of olanzapine increased the risk of diabetes with a magnitude slightly less, though not statistically different, than that of clozapine. In the on/off model, the increased risk of diabetes in olanzapine users is with reference to patients who were not currently using olanzapine *that* month. In the cumulative dose model, the increased risk of diabetes in olanzapine users is in reference

to patients who had accumulated exposure to an antipsychotic drug(s) other than olanzapine.

Compared to patients who were not using antipsychotic medications: Carlson et al.[65] and Gianfrancesco et al.[66] found olanzapine to pose a significantly increased risk for diabetes, and these risks were higher than those found for other antipsychotic drugs. Buse et al.[64], Feldman *et al.*[81] and Koro et al. [82] all found olanzapine to pose a significant risk of diabetes compared to no use of an antipsychotic (these risks were moderate relative to other antipsychotic drugs).

Compared to patients who were using typical antipsychotic medications: Gianfrancesco et al. [66], Guo et al. [67], Koro et al. [61], Lambert et al. [59], Leslie and Rosenheck [58], and Sernyak et al. [60] et al all found olanzapine to pose a significant risk for diabetes. Lambert et al. found olanzapine to pose the highest risk for diabetes, relative to other atypical drugs.

Barner et al. [62] did not find olanzapine to pose a significant risk for diabetes compared to use of typical drugs. A small sample of olanzapine users (n=734) may not have been a large enough sample to detect true risks for olanzapine. Citrome et al. [63] also did not find olanzapine to pose a significant risk for diabetes compared to typical drug users. Again, a small sample size (n=445) may have been too small a sample to detect a significant risk. Similarly, Ostbye et al. [68] did not find olanzapine to pose a significant risk of diabetes compared to typical antipsychotic drugs. A lack of measurement of and control for: obesity, a diagnosis of psychoses/ schizophrenia or length of follow-up may have resulted in a bias in risk estimates.

Overall, our study lends weight to the findings of the majority of other studies which have found olanzapine to be associated with an increased risk of diabetes. In terms of a causal relationship between and olanzapine: associations are strong, results are fairly consistent, temporality has been demonstrated and a biological mechanism, along a

weight gain pathway fits the profile of olanzapine. Also, hyperglycemia may be reversed when treatment with olanzapine is discontinued [82].

4.4.3 Risperidone

This study found that current use of risperidone increased the risk of diabetes. However, this study did not find that past cumulative exposure to risperidone increased the risk of diabetes.

Compared to patients who were not using antipsychotic drugs: Buse et al. [64], Carlson et al. [65], and Feldman et al. [81] all found that use of risperidone significantly increased the risk of diabetes (the risks were moderate relative to other antipsychotic drugs). Gianfransco et al. [66], however, did not find risperidone to significantly increase the risk of diabetes compared to non-antipsychotic users.

Compared to patients who were using typical antipsychotic medications: Buse et al. [64] (comparison specific to haloperidol), Feldman et al. [79] (comparison specific to haloperidol) and Guo et al. [67] found that risperidone significantly increased the risk of diabetes. Barner et al. [62], Citrome et al. [63], Koro et al. [82], Lambert et al. [59], Leslie and Rosenheck [58], Ostbye et al. [68] and Sernyak et al. [60] all failed to find a significant increased risk for risperidone.

Our study reference population of antipsychotic users who used an antipsychotic drug other than risperidone is different than the above mentioned study reference populations, and therefore our results may not directly be comparable to the above studies. In a heterogeneous comparison group of mixed antipsychotic users, current use of risperidone does appear to increase the risk of diabetes. However, past cumulative use of risperidone may not affect the risk of diabetes. Furthermore, risperidone may not pose risks for diabetes that are greater than those of other antipsychotic medications.

In terms of assessing a causal relationship between risperidone and diabetes: the associations are weak and the evidence is inconsistent. However, a temporal relationship

has been demonstrated in specific case reports of diabetes following risperidone initiation [83]. Although risperidone may not cause relatively high weight gain, risperidone may have a direct effect insulin resistance (a viable biological mechanism) [41, 55].

4.4.4 Quetiapine

This study did not find a significant risk of diabetes with current or past cumulative use of quetiapine compared to use of other antipsychotic agents.

