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University of Alberta

The Temporal Relationship Between Diabetes Mellitus and Major Depressive Disorder

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the

requirements for the degree of *Master of Science*

in

Medical Sciences - Public Health Sciences

Edmonton, Alberta

Spring 2005

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ABSTRACT

Objective – To assess the temporal relationship between major depressive disorder and diabetes mellitus.

Methods – We conducted a population-based nested case-control study to evaluate the history of depression in people with and without diabetes. We conducted a population-based cohort study to assess the incidence of depression in people with diabetes. The studies were conducted using the administrative databases of Saskatchewan Health. Cases of type 2 diabetes were identified based on diagnostics codes or prescription records for individuals over the age of 20 years.

Results – People with diabetes were more likely to have had a previous history of depression, whereas the incidence of depression was no different in people with diabetes compared to people without diabetes.

Conclusion – The results suggest that younger people with depression should be screened for diabetes. However, type 2 diabetes is not associated with an increased incidence of subsequent new-onset depression compared to those without diabetes.

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ACKNOWLEDGEMENT

This study was funded by a grant from the Canadian Institutes of Health Research (CIHR). This work was also supported by a New Emerging Team (NET) grant to the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD). The ACHORD NET grant is sponsored by the Canadian Diabetes Association, the Heart and Stroke Foundation of Canada, The Kidney Foundation of Canada, the CIHR - Institute of Nutrition, Metabolism and Diabetes and the CIHR - Institute of Circulatory and Respiratory Health.

Dr. Majumdar holds a Population Health Investigator Award through the Alberta Heritage Foundation for Medical Research (AHFMR) and is a New Investigator of the Canadian Institute of Health Research. Dr. Johnson is a Health Scholar the AHFMR and a Canada Research Chair in Diabetes Health Outcomes.

This study is based in part on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Depression is a highly prevalent disease; it is disabling, substantially interfering with daily functioning. It is a leading cause of disability in developed countries, associated with a 3-fold increase in the number of sick days per month for workers with a depressive illness compared to coworkers without depression (1,2). Depression is also the leading cause of death among people aged 18 to 44 years (2). A number of large-scale community-based prevalence studies of psychiatric disorders have been conducted in Canada, and have found the prevalence of depression to range from 4.1 to 6.5% (3-5).

Incidence rates of major depression are much more difficult to obtain, and published research shows considerably more variability, with some estimates verging on the impossibly large. Newman and Bland (6) review the literature and discuss some of the methodologic problems arising in the estimation of incidence rates of major depression. Perhaps the most valid estimates for major depression diagnosed according to Diagnostic and Statistical Manual (DSM) criteria are those of Eaton et al. (7), who conducted a 13-15 year follow-up and reported incidence rates of 3.6 (per 1000 person-years) for women and 2.0 for men.

Diabetes is also a common chronic disease. The most recent available Canadian data indicate that the physician-diagnosed prevalence of diabetes in adults (people ≥20 years of age) was 5.1% in 1999/2000 (8). However, evidence suggests that true prevalence rates may be 30 – 50% higher, putting the true prevalence at over 7% (9-11). There are two main types of diabetes; the majority of individuals having type 2 diabetes, and are

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over the age of 30 years. Diabetes is a serious health problem, and cardiovascular-related mortality is the leading cause of death in individuals with type 2 diabetes (12-15).

In recent years, considerable research has evaluated the burden of depression in chronic medical conditions. Depression has been associated with poor psychosocial rehabilitation, increased risk of cardiac events, and higher mortality in patients with chronic cardiovascular disease (16,17). Reduced compliance with exercise and medication has also been observed in patients with chronic cardiovascular disease who are depressed (16). As well, poor emotional functioning has been associated with increased mortality in patients with chronic obstructive pulmonary disease (18). There also appears to be a significant relationship between depressive symptoms and stroke mortality (19).

Diabetes, in particular, appears to be adversely affected by comorbid depression. The prevalence of depression in patients with diabetes has been reported in the literature as approximately twice the rate compared to people without diabetes, with odds ratios (OR) ranging from 1.5 to 2.0 (20-23). In the most recently published estimates which used large administrative databases in the United States (22,23), adjustment for age, sex, and cardiovascular disease tends to reduce the previous prevalence estimates from meta-analyses of published studies (20).

The majority of available literature has generated cross-sectional estimates of the prevalence of comorbid diabetes and depression. This leaves unanswered, however, many questions regarding the temporality of the relationship between depression and diabetes (24). Seven prospective studies have evaluated whether presence of depression or depressive symptoms increases the risk of developing diabetes (25-31). Five of these

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studies found that presence of depressive symptoms or depression was associated with an increased risk of developing type 2 diabetes (25-30). Saydah and colleagues (31) found no difference in risk of diabetes in people with and without depressive symptoms. Each of these studies involved relatively small numbers of subjects and cases of diabetes and used different measures to identify depressive symptoms or depression, limiting the ability to compare studies.

Depressive symptoms in patients with chronic illness have been associated with decreased adherence to medications and diet, functional impairment, increased risk of complications, and higher health care utilizations and costs (32). Ciechanowski et al. (33) found that depressive symptom severity in people with diabetes was significantly associated with decreased adherence to medications and diet, as well as functional impairment. Depression was also associated with complications in diabetes such as retinopathy, neuropathy, and macrovascular complications, in a recent meta-analysis (34). As well, patients with diabetes who have comorbid depression have increased health expenditures (21,22,33). Patients with diabetes and depression have been shown to fill more prescriptions, have higher ambulatory care use, and higher total health care expenditures compared to individuals with diabetes that do not have depression (21,22).

