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Incidence of Depression and Associated Factors in Patients With Type 2 Diabetes in Quebec, Canada

A Population-Based Cohort Study

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Abstract: It has been reported that the risk of depression is higher among people with type 2 diabetes compared with a nondiabetic population. Among diabetic patients, depression has been associated with worse self-care behaviors, poor glycemic control, and an increased risk of diabetes complications. Identifying factors associated with the occurrence of depression may help physicians identify earlier diabetic patients at a high risk of developing depression, improve prevention, and accelerate proper treatment. To our knowledge, very few population-

based studies have reported on the incidence of clinically diagnosed depression as a consequence of type 2 diabetes over a long follow-up period. The objective of this study was to estimate the incidence of clinically diagnosed depression among type 2 diabetic patients newly treated with oral antidiabetic drugs (ADs) and to identify factors associated with the occurrence of depression.

Administrative claims data from the public health insurance plan were used to identify a cohort of new oral AD users aged ≥18 years between 2000 and 2006. Patients were followed from oral AD treatment initiation until the diagnosis of depression, ineligibility for the public drug plan, death, or the end of the study, whichever came first. Incidence rates were determined using person-time analysis. Factors associated with depression were identified using multivariable Cox regression analysis.

We identified 114,366 new oral AD users, of which 4808 had a diagnosis of depression. The overall incidence rate of depression was 9.47/1000 person-years (PYs) (10.72/1000 PYs for women and 8.27/1000 PYs for men). The incidence of depression was higher during the year after oral AD treatment initiation. Independent factors associated with depression included having had mental disorders other than depression, hospitalization, a higher number of different drugs taken and of physicians visited during the year before oral AD initiation. Moreover, we observed a statistically significant age-by-socioeconomic status interaction.

The incidence of diagnosed depression is higher during the first year after oral AD treatment initiation. Clinicians could pay particular attention to women, patients starting an AD at a young age, those with a low socioeconomic status, and especially those with a history of anxiety or dementia.

(*Medicine* 95(21):e3514)

Abbreviations: AD = antidiabetic drug, CHU = *Centre hospitalier universitaire*, CI = confidence interval, GIS = guaranteed income supplement, HR = hazard ratio, ICD-10 = International Classification of Diseases, Tenth Revision, ICD-9 = International Classification of Diseases, Ninth Revision, Med-Écho = *Maintenance et exploitation des données pour l'étude sur la population hospitalière*, PHQ-9 = Patient Health Questionnaire 9, PYs = persons-years, RAMQ = *Régie de l'assurance maladie du Québec*.

INTRODUCTION

Diabetes and depression have a high prevalence. The number of people with diabetes is expected to increase from 366 million in 2011 (8.3% of the global population) to 552 million in 2030 (9.9% of the global population).[1] Depression is a common and serious mood disorder that represents the leading cause of moderate to severe disability, affecting 350 million people worldwide.[2] It has been reported that the risk of depression is higher among people with type 2 diabetes compared with a nondiabetic population.[3–5] However, these findings are still controversial.[6,7] Depression is also an independent risk factor

for the development of type 2 diabetes.[8] Some hypotheses on the pathophysiological mechanism linking diabetes and depression have been suggested, namely the psychological burden of a chronic condition, the stress-related hormonal changes, and the role of inflammation.[9,10] Indeed, diabetes causing depression and depression causing diabetes are 2 mechanisms that could coexist.[8] Many studies have referred to the bidirectional relationship between these 2 conditions.[11–13]

Patients suffering from both diabetes and depression are more likely to experience unfavorable health outcomes. Their prognosis of type 2 diabetes, in terms of disease severity, complications, and mortality, is worse than patients with diabetes alone.[14–16] Among type 2 diabetic patients, depression is associated with poor glycemic control[16] and an increased risk of microvascular and macrovascular complications.[4,14] In addition, depression negatively affects patients' quality of life and self-care behaviors, such as dieting, physical activities, and adherence to drug therapy.[17]

Although studying the incidence of depression could help predict the risk for the onset of new depression cases and could sensitize physicians to check for symptoms of depression in diabetic patients, few studies on depression among diabetic patients have reported on incidence.[18] Preville et al[19] estimated the incidence of depression for the older adult Quebec population, although it was based on 2 points in time during a 1-year follow-up period. To our knowledge, only 3 studies reported data on the incidence rate of depression among diabetic patients using a time-to-event analysis.[6,11,12] Moreover, because the purpose of those studies was to observe a difference between diabetic and non-diabetic patients, the incidence over time or across subgroups was not studied. Past studies on the factors associated with depression in diabetic patients had a cross-sectional design, and thus they could not imply any causal relationship.[20–23] Identifying factors associated with the occurrence of depression may help physicians identify earlier diabetic patients at a high risk of developing depression, improve prevention, and accelerate proper treatment for depressed patients, which could improve patient self-care and reduce the long-term complications of diabetes.

