Type 2 diabetes does not increase risk of depression

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**Abstract**

**Background:** Although diabetes mellitus has a strong association with the presence of depression, it is unclear whether diabetes itself increases the risk of developing depression. The objective of our study was to evaluate whether people with diabetes have a greater incidence of depression than those without diabetes.

**Methods:** We conducted a population-based retrospective cohort study using the administrative databases of Saskatchewan Health from 1989 to 2001. People older than 20 years with newly identified type 2 diabetes were identified by means of diagnostic codes and prescription records and compared with a nondiabetic cohort. Depression was ascertained via diagnostic codes and prescriptions for antidepressants. Cox regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for age, sex, frequency of visits to physicians and presence of comorbidities.

**Results:** We identified 31,635 people with diabetes and 57,141 without. Those with diabetes were older (61.4 v. 46.8 yr; \( p < 0.001 \)), were more likely to be male (55.4% v. 49.8%; \( p < 0.001 \)) and had more physician visits during the year after their index date (mean 14.5 v. 5.9; \( p < 0.001 \)). The incidence of new-onset depression was similar in both groups (6.5 v. 6.6 per 1000 person-years among people with and without diabetes, respectively). Similarity of risk persisted after controlling for age, sex, number of physician visits and presence of unspecified comorbidities (adjusted HR 1.04, 95% CI 0.94–1.15). Other chronic conditions such as arthritis (HR 1.18) and stroke (HR 1.73) were associated with the onset of depression.

**Interpretation:** Using a large, population-based administrative cohort, we found little evidence that type 2 diabetes increases the risk of depression once comorbid diseases and the burden of diabetes complications were accounted for.

Ethics approval to conduct this study was granted from the Health Research Ethics Board at the University of Alberta. Saskatchewan Health databases include information on most residents (99%) of the province of Saskatchewan (pop-
Patients whose information is not included in the Saskatchewan Health databases include those with federally funded health care, such as members of the Royal Canadian Mounted Police and the Canadian Forces. Some 90% of the covered population are eligible for prescription drug benefits. Those ineligible include registered First Nations peoples, who receive prescription benefits through a federal program. Data from 4 different sets of data files were used in this study: health registration, outpatient prescription drug, medical services and hospital separation files. The data files are linkable via personal health numbers and therefore provide demographic information, prescription drug usage and diagnostic codes for outpatient visits and hospital stays.

Individuals with incident cases of diabetes and randomly selected people without diabetes were identified between January 1, 1992 and December 31, 2000 (the index period). To ensure that the cases of diabetes we identified were of new onset, we applied a 3-year diabetes washout period: people who met the case definition between January 1, 1089 and December 31, 1991 were excluded. All subjects were followed until death, termination of coverage (e.g., because of departure from the province) or December 31, 2001.

Included in this study were residents of Saskatchewan who were 20 years of age or older and eligible for prescription drug benefits during the study period. Two study groups were identified: people with diabetes and a cohort of people without diabetes for comparison.

People with diabetes were identified within the index period according to the established case definition for the National Diabetes Surveillance System (NDSS): if they had 2 or more physician service claims for diabetes (International Classification of Disease, 9th Revision (ICD-9) code 250) within a 2-year period, or one or more hospitalizations with a diabetes code as the primary, secondary or tertiary diagnosis. Dispensation for an oral antidiabetic agent (Appendix 1) was used to limit the sample to type 2 diabetes. The study index date for each case was identified as the date either that the NDSS criteria were met or of the first dispensation of an oral antidiabetic agent, whichever came first. Women with service claims for gestational diabetes (ICD-9 codes 648.8) were excluded.

Subjects without diabetes (i.e., who did not meet the definition for having diabetes during the washout or index periods) were identified by randomly selecting subjects from the “nondiabetes” population. For each subject with diabetes, 2 people without diabetes were chosen within the same index year and assigned the same study index date as their respective diabetes subject, but not matched to the subject for any clinical or demographic characteristic. In all analyses and calculations of hazard ratios (HRs), the diabetes-absent cohort served as the reference group.

