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

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OBJECTIVE — The purpose of this study was to assess the history of previous depression in people with incident diabetes compared with people without diabetes.

RESEARCH DESIGN AND METHODS — We conducted a population-based nested case-control study using the administrative databases of Saskatchewan Health to assess the study objective. We identified cases of type 2 diabetes based on diagnosis codes and prescription records for individuals over the age of 20 years. For each case subject, two control subjects were randomly selected from the nondiabetic population during the same index year. History of depression, based on diagnostic codes and antidepressant prescription, was ascertained up to 3 years before index date. Simple and multivariate logistic regression analysis was used to estimate the odds ratio (OR) and 95% CIs, after adjusting for age, sex, and frequency of physician visits.

RESULTS — Individuals with newly diagnosed diabetes (1,622 of 33,257; 4.9%) were 30% more likely to have had a previous history of depression compared with people without diabetes (2,279 of 59,420; 3.8%). This increased risk remained after controlling for sex and number of physician visits but was limited to subjects 20–50 years of age (adjusted OR 1.23 [95% CI 1.10–1.37]) and not in those aged ≥51 years (0.92 [0.84–1.00]).

CONCLUSIONS — Depression appears to increase the risk of developing diabetes by ~23% in younger adults. This provides information regarding the temporality of the relationship between diabetes and depression.

Depression is a highly prevalent disease associated with substantial morbidity and mortality (1–6) and 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 1.5–2 times more likely to have depression compared with people without diabetes (11–14). In the most recent estimates using large administrative databases from the U.S. (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 decreased self-care measures such as exercise. Also, people with depression are more likely to abuse alcohol and smoke cigarettes compared with individuals without depression. These behaviors can potentially increase the risk of developing type 2 diabetes. However, the literature evaluating depression as a risk factor for diabetes is quite inconsistent.

Nine prospective observational studies (15–23) 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. The majority of these studies relied on self-reported measures to identify depressive symptoms or depression and diabetes. Also, some of the studies involved limited follow-up or relatively homogenous samples with limited generalizability. For example, Arroyo et al. (20) evaluated women aged 45–72 years, Kawakami et al. (18) only evaluated men, and Palinkas et al. (19) assessed risk of diabetes in people aged ≥50 years, limiting the applicability of these studies to the general population. In contrast, Saydah et al. (24) observed no difference in the incidence of diabetes between those who reported high depressive symptoms or moderate symptoms compared with individuals with no depressive symptoms. Likewise, Kessing et al. (25) found no increased risk of developing type 1 or 2 diabetes in people with depression or bipolar disorder. However, these studies were also not without their limitations. The study conducted by Saydah et al. (24) relied on self-reported measures for both depressive symptoms and identification of diabetes. Kessing et al. (25) required patients to be rehospitalized to identify a diagnosis of diabetes after a previous hospital admission for an affective disorder, excluding individuals who may have been diagnosed with diabetes outside of the hospital.

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 relat-
Depression and diabetes

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 a history of previous depressive episodes were at increased risk compared with those without such a history to develop type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

Saskatchewan Health databases

Saskatchewan Health databases include information on most residents (99%) of the province of Saskatchewan (population ~1 million) (26,27). 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 (26). 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.

**Study periods**

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

**Selection of case and control subjects**

Individuals eligible for inclusion in this study were residents of Saskatchewan, eligible for prescription drug benefits during the study period, and aged 20–20 years. Two study groups were identified: people with diabetes (case subjects) and people without diabetes (control subjects).

Case subjects were identified based on the established case definition of the National Diabetes Surveillance System (28–30) within the diabetes index period. Subjects were identified as having diabetes if they had two or more physician service claims for diabetes (ICD-9 code 250) within a 2-year period or one or more hospitalizations with a diabetes code as the primary, secondary, or other diagnosis. Dispensation of oral antidiabetic agents (see appendix) was used to restrict the diabetes cohort to type 2 diabetic patients. Diabetes index date was identified as the date of first dispensation for an oral antidiabetic agent or the date the National Diabetes Surveillance System criteria were met, whichever came first. Women with services claims for gestational diabetes (ICD-9 648.8) were excluded.

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

**Prior 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. (31). 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 services records within a 6-month reference period (i.e., ±3 months). The criteria evaluated by West et al. for identifying people with depression in the Saskatchewan Health administrative databases provide a sensitivity of 71% and a specificity of 85%. We identified individuals with at least one depressive episode at least 1 year and up to 3 years before the diabetes index date. Individuals identified as having depressive episodes, diagnosed >3 years before diabetes identification, were considered to have ongoing depression if they had a dispensation for an antidepressant medication within 3 years before index date.

**Data analysis**

All study groups were described in terms of age, sex, and number of physician visits in the year before diabetes index date. We initially estimated the unadjusted OR and 95% CI of the association between depression and new-onset diabetes using simple logistic regression, with case versus control subject 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 before index date, to adjust for comorbidity and medical surveillance bias in case subjects (32). We tested for the possibility of statistically significant interaction terms between depression status and all available covariates. We prespecified that we would only consider as important those interaction terms that achieved a level of statistical significance of $P < 0.10$.

Age was initially included in the analysis as a continuous variable, along with a quadratic term to adjust for the nonlinearity of the relationship between age and diabetes onset. In this continuous and quadratic form, we found a highly significant interaction between age and depression. To better evaluate this interaction, we recoded age into a categorical variable grouped by decade. In this form, it was found that the rate of depression was relatively equivalent in those aged 20–50 years and in those aged ≥51 years. Therefore, to further simplify the interpretation of our results, we included age in the final regression model as a dichotomous variable split at the age of 51 years. All analyses were conducted using SPSS version 12.0.