Some studies have reported on diabetes as a risk factor for the onset of depression.[5,24] However, to our knowledge, only a few population-based studies have been conducted to estimate the incidence rate of clinically diagnosed depression among patients with type 2 diabetes over a long follow-up period,[6,11,12] and none of them in the Canadian province of Quebec. In addition, factors associated with the occurrence of depression in this particular population have yet to be studied. In this study, we focused on a particular subgroup of diabetic patients, namely the type 2 diabetes population initiating an oral AD treatment. Therefore, our study sought to:

1. estimate the incidence rate of clinically diagnosed depression among type 2 diabetic patients newly treated with oral ADs in the Canadian province of Quebec; and
2. identify factors associated with the occurrence of depression in this population.

METHODS

Study Design, Data Sources, and Study Population

We performed this population-based cohort study using the administrative databases of the Quebec Public Health Insurance Board (ie, the *Régie de l'Assurance Maladie du Québec*

[RAMQ]) and the Quebec Registry of Hospitalizations (*Maintenance et exploitation des données pour l'étude sur la population hospitalière* [Med-Écho]). In the Canadian province of Quebec, the RAMQ administers medical services for all permanent residents of the province, and also the public drug insurance plan for recipients of guaranteed income supplement (GIS) or welfare, those without a private drug insurance plan, and all citizens aged 65 years and above. In 2014, approximately 3.48 million people (over 40% of the Quebec population) were enrolled in the public drug insurance plan.[25] The RAMQ databases are composed of claims data from physicians and pharmacists, and therefore, the accuracy and integrity of the data are related to the politics of refusing payment if not all required fields are completed. The RAMQ data file for pharmaceutical services has been deemed accurate.[26]

The data file on beneficiaries provides details on demographics (age, region of residence [urban/rural], and sex). The data file on eligibility periods of drug insurance plan provides details on start and end dates of eligibility for the plan, and GIS and welfare details. The pharmaceutical services data file provides information about drugs (date of dispensing, drug identity, days' supply and prescriber's specialty). The medical services data file supplies information on medical services (date and diagnosis, as defined by the International Classification of Diseases, Ninth Revision [ICD-9] and the physician's specialty). Med-Écho provides information on hospitalizations (date, primary and up to 16 secondary diagnoses, as defined by the ICD-9 or the ICD-10, starting in 2006). We used a unique encrypted health insurance number to link the data files and Med-Écho at the patient level. The Ethics Review Board of the *Centre hospitalier universitaire* (CHU) *de Québec* Research Center approved the study, and the Quebec Information access commissioner—*Commission d'accès à l'information du Québec*—authorized the RAMQ to send us the data.

We asked the RAMQ to identify all beneficiaries of the public drug insurance plan for whom there was at least 1 claim for an AD between January 1, 2000 and December 31, 2006. The date of the first claim after January 1, 2000 were considered as AD initiation. We further asked RAMQ to exclude all patients who received an AD in the 1-year period before AD initiation, to ensure that only new users were included, and also patients who had not been eligible for the Quebec drug plan for the full 1-year period before AD initiation. This ensured that we had complete information about the use of physicians' and pharmaceutical services and mental health history, other than depression, during the year preceding AD initiation. We excluded patients who were under age 18. To focus on type 2 diabetes, we used oral AD as a marker, and we excluded patients who had received only insulin as initial AD therapy. The date of inclusion in the study was the date of the first claim for any oral AD. To limit our study to patients without depression at the time of oral AD initiation, we excluded patients who had at least 1 inpatient or outpatient claim with the ICD-9 or ICD-10 code for depression (ICD-9 codes: 311, 300.4; ICD-10 codes: F32, F33, F34.1, F41.2) or a claim for an antidepressant drug (see Supplemental Table S1, http://links.lww.com/MD/A995) during the 1-year period before AD initiation.