To identify episodes of depression within the administrative databases we used a composite definition that had previously been validated in the administrative databases of Saskatchewan Health: a prescription for an antidepressant medication along with any of three ICD-9 codes for depressive disorders (296, 309 or 311) within a 6-month reference period (i.e., ± 3 months) from the physician services records. This criterion yielded a sensitivity of 71% and a specificity of 85% for identifying people with depression. To capture only new-onset cases of depression, individuals with a depressive episode within up to 3 years before the study index date were excluded from the analysis. Because information from the physician services record was used in the composite definition, all people identified as having depression were identified through community-based physician visits rather than through hospital admission for depression.

Subjects with an incident depressive episode were then evaluated for continuation of antidepressant therapy. Those with at least 1 subsequent dispensation of antidepressant medication were considered to have ongoing depression and were included in the analysis. Those dispensed an antidepressant only once were considered to have a limited depressive episode and were excluded from the analysis.

We assessed the incidence of new-onset depression and initially estimated the unadjusted HRs and 95% confidence intervals (CIs) using Cox regression, with time until depression as the dependent variable and presence of diabetes as the main independent variable. We then used multivariable Cox regression to control for potential confounding by age, sex and number of physician visits during the year after the index date. To control for the nonlinear relation between age and depression, we used a mean-centred quadratic function. Number of physician visits in the year after the study index date was used to control for both comorbidity and the potential influence of medical surveillance bias among people diagnosed with diabetes. To better meet the assumptions of proportional hazards, the number of physician visits was categorized into quarters (0 or 1 visit, 2–6 visits, 7–12 visits, and 13 or more visits during the year after the study index date) by quartile. We also included information on insulin use as a measure of diabetes severity.

Several chronic medical conditions have been shown to be associated with an increased risk of depression. We therefore preselected 5 comorbidities, identified within 2 years after the study index date, to be included in our analyses: arthritis, cancer, cerebrovascular disease (stroke), coronary artery disease and peripheral arterial disease. Patients with arthritis were identified if they had been admitted to hospital or visited a physician because of a disease of the musculoskeletal system or connective tissue (ICD-9 codes 710–739). Cancer was identified via hospital admissions or physician visits for neoplasm (ICD-9 codes 140–239); cerebrovascular disease, through those for stroke or transient ischemic attack (ICD-9 codes 430–438); and coronary artery disease, via those for myocardial infarction, angina, cardiomyopathy, arrhythmia, congestive heart failure, cardiomegaly (ICD-9 codes 410–414 or 425–429), coronary-artery bypass graft, angioplasty or a dispersion of nitrates. Peripheral arterial disease was noted for subjects who were dispensed pentoxyfylline or who had a lower limb amputated.

Results

We identified 92 677 subjects (33 257 with diabetes and 59 420 without) during the index period. Of these, 3901 people were excluded (1622 [4.9%] with diabetes and 2279 [3.8%] without) because of a history of depression before their study index date. This left 88 776 subjects, of whom 31 635 were
identified as having new-onset diabetes. The mean age of the entire cohort was 52 years (median 51, range 20–95 years); 48% were female. The whole cohort had an average of 8.9 physician visits (range 0–209) during the year after their study index date. Among people with diabetes, the mean age was 61.4 years (range 20–95 yr) and 45% were female (Table 1). The mean number of physician visits for people with diabetes within a year of their index date was 14.5 (range 0–209). Among those with diabetes, 47% had arthritis, 17% cancer, 6.4% a history of stroke, 28.9% coronary artery disease and 1.3% peripheral arterial disease; 12.6% used insulin.

The nondiabetes cohort had a mean age of 46.8 (range 20–94) years; 50.2% were female. Their average number of physician visits in the year after the study index date was 5.9 (range 0–168). Presence of comorbidities was less common in the nondiabetes cohort, with 34.9% having arthritis, 10.5% cancer, 1.8% a history of stroke, 8.9% coronary artery disease and 0.3% peripheral arterial disease.