In summary, it is clear that diabetes and depression are important comorbid conditions. It is not entirely clear from these previous studies, however, whether or not a chronic illness such as diabetes "causes" depression, or whether those with a history of depression are somehow predisposed to diabetes. The answer to this question may have important implications for case-finding and screening for depression on the one hand, and exploration of the mechanisms whereby depression might predispose to diabetes on the

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other. The majority of available literature has used cross-sectional estimates of the prevalence of diabetes and depression. The available prospective studies have identified only a small number of cases of diabetes. Only a study that has longitudinal follow-up, in a large population, with the ability to separate incident from prevalent cases of depression, can address these issues.

1.2 Objectives

The overall objective of this research was to assess the temporal relationship between diabetes and depression. This objective was met by conducting two population-based epidemiologic studies: a case-control study to assess the risk of diabetes in people with a history of depression, and a retrospective cohort study to assess the incidence of depression in people with new-onset diabetes (Appendix A).

1. The objective of the case-control study was to assess whether a history of depression increased the risk of developing diabetes.
2. The objective of the retrospective cohort study was to derive population-based estimates of the incidence of depression among people with diabetes.

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CHAPTER 2

History of Depression Increases Risk of Type 2 Diabetes in Younger Adults

2.1 Introduction

Depression is a highly prevalent disease; it is disabling and can substantially interfere with daily functioning. It is a leading cause of disability in developed countries, associated with a 3-fold increase in the number of sick days for workers with a depressive illness compared to coworkers without depression (1,2). Depression is also the leading cause of death among people aged 18 to 44 years (2). A number of large-scale community-based prevalence studies of psychiatric disorders have been conducted in the United States and Canada, which estimate the prevalence of depression in the range of 4 to 5% (3-6).

Depression is recognized as an important comorbidity for a number of chronic medical conditions (7-10). Diabetes is among many chronic medical conditions that appear to be adversely affected by comorbid depression. Numerous reports have indicated that patients with diabetes are 1.5 to 2 times as likely to have depression compared to people without diabetes (11-14). In the most recent estimates, using large administrative databases from the US (13,14), adjustment for age, sex and cardiovascular disease tends to reduce the previous prevalence estimates from meta-analyses of published studies (11).

The majority of this literature, however, has reported only cross-sectional assessments of comorbid diabetes and depression. Little information is available on the temporal association between diabetes and depression. Onset of depression may result in increased weight gain (as a result of the disorder or in relation to antidepressant treatment) and

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decreased self-care measures such as exercise. Also, people with depression are more likely to abuse alcohol and smoke cigarettes more than individuals without depression. These behaviours can potentially increase the risk of developing type 2 diabetes. However, the literature evaluating depression as a risk factor for diabetes is quite conflicting.

Six prospective observational studies suggest that depression and depressive symptoms may be a risk factor for the development of type 2 diabetes, with relative risk estimates ranging from 1.3 to 3.0 (15-20). These studies involved relatively small numbers of subjects and cases of depression, limited follow-up, or involved relatively homogenous samples with limited generalizability. In contrast, Saydah et al. observed no difference in the incidence of diabetes between those who reported high depressive symptoms or moderate symptoms, compared to individuals with no depressive symptoms (21).

In summary, it is clear that diabetes and depression are important comorbid conditions, and comorbid depression is associated with worse outcomes in people with diabetes. It is not entirely clear, however, whether those with a history of depression are somehow predisposed to developing diabetes. The temporal relationship has important implications for the mechanisms whereby depression might predispose to diabetes, and management of diabetes risk in individuals diagnosed with depression. We therefore conducted a nested case-control study, using a large, population-based administrative dataset, to assess whether people with diabetes are more likely to have had prior episode of depression compared to those without diabetes.

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2.2 Study Design

2.2.1 Saskatchewan Health Databases

Saskatchewan Health databases include information on most residents (99%) of the province of Saskatchewan (population approximately 1 million) (22,23). Individuals not covered by Saskatchewan Health include those with federally-funded health care, such as members of the Royal Canadian Mounted Police and Canadian Forces (22). About 90% of the covered population is eligible for prescription drug benefits. Those ineligible include registered Indians who receive prescription benefits through a federal program. Data from four different data files were used in this study: the health registration, outpatient prescription drug, medical services, and hospital separation. The data files are linkable based on personal health numbers and provide demographic information, prescription drug usage, and diagnostic codes for outpatient visits and hospital stays.

2.2.2 Study Periods

Incident cases of diabetes and randomly selected controls were identified between January 1, 1992 and December 31, 2000 (i.e., index period). Study index date was defined as date diabetes was identified, and randomly selected controls were given the same index date as their respective diabetes cases. To ensure we identified people with new-onset diabetes, individuals who met the case definition from January 1, 1989 to December 31, 1991 were excluded (i.e., a 3-year diabetes washout period). Exposure period was defined as a 3-year period prior to study index date.

2.2.3 Case and Control Selection

Individuals eligible for inclusion in this study were residents of Saskatchewan eligible for prescription drug benefits during the study period, over the age of 20 years. Two

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study groups were identified: people with diabetes (cases), and people without diabetes (controls).

Cases were identified based on the established case definition of the National Diabetes Surveillance System (NDSS) (24-26), or the dispensation for an oral antidiabetic agent (Appendix B) within the diabetes index period. Subjects were identified as having diabetes if they had two or more physician service claims for diabetes (International Classification of Disease, 9th Revision [ICD-9] code 250) within a two year period, one or more hospitalizations with a diabetes code as the primary, secondary, or other diagnosis, or dispensation of an oral antidiabetic agent. Diabetes index date was identified as the date of first dispensation for oral antidiabetic agent, or the date the NDSS criteria were met, whichever came first. Women with services claims for gestational diabetes (ICD-9 648.8) were excluded.