Definition of Variables

Depression occurrence was assessed using an algorithm proposed and validated by Alaghehbandan et al[27]: 1 inpatient claim or 1 outpatient claim made by a psychiatrist with an ICD-9 or ICD-10 code for depression (ICD-9 codes: 311, 300.4; ICD-

10 codes: F32, F33, F34.1, F41.2); or 2 outpatient physician claims with an ICD-9 code for depression (311 or 300.4) within 2 years; or 1 non-psychiatrist physician outpatient claim and a claim for an antidepressant drug (see Supplemental Table S1, http://links.lww.com/MD/A995) within 2 years. The date of depression diagnosis was based on whichever occurred sooner: the date of hospitalization, the first physician visit during which the diagnosis was made, or the date of the first claim for an antidepressant drug. Patients were followed from their oral AD treatment initiation until the depression diagnosis, loss of eligibility for the drug plan, death, or December 31, 2008, whichever came first.

At the time of oral AD initiation, we identified sociodemographic variables such as age, sex, region of residence (urban, rural), and socioeconomic status. Socioeconomic status was estimated with the GIS and welfare details (high = no GIS, medium = partial GIS, low = maximum GIS, or welfare). We also identified the initial oral AD treatment (metformin, secretagogue, polytherapy, and others) and the initial prescriber's specialty (general practitioner, endocrinologist, internist, and others). In addition, we assessed the number of physician visits, number of different physicians visited, number of different drugs claimed, number of hospitalizations (except those with diabetes or depression as the main cause), and the occurrence of mental health disorders other than depression (eg, anxiety disorders, adjustment disorders, bipolar disease, schizophrenia, Alzheimer disease, dementia) during the 1-year period before oral AD initiation.

Statistical Analysis

We performed a descriptive analysis of the studied population and determined the incidence rates of new-onset depression using person-time analysis. The person-years (PYs) of follow-up comprised the interval between the date of oral AD initiation and the date of depression diagnosis. Because differences by age group and sex are reported for the occurrence of depression in the literature, we calculated incidence rates by age and sex. We also analyzed data based on the time since oral AD treatment initiation (1, 2, and 5 years from initiation) to

detect patterns in the incidence of diagnosed depression. To identify factors associated with depression, and also the interaction term between variables, we calculated unadjusted and adjusted hazard ratios (HRs), along with their 95% confidence interval (CI) and 2-tailed P values, using Cox regression analyses. Variables were selected using a backward procedure with a significant P value of 0.05 for their removal from the model. The hazards proportionality assumption was verified by plotting the graph of the ln[-ln(survival)].[28] To better meet the proportionality assumption, the number of physician visits, number of different physicians visited, and number of different drugs claimed were not categorized, but were kept as continuous variables. Because the number of hospitalizations and the presence of mental health disorders, other than depression, during the year preceding oral AD initiation did not satisfy the proportionality assumption, these variables were categorized in 2 periods (the first 6 months, corresponding to a higher probability of depression, and the period starting after the sixth month until the end of follow-up, corresponding to a lower probability of depression). We considered 2-tailed P values lower than 0.05 statistically significant. Analyses were carried out using SAS version 9.4 software (SAS Institute, Cary, NC).

RESULTS

Out of 145,973 patients who were dispensed an AD between 2000 and 2006, 114,366 were new oral AD users free of depression at the time of AD initiation (see Figure 1). Of them, 4808 had a diagnosis of depression during follow-up. The median follow-up period was 4.23 years for the whole cohort (2.06 yrs for patients diagnosed with depression and 4.31 for the others). The average age at oral AD treatment initiation was 65 years (median 67, range 18–105), and 48.4% were female. The majority lived in an urban area (78.8%) and had a high socioeconomic status (56.6%) (Table 1). During the 1-year period before oral AD initiation, on average, patients visited a physician 3.9 times and had claims for 6.4 different drugs.
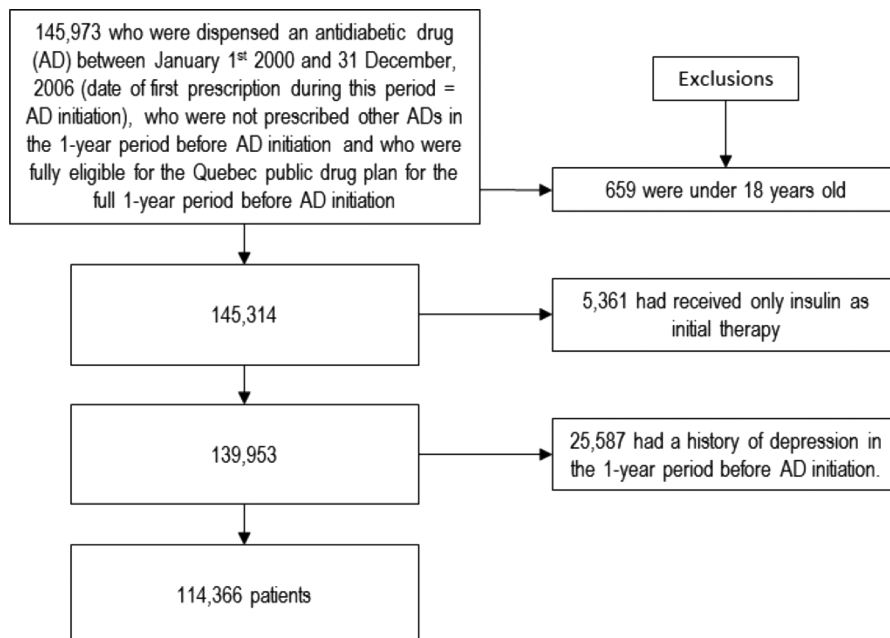