The average follow-up for the entire cohort was 4.5 years (standard deviation (SD) 2.9; Table 1), during which a total of 2534 episodes of depression were identified. The unadjusted incidence rate of depression in the diabetes and nondiabetes cohorts was similar (6.5 and 6.6 per 1000 person-years, respectively). The unadjusted HR was 1.10 (Table 2). Multivariable adjustment for sex, age, physician visits and preselected comorbidities yielded a hazard ratio of 1.04. Of note, the 5 symptomatic comorbidities we examined were each associated with an increase in the risk of depression, although only arthritis, stroke and peripheral arterial disease achieved statistical significance in multivariable models (Table 2).

Interpretation

After adjustments for age, sex, number of physician visits and the presence of other comorbidities in this large, population-based, retrospective cohort study, newly identified type 2 diabetes was not associated with an increased risk of incident depression. It is possible, however, that the onset of symptomatic long-term macrovascular complications, such as coronary disease, stroke and peripheral arterial disease, can lead to depression in people with type 2 diabetes. Numerous cross-sectional studies have shown an association between depression and diabetes, and prospective observational studies have found an increased risk of diabetes among people experiencing depression or symptoms that are highly depressive. Our results here are in accord with the conclusion that depression increases the risk of diabetes, rather than vice-versa.

As with all studies that use administrative data to evaluate a research question, this study has its limitations. Our figures may underestimate the prevalence of all symptomatic conditions, including undiagnosed diabetes, because patients with milder symptoms are less likely to seek treatment or be admitted to hospital and would not be captured in the databases. The stigma associated with mental illness makes many people reluctant to seek treatment for depressive disorders, which would lead to an underestimation of the number of subjects with depression. The set of criteria we used to identify people with depression had a sensitivity of 71% and a specificity of 85%; it is therefore possible that people in this data set undergoing depression were not identified as such, and that those without depression were attributed depression. Despite a maximum intended follow-up of 10 years, the mean length of follow-up in our cohort was only 4.5 years, possibly too short to observe depression subsequent to new-onset diabetes. And although we included use of insulin as a marker for diabetes severity in the statistical analysis, the lack of clinical data typical of administrative databases limited our ability to investigate the relation of severity of diabetes or comorbidities with depression. As mentioned, as diabetes progresses...
Table 2: Unadjusted and adjusted* risk of developing depression

| Factor                  | Unadjusted Hazard ratio (95% confidence interval) | Adjusted Hazard ratio (95% confidence interval) |
|-------------------------|--------------------------------------------------|-----------------------------------------------|
| Diabetes                | 1.10 (1.01–1.19)                                  | 1.04 (0.94–1.15)                              |
| Sex (male)              | 0.64 (0.59–0.70)                                  | 0.73 (0.67–0.79)                              |
| Age, yr                 |                                                  |                                               |
| Mean-centred            | 1.00 (0.99–1.00)                                  | 0.99 (0.99–0.99)                              |
| Mean-centred squared    | 1.00 (1.00–1.00)                                  | 1.00 (1.00–1.00)                              |
| Physician visits in 1 yr†|                                                  |                                               |
| 0-1 (reference group)   | 1                                                | 1                                             |
| 2-6                     | 1.11 (0.98–1.26)                                  | 1.03 (0.90–1.17)                              |
| 7-12                    | 1.50 (1.32–1.70)                                  | 1.41 (1.23–1.63)                              |
| 13 or more              | 2.00 (1.77–2.25)                                  | 1.81 (1.56–2.10)                              |
| Comorbidities in 2 yr†  |                                                  |                                               |
| Arthritis               | 1.33 (1.23–1.47)                                  | 1.18 (1.09–1.29)                              |
| Cancer                  | 1.21 (1.08–1.35)                                  | 1.07 (0.96–1.21)                              |
| Vascular disease        |                                                  |                                               |
| Coronary artery         | 1.09 (0.98–1.21)                                  | 1.06 (0.93–1.19)                              |
| Cerebrovascular         | 1.51 (1.24–1.84)                                  | 1.73 (1.41–2.13)                              |
| Peripheral arterial     | 1.87 (1.26–2.77)                                  | 1.79 (1.20–2.66)                              |
| Insulin use             | 1.34 (1.16–1.55)                                  | 1.11 (0.95–1.30)                              |

*Adjusted for all the variables listed in the table.
†Period begins at the study index date.

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