**RESULTS**

The data for the study comprised 92,677 people, of whom 33,257 were case subjects. The mean age of the sample was 52 years (median 51 years [range 20–95]), and 49% of the subjects were women, with an average of 8.2 (median 5.0) physician visits in the year before study index date. The mean age of case subjects was 61.3 years (range...
20–95), and 45% of them were women, whereas the mean age for control subjects was 46.9 years (range 20–94), and 51% were women. Case subjects had an average of 11.5 physician visits (range 8–223) and control subjects an average of 6.3 (range 4–170) in the year before index date. Of 3,901 individuals found to have depression, 2,160 episodes occurred within 3 years before 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).

A history of depression was more common in people with new-onset diabetes (1,622 of 33,257; 4.9%) when compared with the control subjects (2,279 of 59,420; 3.8%); the overall unadjusted OR for this association was 1.29 (95% CI 1.20–1.37). For people 20–50 years of age, the unadjusted OR 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 aged ≥51 years.

Multivariate analyses to control for number of physician visits (five or more), age as a continuous and quadratic variable, and sex resulted in an adjusted OR of 1.47 (95% CI 1.14–1.90) (Table 1). Without the quadratic term for age, the adjusted OR for depression was 1.60 (1.26–2.04). In the full multivariate model, however, there was statistically significant interaction between depression and age (P = 0.002) (Table 1). To further explore the interaction term between age and depression and still recognize the nonlinearity for age, we explored the relationship with age divided into decades. We observed that the relationship between history of depression and diabetes was more similar in people aged 20–50 years and individuals aged ≥51 years (Fig. 1).

We therefore conducted multivariate analyses that adjusted for sex and physician visits after stratifying our sample, which was dichotomized based on age. People with diabetes who were aged 20–50 years were more likely to have had a prior depressive episode compared with those without diabetes (adjusted OR 1.23 [95% CI 1.10–1.37]) (Table 2). Individuals aged ≥51 years with diabetes were no more or less likely to have had a prior episode of depression compared with those without diabetes (0.92 [0.84–1.00]) (Table 2).

Table 1—Adjusted OR for new-onset diabetes with history of depression

<table>
<thead>
<tr>
<th>Prior depression</th>
<th>Sex (male)</th>
<th>Age</th>
<th>Age^2</th>
<th>Age × prior depression</th>
<th>Number of physician visits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.384</td>
<td>0.410</td>
<td>0.179</td>
<td>−0.001</td>
<td>−0.007</td>
<td>1.052</td>
</tr>
<tr>
<td>0.131</td>
<td>0.016</td>
<td>0.003</td>
<td>0.000</td>
<td>0.002</td>
<td>0.017</td>
</tr>
<tr>
<td>0.003</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.000</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.47 (1.14–1.90)</td>
<td>1.55 (1.50–1.60)</td>
<td>1.20 (1.19–1.20)</td>
<td>0.99 (0.99–0.99)</td>
<td>2.86 (2.77–2.96)</td>
<td></td>
</tr>
</tbody>
</table>

*Dichotomous variable based on median split of five physician visits in the year prior to study index date.

CONCLUSIONS—The association between depression and diabetes is becoming well recognized, but the temporal relationship is less well understood (11–25). 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, and number of physician visits before study index date. Our analyses indicate that this increased risk lies mainly in the population of people aged 20–50 years. This is an important observation, as the onset of depression typically occurs between age 20–30 years (33,34).

There are several potential mechanisms at play in this observed relationship. It is possible that depression itself contributes 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 (33). 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 would have manifested. Individuals who were aged ≥51 years 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. That is, having depressive episodes may accelerate the onset of diabetes in at risk individuals. A recent report of higher rates of depression in people with impaired glucose tolerance supports this notion (35).

The strengths of this study include its population-based case-control design, the large sample size, and its detailed data on medication use. Compared with currently available longitudinal literature evaluating the risk of diabetes in people with depression or depressive symptoms (15–24), 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 identifi-

Figure 1—History of depression in people with and without diabetes stratified by age in decades.
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 the hospital and therefore would not be captured in the databases. Also, 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 case and control subjects.

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 with someone without medical illness, increasing the chance of diabetes being diagnosed. To address this potential confounding, we controlled for the number of physician visits in the year before study index date (32). 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 with 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 (15–25).

As we were not able to investigate whether depression increases the risk of other chronic medical conditions during our analysis, the potential exists that diabetes is not isolated in its associated increased risk in people with depression. It may be that prior depression results in an unmasking of other chronic medical conditions; such relationships should be explored. Regardless, our analysis demonstrated an increased risk of diabetes in people with treated depression that may require increased vigilance in this population, particularly in those aged <51 years. This would suggest that the risk of diabetes in young people with depression should be considered over and above other usual risk factors, such as family history, sedentary lifestyle, and BMI.

Finally, with this nested case-control design, we are unable to determine the correlative 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.

We observed that younger individuals with a history of depression had a greater risk of developing new-onset type 2 diabetes compared with individuals who had never been depressed. Further investigation into the relationship between depression and diabetes and the mechanisms through which these illnesses are related is required.

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APPENDIX—Oral antidiabetic agents: metformin, glyburide, gliclazide, rosiglitazone, repaglinide, pioglitazone, nateglinide, acarbose, acetohexamide, tolbutamide, and chlorpropamide.

References