FIGURE 1. Selection of the study population.

TABLE 1. Characteristics of Patients According to the Occurrence of Depression in the Follow-up Period

		Depression	
Characteristics	Total (n = 114,366)	Yes (n = 4808)	No (n = 109,558)
Age at AD treatment initiation, mean (SD)	65.01 (13.19)	63.79 (14.45)	65.07 (13.13)
Age in yrs[*]			
18–44	9377 (8.20)	564 (11.73)	8813 (8.04)
45–54	13,658 (11.94)	677 (14.08)	12,981 (11.85)
55–64	23,793 (20.80)	878 (18.26)	22,915 (20.92)
65–74	40,226 (35.17)	1502 (31.24)	38,724 (35.35)
75–84	22,756 (19.90)	983 (20.45)	21,773 (19.87)
85+	4556 (3.98)	204 (4.24)	4352 (3.97)
Sex[*]			
Male	59,003 (51.59)	2146 (44.63)	56,857 (51.90)
Female	55,363 (48.41)	2662 (55.37)	52,701 (48.10)
Region[*]			
Urban	90,120 (78.80)	3909 (81.30)	86,211 (78.69)
Rural	23,986 (20.97)	889 (18.49)	23,097 (21.08)
Missing	260 (0.23)	10 (0.21)	250 (0.23)
Socioeconomic status[*]			
High (no GIS)	64,683 (56.56)	2453 (51.02)	62,230 (56.80)
Medium (partial GIS)	29,103 (25.45)	1221 (25.40)	27,882 (25.45)
Low (maximum GIS or welfare)	20,580 (17.99)	1134 (23.59)	19,446 (17.75)
Number of physician visits[†,‡], mean (SD)	3.85 (7.39)	4.94 (7.51)	3.80 (7.38)
Number of different physicians visited[†,‡], mean (SD)	2.62 (3.49)	3.41 (4.14)	2.58 (3.45)
Number of different drugs claimed[†,‡], mean (SD)	6.35 (4.94)	7.64 (5.68)	6.29 (4.90)
Hospitalized[†,‡]			
No	89,391 (78.16)	3461 (71.98)	85,930 (78.43)
Yes	24,975 (21.84)	1347 (28.02)	23,628 (21.57)
Mental disorders other than depression[†]			
Yes	9504 (8.31)	868 (18.05)	8636 (7.88)
No	104,862 (91.69)	3940 (81.95)	100,922 (92.12)
Specialty of initial oral AD prescriber[*]			
General practitioner	97,830 (85.54)	4102 (85.32)	93,728 (85.55)
Endocrinologist	5445 (4.76)	236 (4.91)	5209 (4.75)
Internist	5507 (4.82)	222 (4.62)	5285 (4.82)
Other specialty	5218 (4.56)	239 (4.97)	4979 (4.54)
Undisclosed	366 (0.32)	9 (0.19)	357 (0.33)
Initial oral AD treatment[*]			
Metformin	87572 (76.57)	3498 (72.75)	84,074 (76.74)
Secretagogue	19586 (17.13)	975 (20.28)	18,611 (16.99)
Polytherapy	6297 (5.51)	48 (1.00)	863 (0.79)
Others	911 (0.80)	287 (5.97)	6010 (5.49)

Otherwise indicated, values are numbers and proportions (in %).
AD = antidiabetic drug, GIS = guaranteed income supplement, SD = standard deviation.
[*]Collected at the initiation of oral AD treatment.
[†]In the 1-year period before oral AD treatment initiation.
[‡]For other reasons than diabetes or depression.