Compared to patients not using antipsychotic medication: Buse et al. [64] and Feldman et al. [81] both found that use of quetiapine increased the risk of diabetes. The risks for quetiapine were the lowest risk amongst the antipsychotic agents. The Buse and Feldman studies both used a large size that that provided adequate power to detect significant associations. Both studies compared the risk of quetiapine use compared to *no use* of an antipsychotic agent. It is possible that qietiapine in and of itself did not increase the risk of diabetes, but rather, these antipsychotic users in general, had an increased risk of diabetes as a result of underlying factors that are related to antipsychotic use, such as poorer overall health and greater co-morbidities. It could also be possible that patients using antipsychotic medications were monitored more than those not using antipsychotic medications, which may indicate detection bias.

Compared to patients using typical antipsychotic medications: Citrome et al. [63], Guo et al. [67] and Sernyak et al. [60] found quetiapine use to increase the risk of diabetes. Barner et al. [62], Koro et al. [82], Lambert et al. [59], Leslie and Rosenheck [58], and Ostbye et al.[68] did not find quetiapine use to increase the risk of diabetes compared to use of a typical agent. The two studies that did find an increased risk of diabetes in quetiapine users had a small number of quetiapine users and do not provide evidence as strong as a large scale studies (all other study factors being equal).

Overall this study does not add to the evidence that quetiapine increases the risk of diabetes. Reports of increased risks for quetiapine in the literature are weak and inconsistent. Quetiapine has been linked to weight gain relative to low-potency typical

drugs [28], therefore it is possible that quetiapine may increase the risk of diabetes via weight gain or through an independent effect on insulin resistance after quetiapine initiation, however this study does not support this hypothesis, nor is there strong evidence in the literature to support this hypothesis.

4.4.5 Low- Potency Typical Drugs

This study found that current use of, as well as past cumulative exposure to low potency typicals increased the risk for diabetes.

Compared to patients who were not using antipsychotic medications: Buse et al. [64], Carlson et al. [65], Gianfrancesco et al. [66] and Feldman et al. [81], all found that low-potency typical drugs users had an increased risk of diabetes. The Buse and Feldman studies both found the risks for low-potency typical drugs to be larger than the risks of all other antipsychotic drugs, including atypical drugs.

Our study adds support of a causal relationship between low-potency typical drugs and diabetes: the associations are strong and consistent and a temporal relationship exists. In addition, there is a strong biological mechanism via weight gain. Weight gain with low potency drugs is second only to atypical agents clozapine and olanzapine [28].

4.4.6 Other Typical Drugs

This study found that cumulative past use of, but not current use of other typical antipsychotic agents increased the risk of diabetes compared to users of all other antipsychotic agents.

Compared to patients who are not using antipsychotic medications: Buse et al. [64], Giafrancesco et al. [66] and Feldman et al. [81] all found that use of other typical antipsychotic medications to significantly increase the risk of diabetes. However a large study by Carlson (n=60,000) did not find other typical medications to pose an increased risk of diabetes.

This study does not provide clear evidence that other typical drugs pose a risk for diabetes. Although cumulative *past* exposure to other typical drugs does appear to increase the risk of diabetes this finding may be confounded by other factors. For example, past users of other typicals may have used other drugs (as this analysis was not limited to single drug users); they may have been switched from older typical antipsychotic drugs to other agents, and it may be these other drugs that are responsible for the development of diabetes. If other typical drugs truly increase the risk for diabetes, then current use of other typical drugs should increase the risk for diabetes. We did not find this, however.

Our study does not support a causal relationship between other typical drugs and diabetes. The associations between the two are weak and inconsistent across models and the temporal relationship between typical drugs and diabetes is not clear. Although past use of other typical drugs may increase the risk of diabetes, it is not clear how far in the past exposure accumulated and whether there is a viable explanation for lag in drug exposure to development of diabetes. It could be the case that typical antipsychotic drugs have direct insulin resistance effects. This however, has not been reported in the literature.

4.5 Limitations of this Study

A major of limitation of this study was the inclusion of patients who used more than one antipsychotic drug. The inclusion of multiple drug users poses a difficulty in terms of assigning one specific drug as the main causal agent for diabetes. However, this study included a sensitivity analysis of single drug users and the main findings were replicated. Patients who use only one antipsychotic drug may have less follow-up time overall; single users are often deemed so simply because the study duration is not long enough to observe antipsychotic switching.

Another limitation of this study was the lack of data on risk factors for diabetes such as BMI, race, family history of diabetes, receipt of drugs that pose risks for diabetes (such as steroids). In a large database study, it is difficult to measure all of these risk factors.

Smaller chart studies may be able to measure these risk factors. The resultant smaller sample size may however preclude any significant findings.