Controls (i.e., did not meet the definition for diabetes during the washout or index periods) were identified by randomly selecting two subjects from the non-diabetes population for each diabetes subject, within the same index year. Controls were assigned the same index date as their respective case and were not matched on any demographic characteristics.

2.2.4 Exposure-Depression

To identify depression using the administrative databases, we used a composite case definition, previously validated in the administrative databases of Saskatchewan Health by West et al. (27). Based on this definition, we considered the following to be an episode of depression: a prescription for an antidepressant medication and any one of three ICD-9 codes for depressive disorders (i.e., 296, 309, or 311) from the physician

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services records within a 6 month reference period (i.e. +/- 3 months). We identified individuals with at least one depressive episode at least 1 year and up to 3 years prior to diabetes index date. Individuals identified as having depression, diagnosed more than three years prior to diabetes identification, were considered to have ongoing depression if they had a dispensation for an antidepressant medication within three years prior to index date.

2.2.5 Data Analysis

All study groups were described in terms of age and sex, and number of physician visits in the year prior to diabetes index date. We initially estimated the unadjusted odds ratio and 95% confidence intervals (CI) of the association between depression and new-onset diabetes using simple logistic regression, with case versus control status as the dependent variable and a history of previous depressive episodes as the main independent variable. We then used multivariate logistic regression, including age, sex, and number of physician visits in the year prior to index date to adjust for comorbidity and medical surveillance bias in cases (28). We also tested for the possibility of statistically significant interaction terms between depression status and all available covariates. We pre-specified that we would only consider as important those interaction terms that achieved a level of statistical significance of $p<0.10$. There was a highly significant interaction found between age and depression ($p<0.001$), therefore we present our multivariate analyses stratified by age (20 to 50 years versus 51 years and older). All analyses were conducted using SPSS Version 12.0.

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2.3 Results

The data for the study comprised 92,677 people, of whom 33,257 were cases. The mean age of the sample was 52 years (median 51, range: 20 – 95 years), 49% of the subjects were female, with an average of 8.2 (median of 5.0) physician visits in the year prior to study index date. The mean age of cases was 61.3 years (range: 20 – 95) and 45% of them were female, whereas the mean age for controls was 46.9 years (range: 20 – 94) and 51% were female. Cases had an average of 11.5 physician visits (range: 8 – 223), and controls an average of 6.3 (range: 4 – 170) in the year prior to index date. Of the 3,901 individuals found to have depression, 2,160 episodes occurred within 3 years prior to index date. For the 1,741 individuals with ongoing depression, onset was an average of 5.9 (SD 2.1) years before diagnosis of diabetes (range: 3 – 11 years).

A history of depression was more common in people with new-onset diabetes (1,622/33,257 – 4.9%) when compared with the controls (2,279/59,420 – 3.8%); the overall unadjusted odds ratio for this association was 1.29 (95% CI: 1.20-1.37). For people 20 to 50 years of age, the unadjusted odds ratio for the association between depression and diabetes was 1.76 (1.58 – 1.95), while it was 1.07 (0.98 – 1.17) for people 51 years and older (**Table 1**).

Multivariate analyses to control for number of physician visits (5 or more), age (51 years or older), and sex resulted in an adjusted OR of 1.04 (95% CI: 0.97 – 1.12). In this multivariate model, however, there was statistically significant interaction between depression and age ($p<0.001$) (**Figure 1**); we therefore conducted multivariate analyses that adjusted for sex and physician visits after stratifying our sample on the basis of age. People with diabetes who were age 20 to 50 were more likely to have had a prior

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depressive episode compared to those without diabetes (adjusted OR: 1.23; 95% CI: 1.10 – 1.37) (**Table 1**). Individuals 51 years and older with diabetes were no more or less likely to have had a prior episode of depression compared to those without diabetes (adjusted OR: 0.92; 95% CI: 0.84 – 1.00) (**Table 1**).

2.4 Discussion

The association between depression and diabetes is becoming well recognized, but the temporal relationship is less well understood (11-21). In this large population-based study, we observed an increased risk of developing diabetes in people with a previous episode of depression. This relationship remained after controlling for potential confounding variables including age, sex, number of physician visits prior to study index date. Our analyses indicate that this increased risk lies mainly in the population of people aged 20 to 50 years. This is very important, as the onset of depression typically occurs between the ages of 20 to 30 years (29,30).

There are several potential mechanisms at play in this observed relationship. It is possible that depression itself to contribute to diabetes. For example, individuals with depression are more likely to have body weight changes, and are less likely to engage in healthy behaviors such as exercise, which increases the risk of developing diabetes (29). Alternatively, many of the medications used to treat depression cause weight gain and sedation, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which could also contribute to developing diabetes. In either case, the onset of depression or its treatment may unmask a tendency for the development of diabetes, perhaps earlier than it otherwise have manifested. Individuals who were 51 years and

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older may have already passed the period of increased risk of developing diabetes, such that a previous history of depression did not alter the risk of subsequently developing diabetes.

The strengths of this study include its population-based case control design, the large sample size, and its detailed data on medication use. Compared to currently available longitudinal literature evaluating the risk of diabetes in people with depression or depressive symptoms (15-21), our study had a much larger sample size, was population-based, and had many more cases of diabetes, which allows for more confidence in our results. Also, our study used previously validated measures which included ICD-9 diagnostic codes and medications to identify individuals with major depressive disorder and diabetes, whereas the majority of currently available studies used self-reported measures to identify diabetes and depressive symptoms. Lastly, only one study controlled for the possibility of surveillance bias influencing the identification of diabetes in people with depression (16).