Incidence of Depression

The overall incidence rate of diagnosed depression was 9.47/1000 PYs for the entire period (10.72/1000 PYs for women and 8.27/1000 PYs for men). We observed that the incidence of depression was higher in the first year after oral AD treatment initiation (12.61/1000 PYs) and lower during the first 2 years and 5 years after oral AD treatment initiation (11.03/1000 PYs and 10.48/1000 PYs, respectively). When only the first year was considered, the incidence of depression was higher in women than in men (14.49/1000 PYs vs 10.84/1000 PYs). However, as shown in Table 2, when stratified by age, this higher incidence in women diminished in magnitude with age and reversed for those aged above 85 years (17.65/1000 PYs for women and 20.35/1000 PYs for men). In both women and men, the incidence of depression showed a U shape tendency with age, with the lowest rates observed for those between 55 and 74 years old (Figure 2). The results for the incidence of depression during the 2 and 5 years after oral AD treatment initiation and the entire period of follow-up showed the same tendency with age and sex (results not shown).

TABLE 2. Incidence Rate of Depression in the 1-Year Period After the Oral AD Initiation, According to Sex and Age

Category	Number of Patients	Persons-yrs (PYs)	Number of Incident Cases	Incidence Rate (Per 1000 PYs)	95% CI
18–44 yrs	9377	8819.43	186	21.09	18.06–24.12
Male	4759	4490.68	79	17.59	13.71–21.47
Female	4618	4328.74	107	24.72	20.03–29.40
45–54 yrs	13,658	13090.45	232	17.72	15.44–20.00
Male	7813	7468.55	117	15.67	12.83–18.50
Female	5845	5621.90	115	20.46	16.72–24.19
55–64 yrs	23,793	23140.19	249	10.76	9.42–12.10
Male	12,789	12396.77	111	8.95	7.29–10.62
Female	11,004	10743.42	138	12.85	10.70–14.99
65–74 yrs	40,226	39150.81	371	9.48	8.51–10.44
Male	21,696	21022.46	168	7.99	6.78–9.20
Female	18,530	18128.34	203	11.20	9.66–12.74
75–84 yrs	22,756	21611.29	272	12.59	11.09–14.08
Male	10,444	9860.93	111	11.26	9.16–13.35
Female	12,312	11750.37	161	13.70	11.59–15.82
85 yrs and above	4556	4034.18	75	18.59	14.38–22.80
Male	1502	1315.24	27	20.35	12.79–28.27
Female	3054	2718.94	48	17.65	12.66–22.65
Total	114,366	109846.35	1385	12.61	11.94–13.27
Male	59,003	56554.63	613	10.84	9.98–11.70
Female	55,363	53291.72	772	14.49	13.46–15.51

AD = antidiabetic drug, CI = confidence interval, PYs = persons-years.

Factors Associated With the Occurrence of Depression

Eleven variables were statistically associated with the occurrence of depression in the multivariable Cox model, as summarized in Table 3. Age strongly interacted with socioeconomic status (Wald $\chi^2 = 328.65$, $P < 0.001$). For both high and low socioeconomic status patients, the younger age group had an increased risk of depression (high socioeconomic status group: $HR_{18-44 \text{ vs } 65-74 \text{ yrs}} = 1.84$, 95% CI 1.59–2.12,