A further concern in this study was the use of a heterogeneous population of antipsychotic users. Reasons for antipsychotic use may be associated with risks for diabetes; for example persons who use antipsychotic medications for schizophrenia may be at an increased risk for diabetes as a result of disease process, sedentary lifestyle etc; and persons who use antipsychotic medications in a nursing home as a sedative may be at increased risk for diabetes as a result of age. However, this study did control for age and diagnosis of schizophrenia.

An additional shortcoming of this study was lack of data on true antipsychotic exposure: this study instead used antipsychotic prescription filling as a proxy for antipsychotic consumption. It is possible that patients may have filled an antipsychotic medication and not consumed the medication. Additionally, antipsychotic dosage may have been subject to measurement error. Based on the method of approximation outlined in the methods section, it is possible that antipsychotic exposure was overestimated for some months and necessarily underestimated the following month.

One more limitation of this study was a failure to analyze specific typical medications. It is possible that medium and high potency typical medications do not pose homogenous risks; however, in line with a weight gain pathway to antipsychotic induced diabetes, our grouping of typical antipsychotic drugs may be adequate. However, if antipsychotic medications increase the risk for diabetes by direct insulin effects then this grouping may obscure differences in risk among drugs.

Furthermore, this study may be subject to measurement error. The study measured incident antipsychotic use by screening a minimum of 6 months prior to first antipsychotic drug use. It is however possible that a patient may have been hospitalized for more than 6 months, and entered the study as an “incident” antipsychotic user although they may have used antipsychotic drugs prior to the 6 month ‘washout’ period.

This seems likely in the case of clozapine users: approximately 10% of clozapine users were prescribed this drug as their "index" or very first antipsychotic drug. Treatment guidelines however, recommend that clozapine only be used when treatment with two other antipsychotic medications have failed. It is quite possible then that in several cases we did not truly capture first time antipsychotic users.

Finally, diagnoses of obesity, schizophrenia and diabetes may not always have been recorded. In our dataset, 12% of patient medical records did not contain an ICD-9 diagnosis and almost 98% of patient hospital records do not contain an admission diagnosis (although main and discharge diagnoses were normally present). A missing diagnosis could simply indicate that a patient did not present with a medical condition. It is also possible that the physician was negligent in recording a diagnosis. Of particular concern is if diagnoses are differentially detected based on exposure group. There is some evidence that persons who use atypical antipsychotic drugs are more likely to be tested for diabetes than patients who use typical antipsychotic drugs [63, 83]. If this is the case, then persons who use atypical drugs may appear to have a greater risk of diabetes, when it may be that they are more likely to have been detected with diabetes. If patients who use other antipsychotic drugs are not screened as often then their risk of diabetes may appear spuriously low. This type of bias is difficult to avoid in large scale studies, but has been addressed in smaller chart studies such as the study by Citrome et al. [63]

4.6 Strengths of this Study

Key strengths of this study include a large sample size that allowed the inclusion of all atypical drugs available in Quebec by 2004. Several of the aforementioned studies lacked adequate samples for atypical drugs such as clozapine and quetiapine. Also, data from recent years allowed drugs such as quetiapine to be included in the study. Another strength of this study was the division of typical drugs into a low potency group and other typical drugs, since low-potency drugs can lead to more weight gain compared to other typical drugs, a clear risk factor for diabetes. Obesity and schizophrenia are two well documented risk factors for diabetes that were, at least to some extent, controlled for in this study. Some of the aforementioned large database studies did not include a diagnosis

of obesity in the model. Furthermore, this study was able to address follow up bias by including the year of entry in the study. Year of study entry was protective in this study, indicating that persons who entered at a later year had a lower risk of diabetes, or rather of diabetes being detected. Another strength of this study was the measurement of diabetes based on *medical* records. Previous studies have used receipt of an antidiabetic medication to indicate diabetes; however antidiabetic medication may be used as a prophylactic, and may be prescribed to a person who presents with risk factors for diabetes in the absence of meeting diagnostic criteria for diabetes. Another key strength of this study was the measurement of exposure in two different ways corresponding to current use and cumulative past use. Many studies did not measure antipsychotic dose, especially in a standardized form. In order to demonstrate causality, it is important to clearly demonstrate a dose-response relationship. This methodological refinement represents an important strength of our study.