As with other studies based solely on administrative databases, however, there are several limitations that must be recognized. It is likely that our figures underestimate the prevalence of all symptomatic conditions, including "undiagnosed" diabetes, as patients with milder presentations are less likely to seek treatment or be admitted to hospital would not be captured in the databases. As well, due to the stigma associated with mental illness, many people are reluctant to seek treatment for depressive disorders. This has likely resulted in an underestimation of individuals with depression. We have no reason to believe, however, that this underestimation would be systematically different between cases and controls.

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An additional drawback to the use of administrative data is the lack of clinical data. This limits our ability to investigate whether severity or other comorbidities associated with depression were present. We also recognize the potential for surveillance bias in the recognition and diagnosis of diabetes in this study. For example, someone with depression may be more likely to have clinical work-ups such as a random or fasting blood glucose level upon diagnosis of depression, compared to someone without medical illness, increasing the chance of diabetes being diagnosed. In order to address this potential confounding, we controlled for the number of physician visits in the year prior to study index date (28). We felt that this variable would control to some extent for both comorbidity and medical surveillance, as one would expect someone with multiple medical conditions or a severe single condition to have a higher number of physician visits compared to an individual without illness. We observed this to be the case, with a considerable change in the estimates of the risk of developing diabetes when physician visits were included in the adjusted analyses. Previous studies, particularly those with greater estimates of risk, neglected or were unable to control for potential surveillance bias and it is clearly an important factor in understanding these associations (15-21).

Finally, with this nested case-control design, we are unable to determine the corollary risk in the association between diabetes and depression, that is, does having type 2 diabetes increase the risk of developing depression? Addressing this question would require a cohort study of new-onset diabetes. Such a study, in combination with the results of this nested case control analysis, would provide important information on the temporal relationship between diabetes and depression.

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2.5 Conclusions

We observed that younger individuals with a history of depression had a greater risk of developing new onset type 2 diabetes compared to individuals who had never been depressed. The results of this study suggest it may be important to screen for diabetes in people diagnosed with depression, especially in those aged 20 to 50 years. More research is needed to further investigate the relationship between depression and diabetes, and the mechanisms through which these illnesses are related.

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Table 1. Unadjusted and Adjusted Risk of Developing Diabetes, Stratified by Age.

	Age 20 – 50 Years		Age 51 years and older	
	Unadjusted (OR; 95% CI)	Adjusted* (OR; 95% CI)	Unadjusted (OR; 95% CI)	Adjusted* (OR; 95% CI)
Prior Depression	1.76 (1.58 – 1.95)	1.23 (1.10 – 1.37)	1.07 (0.98 – 1.17)	0.92 (0.84 – 1.00)
Sex (Male)	1.15 (1.10 – 1.21)	1.64 (1.54 – 1.71)	1.44 (1.39 – 1.50)	1.59 (1.54 – 1.66)
No. of Physician Visits†	3.13 (2.98 – 3.29)	3.53 (3.35 – 3.72)	2.45 (2.35 – 2.55)	2.61 (2.50 – 2.71)

* – Adjusted for other variables in the table

† – Dichotomous variable based on median split of 5 physician visits in year prior to study index date

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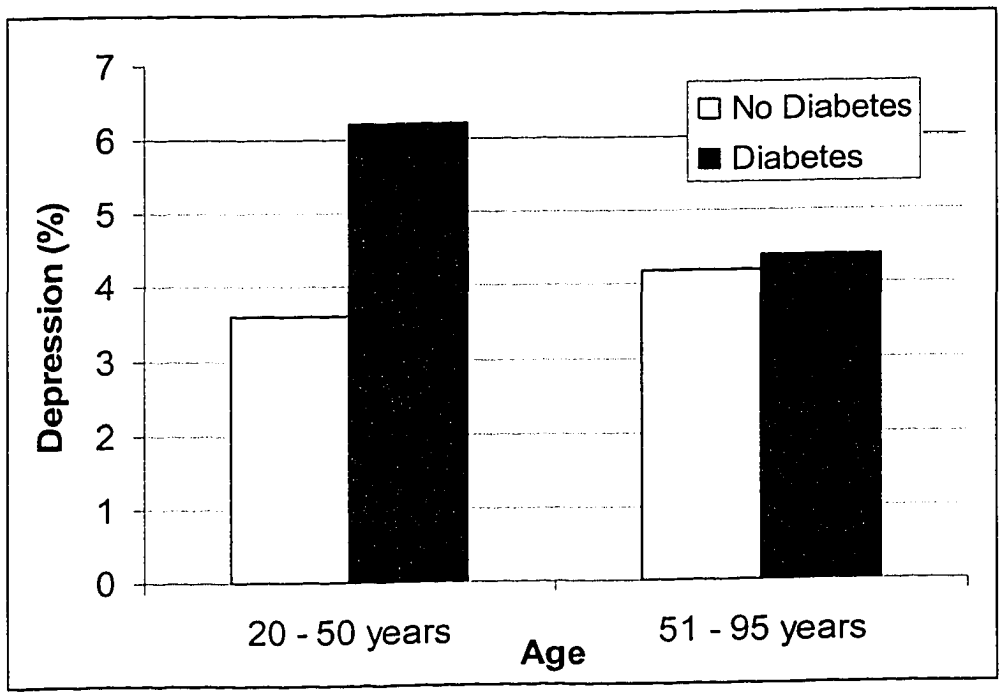
Figure 1. Prevalence of Depression in People With and Without Diabetes, Stratified by Age



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CHAPTER 3

Type 2 Diabetes Does Not Increase Risk of Depression

3.1 Introduction

The increasing prevalence of chronic medical conditions is resulting in a growing health burden, in terms of morbidity and mortality, as well as economic impact. Type 2 diabetes, for example, is associated with excess mortality, largely due to comorbid cardiovascular disease (1-4). Depression is increasingly recognized as an important comorbidity with diabetes (5-15). A number of reports suggest that people with diabetes have approximately 1.3 to 3 times the prevalence of depression compared to individuals without diabetes (5-8). The majority of these reports have been cross-sectional, however, and have not addressed the temporality of the relationship.