$P < 0.001$; low socioeconomic status group: $HR_{18-44 \text{ vs } 65-74 \text{ yrs}} = 2.87$, 95% CI 2.27–3.64, $P < 0.001$). Initiating oral AD treatment at an older age was associated with an increased risk of depression only in the higher socioeconomic group (high socioeconomic status group: $HR_{85+ \text{ vs } 65-74 \text{ yrs}} = 1.78$, 95% CI 1.42–2.23, $P < 0.001$; low socioeconomic status group: $HR_{85+ \text{ vs } 65-74 \text{ yrs}} = 0.93$, 95% CI 0.51–1.66, $P = 0.8068$). Having mental disorders other than depression during the year before oral AD treatment initiation was associated with an increased
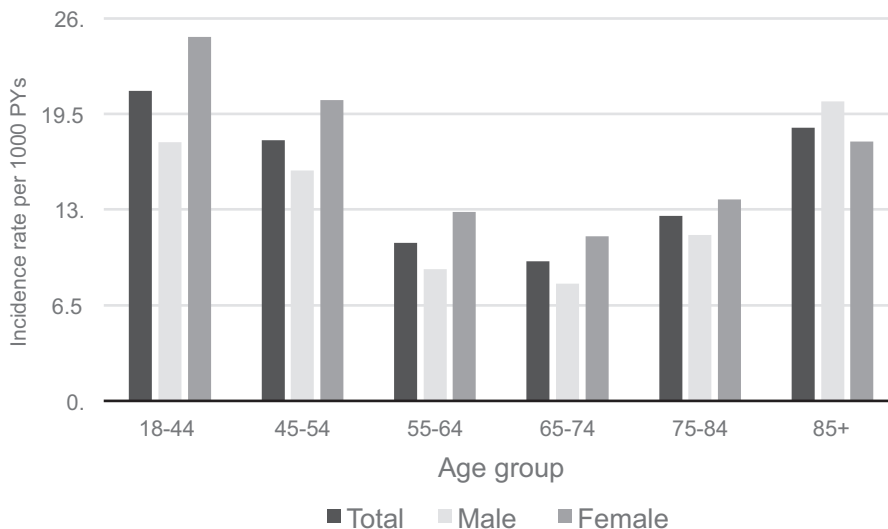

FIGURE 2. One-year incidence rate following oral antidiabetic drug initiation by age group and sex.

TABLE 3. Factors Associated With the Occurrence of Depression

Characteristics	Unadjusted HR	95% CI	P	Adjusted HR*	95% CI	P
Age—high socioeconomic status§						
18−44	1.55	1.34−1.78	<.0001	1.84	1.59−2.12	<0.0001
45−54	1.12	0.98−1.28	0.0833	1.28	1.13−1.46	0.0002
55−64	0.90	0.80−1.00	0.0526	0.96	0.86−1.07	0.42
65−74	1			1		
75−84	1.40	1.25−1.57	<.0001	1.24	1.11−1.40	0.0002
85+	2.34	1.87−2.92	<.0001	1.78	1.42−2.23	<0.0001
Age—medium socioeconomic status§						
65−74	1			1		
75−84	1.23	1.09−1.39	0.0006	1.11	0.98−1.25	0.09
85+	1.61	1.31−1.98	<.0001	1.25	1.02−1.54	0.0320
Age—low socioeconomic status§						
18−44	2.84	2.25−3.60	<.0001	2.87	2.27−3.64	<0.0001
45−54	2.28	1.80−2.87	<.0001	2.25	1.78−2.84	<0.0001
55−64	1.57	1.24−1.99	0.0002	1.58	1.25−2.00	0.0002
65−74	1			1		
75−84	1.11	0.79−1.55	0.5535	0.98	0.70−1.37	0.93
85+	1.11	0.62−1.99	0.7255	0.93	0.51−1.66	0.81
Sex§						
Male	1			1		
Female	1.30	1.23−1.37	<.0001	1.20	1.13−1.27	<0.0001
Region§						
Urban	1			1		
Rural	0.85	0.79−0.91	<.0001	0.89	0.83−0.96	0.0017
Missing	0.96	0.51−1.78	0.8888	0.86	0.46−1.61	0.64
Nb. of physician visits†,‡	1.02	1.02−1.03	<.0001	0.99	0.98−1.00	0.0017
Nb. of different physicians visited†,‡	1.07	1.06−1.07	<.0001	1.05	1.04−1.06	<0.0001
Nb. of different medications claimed†,‡	1.06	1.06−1.07	<.0001	1.04	1.03−1.05	<0.0001
Hospitalized†,‡—first 6 mos of follow-up						
Non	1			1		
Yes	2.48	2.15−2.85	<.0001	1.67	1.44−1.94	<0.0001
Hospitalized†,‡—from the seventh month to the end of follow-up						
Non	1			1		
Yes	1.45	1.35−1.55	<.0001	1.06	0.97−1.15	0.18
Mental disorders other than depression†—first 6 mos of follow-up						
Non	1			1		
Yes	3.61	3.07−4.25	<.0001	2.61	2.21−3.09	<0.0001
Mental disorders other than depression†—from the 7th month to the end of follow-up						
Non	1			1		
Yes	2.56	2.36−2.78	<.0001	2.05	1.88−2.23	<0.0001
Specialty of physician who prescribed the initial AD§						
General practitioner	1			1		
Endocrinologist	1.04	0.91−1.19	0.5634	0.88	0.77−1.00	0.0581
Internist	0.97	0.85−1.11	0.6471	0.84	0.73−0.96	0.0099
Other specialty	1.22	1.07−1.39	0.0032	0.97	0.85−1.11	0.66
Undisclosed	0.64	0.33−1.22	0.1725	0.68	0.35−1.31	0.24
Initial oral AD treatment§						
Metformin	1			1		
Secretagogue	1.15	1.07−1.23	0.0002	1.10	1.02−1.18	0.0095
Polytherapy	1.17	1.04−1.32	0.0106	1.11	0.98−1.25	0.10
Others	1.23	0.92−1.63	0.1578	1.13	0.85−1.51	0.39