4.7 Conclusions

We found that clozapine, olanzapine and low-potency typical drugs increased the risk of diabetes compared to use of other antipsychotic drugs. Other typical drugs were found to increase the risk of diabetes only when past cumulative exposure was considered. It could be that the development of diabetes takes longer with these drugs; perhaps weight is gained slowly with these drugs and time to diabetes is greater than a month which could explain why current use of the other typical drugs might not appear to increase the risk of diabetes. It is also possible that current users of the newer atypical drugs have accumulated past exposure to other typical drugs and the risk attributed to other typical drugs may be influenced by the current use of atypical drugs which may lead an overstatement of the risks associated with other typical drugs. In the sensitivity analysis of single drug users, past cumulative use of other typical drugs did not pose a risk for diabetes, indicating that perhaps use of other typical antipsychotic drugs does not pose an increased risk of diabetes relative to use of another antipsychotic drug.

Current use of risperidone increased the risk of diabetes. Although past cumulative use of risperidone did not appear to increase the risk of diabetes in the main study group, past

cumulative use of risperidone did significantly increase the risk of diabetes in the single user group. Risk estimates for the main study group may understate true drug effects, as the risk may be split amongst multiple drugs that a patient used. The risk estimates from the single user group may be more relevant; however the smaller sample of single users does not allow as much precision in estimates.

The risks of diabetes for each antipsychotic drug should be carefully considered and weighed against their benefits. The consequences of diabetes can be severe, especially in the presence of weight gain, which can be distressing to a patient and may lead to drug non-compliance. In the case of severe mental disorders such as schizophrenia, non-compliance can seriously hinder treatment. Also, treatment for diabetes can be a burden to the healthcare system (costs of antidiabetics and numerous complications that are costly to treat) [84]. Furthermore, persons with diabetes have increased risks of cardiovascular disease which increases the risk of mortality [83].

In this dataset, the most frequently filled prescription for an antipsychotic drug was olanzapine. However, evidence from this study and others show this drug to pose a substantial risk for the development of diabetes. Careful consideration should be given when prescribing olanzapine, considering also evidence that it may not be more effective than other antipsychotic agents [32, 33].

This study, along with several others, found clozapine to pose a significant risk for the development of diabetes. However, no drug has been found equal to or superior to clozapine for treatment-refractory patients; it may therefore not be possible to select another antipsychotic drug for these patients.

Future studies might address differential testing for diabetes in patients using specific antipsychotic drugs and explore how many cases of diabetes occur in the presence of weight gain (which could help determine which model of antipsychotic induced diabetes is most plausible). Other studies might also differentiate between the severity of diabetes by using different outcomes such as diabetes that does not require antidiabetic

medication, diabetes that requires low doses of medication and diabetes that requires high doses of medication and/or diabetes that occurs with complications. Additionally, future studies might use different models to measure antipsychotic exposure. Perhaps the risks posed by antipsychotic drugs are not constant throughout time but level off at certain point. If this is the case, then dose could be measured using an autoregressive moving average model.

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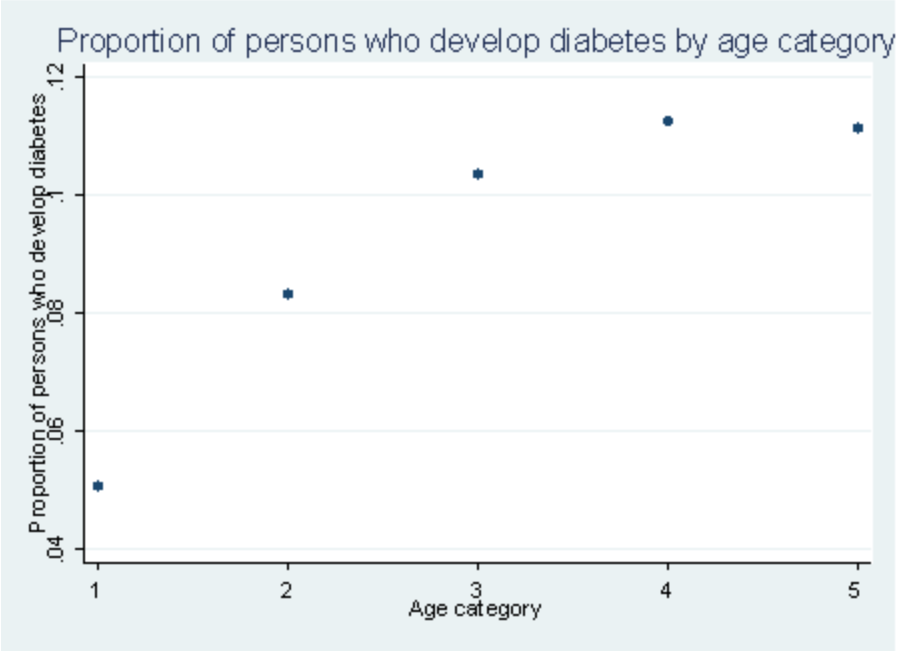
Appendix

Entry Age as A linear Term

In order to examine the relationship between entry age and the development of diabetes, the proportion of patients who developed diabetes was plotted against five broad age groups (a rough approximation): 18-30 years, 30-40 years, 40-50 years, 50-60 years and 60+ years.