Depression itself is a highly disabling illness leading to considerable morbidity and mortality (16,17). Diabetes with comorbid depression is associated with poorer self-management, resulting in poor glucose control (18-21). Individuals with diabetes and comorbid depression have also demonstrated an increased risk of macrovascular and microvascular complications (22,23). Individuals with diabetes and comorbid depression have higher medical expenditures and more functional disability compared to individuals with diabetes but without depression, and people without diabetes or depression (10,11,24,25).

A number of studies have evaluated the risk of diabetes in those with previous depression (9,12-15, 26,27). The majority of these studies observed an increased risk of diabetes associated with a history of depression or depressive symptoms, but often only in selected subpopulations. Carnethon noted the increased risk was limited to those with

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less education (12); Arroyo studied only women (27), and Palinkas evaluated middle-class individuals aged 50 years and older (15). We recently conducted a large population-based nested case-control study which also suggested that history of depression was associated with an increased risk of developing type 2 diabetes, but this risk was limited to those 50 years and younger (28).

There is currently little information available evaluating the other side of the temporal chain, that is, the incidence of depression in people with diabetes. The results of such a study can potentially influence clinical practice by suggesting screening for depression and evaluating ways to prevent people with diabetes from developing depression, decreasing the risk of complications and costs of treatment in these individuals. We therefore conducted a population-based retrospective cohort study to evaluate the incidence of new-onset depression in people with diabetes, compared to those without diabetes.

3.2 Study Design

3.2.1 Saskatchewan Health Databases

Saskatchewan Health databases include information on most residents (99%) of the province of Saskatchewan (population approximately 1 million) (29). Individuals not covered by Saskatchewan Health include those with federally-funded health care, such as members of the Royal Canadian Mounted Police and Canadian Forces (29).

Approximately 90% of the covered population is eligible for prescription drug benefits. Those ineligible include registered Indians who receive prescription benefits through a federal program. Data from four different data files were used in this study: the

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health registration, outpatient prescription drug, medical services, and hospital separation. The data files are linkable based on personal health numbers and provide demographic information, prescription drug usage, and diagnostic codes for outpatient visits and hospital stays.

3.2.2 Study Periods

Individuals with incident cases of diabetes and randomly selected people without diabetes were identified between January 1, 1992 and December 31, 2000, referred to subsequently as the index period. To ensure we identified people with new-onset diabetes, individuals who met the case definition from January 1, 1989 to December 31, 1991 (i.e., a 3-year diabetes washout period) were excluded. All individuals were followed until death, termination of coverage (e.g., departure from the province), or December 31, 2001.

3.2.3 Study Subjects

Individuals included in this study were residents of Saskatchewan eligible for prescription drug benefits during the study period, over the age of 20 years. Two study groups were identified: people with diabetes and people without diabetes as the comparison group.

People with diabetes were identified based on the established case definition for the National Diabetes Surveillance System (NDSS) (30-32), or dispensation for an oral antidiabetic agent (Appendix B), within the index period. Subjects were identified as having diabetes if they had two or more physician service claims for diabetes (International Classification of Disease, 9th Revision [ICD-9] code 250) within a two year period, one or more hospitalizations with a diabetes code was either the primary,

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secondary, or tertiary diagnosis, or dispensation of an oral antidiabetic agent. Study index date was identified as the date of first dispensation of oral antidiabetic agent, or the date the NDSS criteria were met, whichever came first. Women with service claims for gestational diabetes (ICD-9 648.8) were excluded.

Subjects who did not have diabetes (i.e., did not meet the definition for diabetes during the washout or index periods) were identified by randomly selecting two subjects from the non-diabetes population for each diabetes subject, within the same index year. Non-diabetes subjects were assigned the same study index date as their respective diabetes subject. Non-diabetes subjects were not matched to diabetes subject on any clinical or demographic characteristics.

3.2.4 Depression

To identify episodes of depression using the administrative databases, we used a composite definition that had previously been validated in the administrative databases of Saskatchewan Health by West et al. (33). Based on this definition, we considered the following as an episode of depression: a prescription for an antidepressant medication and any one of three ICD-9 codes for depressive disorders (296, 309, or 311) from the physician services records within a 6 month reference period (i.e., +/- 3 months). To capture only cases of new-onset depression, individuals with a depressive episode up to 3 years prior to study index date were excluded from the analysis. Individuals with an incident depressive episode were then evaluated for continuation of antidepressant therapy; individuals with at least one other dispensation of antidepressant were considered to have ongoing depression and were included in the analysis.

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3.2.5 Data Analysis

All study groups were described in terms of age and sex, and number of physician visits in the year following their index date. We assessed the incidence of new-onset depression and initially estimated the unadjusted hazards ratio (HR) and 95% confidence intervals (CI) using Cox regression, with time to depression as the dependent variable and presence of diabetes as the main independent variable. In all analyses and HR calculations, the diabetes-absent cohort served as the reference group. We then used multivariate Cox regression to control for potential confounding by age, sex, and number of physician visits in the year after index date. The number of physician visits in the year after study index date was used to control for both comorbidity and the potential influence of medical surveillance bias in people diagnosed with diabetes (34). Age was coded as a dichotomous variable in the analysis, divided at the median. Number of physician visits was categorized into quartiles (0 – 1 visit, 2 – 6 visits, 7 – 12 visits, and 13 or more visits in the year following study index date). All analyses were conducted using SPSS Version 12.0.