AD = antidiabetic drug, CI = confidence intervals, HR = hazard ratio.
*For all variables presented in the table.
†In the 1-year period before oral AD treatment initiation.
‡For other reasons than diabetes or depression.
§Collected at the initiation of oral AD treatment.

risk of depression in both the following 6-month period (HR = 2.61, 95% CI 2.21–3.09, $P < 0.001$) and the period starting at the seventh month until the end of follow-up (HR = 2.05, 95% CI 1.88–2.23, $P < 0.001$). Similarly, being hospitalized during the year before oral AD initiation was associated with an increased risk of depression in the first 6-month period of follow-up (HR = 1.67, 95% CI 1.44–1.94, $P < 0.001$), but not after the sixth month (HR = 1.06, 95% CI 0.97–1.15, $P = 0.1828$).

DISCUSSION

Our main objective was to analyze the incidence of diagnosed depression in a large cohort of type 2 diabetic patients newly treated with ADs in the province of Quebec. In our population, the 1-year incidence rate after cohort entry was 12.61/1000 PYs, and the incidence rate during the entire period was 9.47/1000 PYs, which is similar to those reported by Brown et al[6] (6.5/1000 PYs) and Chen et al[11] (7.03/1000 PYs) for the Canadian province of Saskatchewan and Taiwan, respectively. In these 2 studies, the researchers used diagnostic codes and claims of antidepressants to assess the occurrence of depression over a similar follow-up period. The only study we found for the Quebec population was performed among 965 individuals with type 2 diabetes and without symptoms of depression at baseline. In that study, authors used the 9-item Patient Health Questionnaire (PHQ-9) to assess the presence of symptoms for both major and minor depression combined, which is different from the algorithm we used based on diagnostic codes and antidepressant claims, and they found a cumulative incidence of depressive symptoms of 14% after 1 year of follow-up.[29] Differences in the methods used to assess depression and in age distribution (their population was younger than ours, and the incidence of depression is higher in younger subjects[30]) could partly explain the difference in results between the studies. Moreover, our results reflect the rate of depression diagnosed by physicians, whereas theirs show the cumulative incidence of minor and major depressive symptoms over 1 year in the diabetic population of Quebec. Subjects who did not consult a physician for their symptoms of depression or those consulting a psychologist (a service not covered by the RAMQ) could not be computed in our incidence calculation because this information is not captured by RAMQ. It is known that depression is underdiagnosed in primary care, especially among the older population.[31–33] Our results suggest that this may also be the case among diabetic patients in Quebec, as the incidence rate we found is lower than that expected based on cumulative incidence data reported by Messier et al.[29] Nevertheless, it is important to stress that these results should be interpreted with caution, as our aim was not to compare the incidence of depression between patients with and without diabetes. Our objective was rather to estimate the incidence of depression among newly treated type 2 diabetes patients and to explore some characteristics potentially associated with this incidence.

An important observation is that the incidence of depression was higher in the year after oral AD treatment initiation than in subsequent years. This increased incidence observed in the first months after oral AD treatment initiation could be related to an increased burden associated with this chronic condition[34] or an increased attention from the medical team to any symptoms that could be related to diabetes during the first year of treatment.[35] We could not confirm these reasons with our data, nor we did determine if the incidence of diagnosed depression is higher in patients with treated type 2 diabetes than in individuals without diabetes, because our study was not designed to answer these questions.