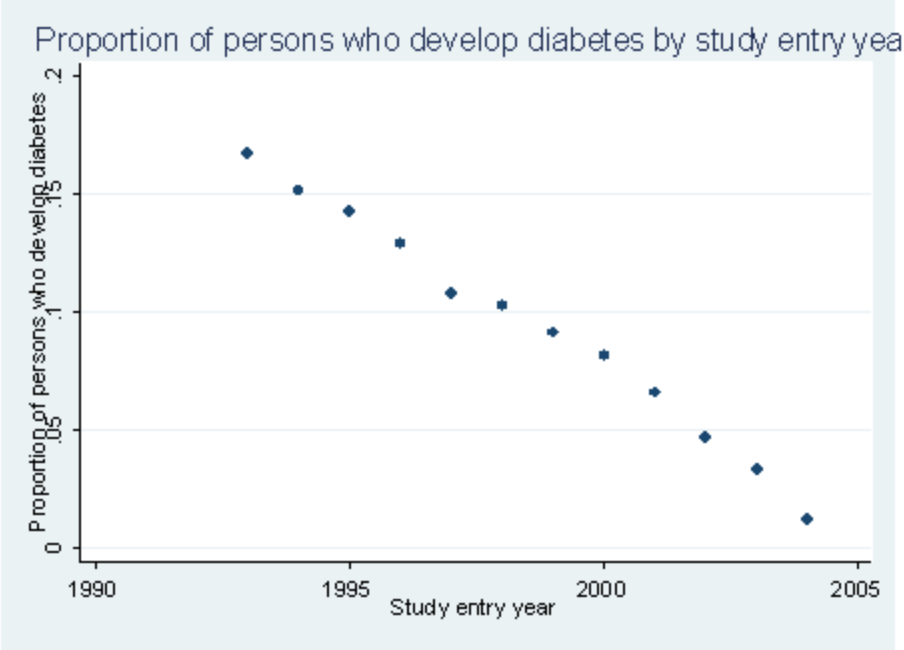


Age category: 1= 18-30 years, 2=30-40 years, 3=40-50 years, 4=50-60 years
5= 60+ years

The above figure indicates that the relationship between entry age and the development of diabetes is not linear. Entry age was modeled as a quadratic function in the main analyses. The AIC was lower in the model with the quadratic term than in the model with the linear term (62,400 and 62,407 respectively) indicating that the model with the quadratic term better fits the data.

Entry Year as a Linear Term

The proportion of patients who developed diabetes was plotted against year of entry into the study in order to asses the relationship between the two.



The above figure indicates the relationship between study entry year and the development of diabetes is approximately linear.

The Proportional Hazards Assumption

The linktest command in Stata is a specification test that checks if the coefficient of a squared linear predictor is insignificant [85]. The squared term in both models was insignificant (P>|z| >0.50), indicating that the models passed this test.

Ethical Approval

A letter indicating ethical approval from the Douglas Hospital Research Ethics Boards for the main study from which these data were derived is shown below.

Hôpital Douglas Hospital

Research Ethics Board

At a Meeting of the Douglas Hospital Research Ethics Board Held on *February 8, 2005*

A Committee consisting of:

GAUTHIER, Serge, M.D., F.R.C.P(c), Chairperson	Neurologist
BEUZERON, Joëlle-Helen, M.D.	General Practioner
BRUCE, Kenneth, Ph.D.	Psychologist
BRUNET, Alain, Ph.D.	Psychologist
CAPEK, Radan, M.D., Ph.D.	Psychopharmacologist
EDWARDS, Moïra	Community Representative
HAMEL, Geneviève, M.Sc.	Pharmacist
SKLAR, Ron, Prof.	Ethicist
THOMAS, Françoise	Community Representative
TREMBLAY, Jacques, M.D.	General Practioner

has confirmed the approval of the research protocol titled:

Use of Medications for People with Severe Mental Illness in Quebec: Implications for the Transformation of Services and Policies

as proposed by: Dr. Éric Latimer

This protocol is approved for a one year period

Serge Gauthier, M.D., F.R.C.P(c),Chairperson
Douglas Hospital Research Ethics Board
/lb

Date: 08/02/05
REB #: 04/17