3.3 Results

We identified 92,677 individuals (33,257 diabetes and 59,420 controls) during the index period. A total of 3,901 people were excluded because of history of depression prior to their study index date (28). This left 88,776 people, of whom 31,635 were identified as having diabetes. The mean age of the entire cohort was 52 years (median 51, range: 20 – 95 years) and 48% were female. The entire cohort had an average of 8.9 physician visits (range: 0 – 209) in the year following study index date. The mean age for

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people with diabetes was 61.4 years (range: 20 – 95 years) and 45% were female. The mean number of physician visits for people with diabetes within one year of index date was 14.5 (range: 0 – 209 visits). The non-diabetes cohort had a mean age of 46.8 (range: 20 – 94 years), and 50.2% were female. There was an average of 5.9 physician visits in the year after study index date for the non-diabetes cohort (range: 0 – 168).

The average follow-up for the entire cohort was 4.5 years (SD: 2.9), during which time a total of 2,534 episodes of ongoing depression were identified. The unadjusted incidence rate of depression was very similar in the diabetes cohort (6.5 per 1000 person-years) compared to the non-diabetes cohort (6.6 per 1000 person-years) (**Table 2**). The unadjusted HR was 1.10 (95% CI: 1.01 – 1.19). Multivariate analyses to control for age and sex increased the HR to 1.30 (95% CI: 1.19 – 1.42). Further adjustment to control for physician visits resulted in a HR of 0.97 (95% CI: 0.88 – 1.07) (**Table 3**).

3.4 Discussion

In this large population-based cohort study, new-onset type 2 diabetes was not associated with an increased risk of developing incident depression, after adjusting for age, sex, and number of physician visits. Our results here, combined with many previous studies (9,12-15, 26-28), suggest that the true relationship may be depression increasing the risk of diabetes, but not diabetes leading to depression. Based on these results, screening for diabetes in those with depression may be more valuable than screening for depression in those with diabetes. Further, as depression is a commonly recurring condition, it may be important to assess for any past history of depressive symptoms in individuals with new-onset type 2 diabetes (12-15, 28).

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There are likely several mechanisms involved in the relationship between depression and diabetes. Previous research that has demonstrated an increased risk of diabetes in people with depression or depressive symptoms suggests that depression or its treatments potentially unmask the risk of diabetes earlier than what would be seen without depression present (9,12-15,28). The foundation of this relationship could be due to a number of factors, either biologic or socio-behavioral. Biologic factors such as the effect depression has on the hypothalamic-pituitary-adrenal axis may increase the risk of hyperglycemia and diabetes through increased release of cortisol (35). Previous studies have observed different risk estimates in different socioeconomic strata, however, suggesting that biologic mechanisms are perhaps less important than social or behavioral factors.

Behavioral factors associated with depression such as increased smoking, poor diet, weight gain, and sedentary lifestyle could also result in an increased risk of diabetes. Similarly, the treatments used for depression can potentially increase weight and sedentary lifestyle due to increased sedation and a direct effect on weight. Alternatively, having being diagnosed with a chronic disease associated with considerable morbidity and mortality such as diabetes can be devastating, decreasing mood as a result. As well, complications associated with diabetes such as retinopathy, nephropathy, and macrovascular disease, can severely limit functioning, further decreasing mood. However, based on the results of this study, having diabetes does not appear to increase the risk of developing ongoing depression.

The change of the risk estimate between diabetes and incident depression after the number of physician visits was controlled for suggests that a surveillance bias was

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present. Individuals with diabetes had, on average, almost 10 more physician visits in the year after study index date compared to the cohort of individuals without diabetes (14.5 compared to 5.9 visits, respectively). It is expected that individuals with more physician visits are more likely to have illnesses such as depression recognized. Previous studies, particularly those with greater estimates of risk, neglected or were unable to control for potential surveillance bias. It is clearly an important factor in understanding these associations that needs to be controlled for in analysis.

As with all studies which utilize administrative data to evaluate a research question, this study is not without limitations. It is likely that our figures underestimate the prevalence of all symptomatic conditions, including "undiagnosed" diabetes, as patients with milder presentations are less likely to seek treatment or be admitted to hospital and therefore would not be captured in the databases. As well, due to the stigma associated with mental illness, many people are reluctant to seek treatment for depressive disorders. This has likely resulted in an underestimation of individuals with depression. However, there is no reason to believe that this underestimation would be systematically different between cases and controls.

An additional drawback to the use of administrative data is the lack of clinical data. This limits our ability to investigate whether severity or other comorbidities associated with depression were present. However, controlling for the number of physician visits in the year after study index date likely provides a good marker for comorbidity (34), as an individual with an increased number of illnesses would be expected to visit the physician more often than someone without illness.

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Our dataset also lacked information on socioeconomic status. Results are inconsistent when evaluating the influence of socioeconomic status on the relationship between depression and diabetes. Carnethon et al. (2003) observed an increased risk of diabetes in people with high depressive symptoms, but this relationship was limited to people with less than a high school education, suggesting that socioeconomic status may play a role in potentiating the relationship between depression and diabetes (12). However, Palinkas and colleagues (2004) found depression to be a risk factor for development of diabetes in a population of middle-class men and women (15). Eaton et al. (1996), however, found socioeconomic status had no effect on the relationship between depression and diabetes (9). More information is needed on the influence socioeconomic status has on the relationship between depression and diabetes.

3.5 Conclusions

The results of this large, population-based cohort study have demonstrated that type 2 diabetes is not associated with an increased incidence of new-onset depression, compared to individuals without diabetes. Based on these results, people with type 2 diabetes, and no previous history of depression, require no more screening for depression than the overall general primary care population.

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Table 2. Incidence of depressive episodes

	Total N	Depressive episodes	Average Length of Follow-Up (range; SD)	Incidence Rates (per 1000 person-yrs)
Diabetes	31,635	919 (2.9%)	4.47 Years (0 – 10; 2.8)	6.5
No Diabetes	57,141	1,615 (2.8%)	4.27 Years (0 – 10; 2.8)	6.6

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Table 3. Unadjusted and Adjusted Risk of Developing Depression

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Diabetes	1.10 (1.01 – 1.19)	0.97 (0.88 – 1.07)
Sex (Male)	0.64 (0.59 – 0.70)	0.70 (0.65 – 0.76)
Age (51 years and older)	0.76 (0.70 – 0.82)	0.62 (0.57 – 0.68)
Physician Visits [a]		
(2 – 6 visits)	1.11 (0.98 – 1.26)	1.13 (1.00 – 1.29)
(7 – 12 visits)	1.50 (1.32 – 1.70)	1.65 (1.44 – 1.89)
(13 or more visits)	2.00 (1.77 – 2.25)	2.31 (2.02 – 2.65)

a – Physician visits in the year following study index date; 0 to 1 visit is reference group (HR=1.0)

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CHAPTER 4

General Discussion and Conclusions

4.1 General Discussion

Diabetes and depression are two serious medical conditions, each associated with considerable morbidity and mortality. Previous literature has demonstrated a clear relationship between the illnesses, with the prevalence of depression estimated to be 1.5 – 2.0 times higher in people with diabetes compared to individuals without diabetes. However, the temporality of this relationship is less clear. The objectives of this research were to clarify this relationship, through two different epidemiologic studies which evaluated the risk of developing diabetes after depression, and the risk of developing depression after diabetes.

A number of studies have demonstrated an increased risk of diabetes in people with a history of depression or depressive symptoms (1-6). However, the results of these studies have been inconsistent, as Saydah et al. (7) found no increased risk of diabetes in people with depressive symptoms compared to those without. As well, of the studies that did observe an increased risk of diabetes in people with depression or depressive symptoms, all used different measures to investigate depressive symptoms or depression, each study used different populations to test the research question, most used self-reported measures to identify diabetes, and each study controlled for different potential confounding variables in multivariate analysis. These considerations make it difficult to compare the results of each of the studies. Nevertheless, we found an increased risk of diabetes associated with a previous history of depression, and this relationship was limited to

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individuals under 51 years of age. The results of this study are especially important, as the onset of depression typically occurs between the ages of 20 and 30.

To date there have been no studies conducted evaluating the incidence of depression in individuals newly diagnosed with diabetes. After evaluating this research question , we found no increased risk of depression in people with new-onset diabetes compared to individuals without diabetes. This remained true after controlling for potential confounding variables, including age, sex, and number of physician visits in the year after study index date. This suggests, based prior cross-sectional and longitudinal estimates of the prevalence of depression in people with diabetes, that the true relationship is presence of depression increases the risk of developing diabetes, and diabetes is not associated with an increased risk of depression.

There are many mechanisms postulated behind the relationship between diabetes and depression, including biological and socio-behavioral factors. For example, it has been theorized that depression increases the risk of diabetes due to the stimulating effect depression has on the hypothalamic-pituitary-adrenal axis, increasing circulating cortisol in the body, which can contribute to hyperglycemia and diabetes (8). Alternatively, onset of depression often results in weight gain (as a result of the disorder or in relation to antidepressant treatment) and decreased self-care measures such as exercise. Also, people with depression tend to abuse alcohol and smoke cigarettes more than individuals without depression. These behaviors can potentially increase the risk of developing type 2 diabetes.

In terms of the mechanisms suggested to increase risk of depression in people with diabetes, Talbot and Nouwen (9) reviewed the literature pertaining to two different

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hypotheses: that biochemical changes in diabetes leads to depression or that psychosocial demands imposed by diabetes leads to depression. They concluded that depression likely predisposes individuals to type 2 diabetes. The authors also concluded that diabetes-related psychological and physiological processes may be involved in higher recurrence of depressive disorders (9). However, based on the results of our retrospective cohort study, diabetes does not appear to increase the risk of developing depression.

Because of the observational nature of all of the research, several limitations and potential biases must be recognized. Surveillance bias is a potential confounding variable that other studies did not control for in their analysis. As demonstrated by both of our analyses, however, surveillance bias appears to substantially influence the relationship between depression and diabetes. Individuals who are diagnosed with an illness are seen by a physician more often than someone without a chronic disease, increasing the likelihood that an illness such as depression will be recognized. Likewise, when someone is diagnosed with depression, they are likely worked up by the physician for other illnesses, such as diabetes. As a result, the number of cases of depression in someone with diabetes can appear much higher than someone without diabetes, and vice versa, falsely increasing the risk of each illness being associated with the other. As was seen with the multivariate analyses in both studies, the strength of the relationship between depression and diabetes was significantly reduced when number of physician visits was added to the multivariate analysis. This was especially true when assessing the risk of depression in people with diabetes, as the risk of depression in people with incident diabetes was no longer significant after number of physician visits was added to the multivariate analysis (HR: 0.97; 95% CI: 0.88 – 1.07).

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As with all studies with results derived from administrative datasets, there are a number of limitations to consider. Due to the nature of type 2 diabetes as a slowly progressing illness, it is likely that we have not captured individuals with milder cases of diabetes, that is, diabetes that is currently being treated with diet and not requiring close monitoring. As well, due to the stigma associated with mental illness, it is also likely that we did not capture all people with depression. Additionally, many psychiatrists that practice in the province of Saskatchewan are salaried, limiting their need to bill for their service, also decreasing the likelihood of capturing everyone with depression because our composite definition for identifying people with depression included ICD-9 codes. It is unlikely, however, that these limitations would be systematically different between cases and controls.

Another limitation associated with the use of administrative data is the lack of clinical information provided by the dataset. Although people with depression were identified based on use of antidepressant medications, there is no way to tell whether they are being adequately treated or whether they are still suffering from depressive symptomatology. Likewise, we were unable to tell if individuals with diabetes were being treated within target ranges for blood glucose levels and hemoglobin A1c levels. Access to this information would allow us to further investigate the relationship between diabetes and depression. For example, knowing which patients with depression who were still suffering from depressive symptoms and those who are symptom free could provide answers to whether depression itself is related to diabetes, or if it is the symptoms associated with depression that increase the risk of diabetes, indicating that once depression is treated, the risk for diabetes disappears.

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Future research based the results of these studies include the evaluation of the risk of diabetes associated with individual medications used to treat depression, including selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and serotonin norepinephrine reuptake inhibitors (SNRIs). As each of these classes of medications are associated with different side effect profiles, one class of medication may potentially increase the risk of developing diabetes compared to another class. For example, SSRIs and TCAs are associated with weight gain and sedation, which could potentially increase the risk of developing diabetes compared to the class MAOIs, which are associated with weight loss. The results of such a study could potentially influence antidepressant prescribing in the future, and will provide more information on the role antidepressants have, if any, in the development of diabetes.

4.2 Conclusion

After investigating the relationship between depression and diabetes in these large, population-based studies, a prior history of depression was found to be a risk factor for developing diabetes, especially in younger adults, whereas diabetes does not seem to increase the risk of developing depression. The results of these studies suggest we should be screening for diabetes in people with depression, especially in those under 51 years of age. People with diabetes should be assessed on a case-by-case basis for their risk of depression.

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4.3 References

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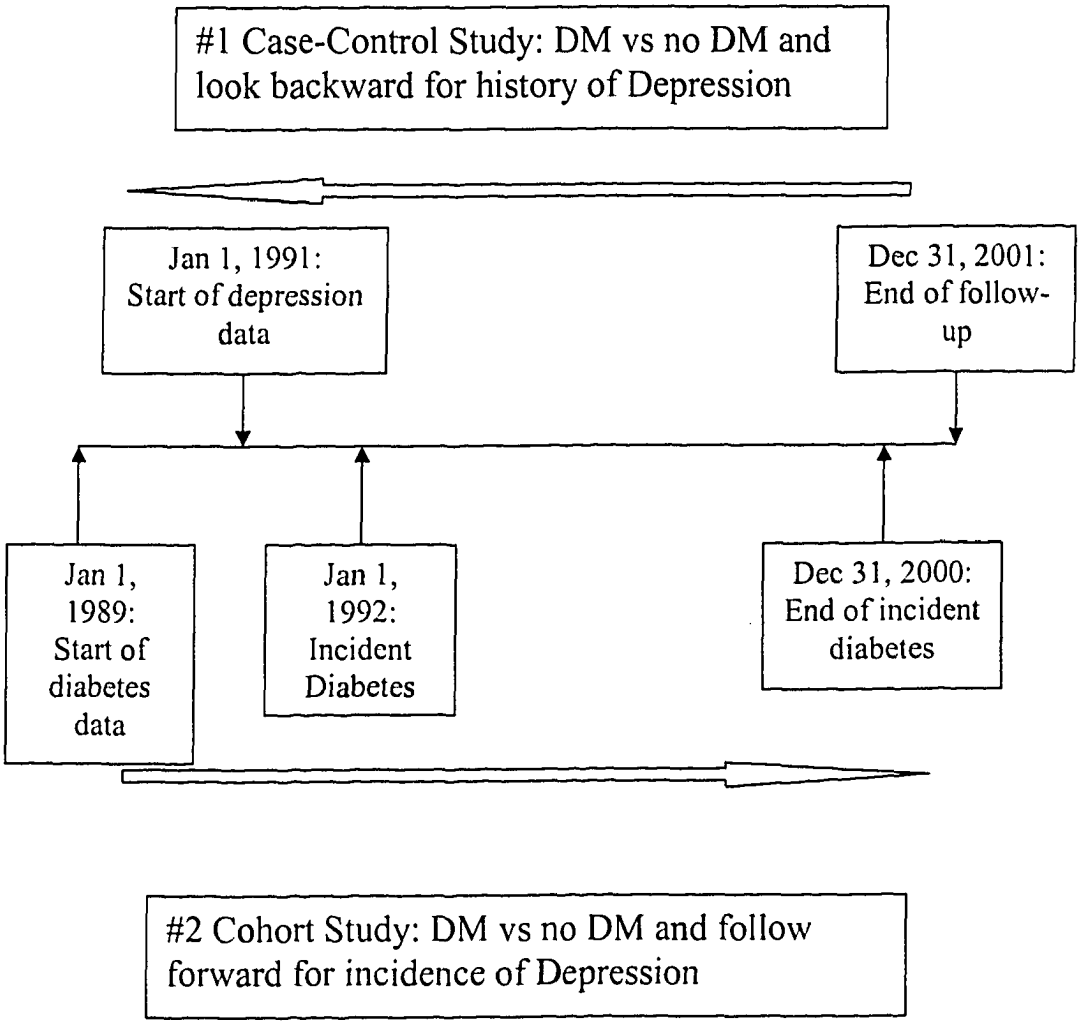
APPENDIX A: Study Design



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APPENDIX B: Oral Antidiabetic Agents

Metformin

Glyburide

Gliclazide

Rosiglitazone

Repaglenide

Pioglitazone

Nateglinide

Acarbose

Acetohexamide

Tolbutamide

Chlorpropamide

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