We observed that the incidence of depression was higher in women than in men, which is a well-established consensus.[30,36] However, for those aged 85 years and above, we found that the incidence of depression was higher in men than in women. In Canadian literature, we did not find any evidence of a reversal of the difference in depression incidence between women and men with aging. The reversal we observed could be because we used narrower age categories for older patients (ie, 65–74, 75–84, and 85 and above), whereas 65 years and above was the most common category used in other studies.[30,37,38] Moreover, for both men and women, we observed that the incidence of depression continuously decreased between the 18 to 44 and the 65 to 74 age groups, and increased afterward. In an earlier study conducted in the Canadian general population, an increased incidence of depression was reported for both men and women aged over 75 years.[39] However, in another study, Murphy et al[37] found that the incidence of depression was not different between individuals aged <55 years and those aged ≥55 years, irrespective of sex. The increased incidence of depression we observed for older patients above 74 years could be due to the presence of diseases of aging, such as neurodegenerative diseases or cardiac conditions. Since we did not investigate such diseases, we cannot exclude that these conditions of aging could be present after antidiabetic treatment initiation and therefore could explain this increased incidence rate.

We also observed a statistically significant interaction between age and socioeconomic status, which means that younger patients (<55 years old) with a low socioeconomic status were more likely to be diagnosed with depression than the same age group with high socioeconomic status. Earlier studies found that poverty, low income, or unemployment were associated with a higher risk of depression.[23,40,41] Other social disadvantages, such as low educational level or social deprivation, often accompany low income and could mediate the association between income and depression.[41] However, we observed that patients aged 75 years or above with a high socioeconomic status were more likely than patients between the age of 55 and 64 years in the same socioeconomic group to have a depression diagnosis, but the same was not observed for patients aged 75 years and above with a low socioeconomic status. The higher risk of diagnosed depression for older patients in the higher socioeconomic status group is more difficult to interpret. In fact, the literature provides no other studies with similar findings. Further research is needed to confirm our result and to determine explanations.

Consistent with the findings of other studies, we found a lower risk of depression in patients living in rural versus urban areas.[42,43] This may be because those living in rural areas have a lower tendency to obtain or more difficulty obtaining medical services and thus have a lower chance of diagnosis.[44,45]

We observed that individuals with a history of mental health disorders were more likely to be diagnosed with depression, which is consistent with other studies that found that individuals with a history of anxiety or dementia were more likely to receive a diagnosis of depression.[46–48]

We found a positive association between the occurrence of depression and a higher number of physicians visited during the year preceding oral AD treatment initiation, and also a higher number of different drugs claimed and being hospitalized in that same year. A high number of physicians visited, drugs claimed,

or being hospitalized may indicate that patients have concomitant illnesses. The presence of diabetes complications or other comorbidities, especially chronic conditions, have been previously associated with depression.[6,21,22,41]

We observed that receiving an antidiabetic polytherapy, rather than metformin alone, as the initial AD therapy, was associated with the occurrence of depression only in the univariate model. Polytherapy, including insulin as the initial treatment, may be a proxy for the severity of diabetes.[49] If so, this result would suggest that the severity of diabetes might not influence the occurrence of depression. This hypothesis, however, needs to be confirmed through further research using valid clinical information on diabetes severity.

Finally, individuals for whom the initial oral AD treatment was prescribed by an internist rather than a general practitioner were less likely to be subsequently diagnosed with depression. This result could be explained by the fact that individuals treated by internists might be different from those followed by general practitioners. We further investigated this hypothesis and found that the proportion of male patients who were prescribed the initial oral AD treatment by an internist was higher than among those whose prescriber was a general practitioner (58% vs 51%, results not shown). Since the risk of depression in men is lower than that in women, this difference could partly explain the result we found. Differences in internist practices could also play a role, but, to our knowledge, the association between the initial AD treatment prescriber's specialty and depression has never been assessed. Further research is needed to better understand this association.

Our study has several strengths. First, by using the RAMQ databases, we had access to a large cohort of type 2 diabetic patients, newly prescribed oral ADs, or both oral ADs and insulin throughout the province of Quebec. This study is population-based for age 65 and over because people turning 65 are automatically registered for the RAMQ public drug plan. The study is also population-based for those aged under 65, insured with the public drug plan. However, generalization to the Quebec diabetic population aged under 65 years must be done with caution as employed individuals benefitting from a private group drug plan were not included in our cohort, which resulted in a population with a lower socioeconomic status. Another strength is that for the assessment of depression, we used an algorithm validated in a Canadian setting, which reduces the potential for recall or social desirability biases that can affect survey results.[50] Furthermore, self-administered questionnaires, which are a widely used method of depression assessment, may tend to overestimate depression in diabetic patients. Indeed, most patients with diabetes and high levels of depressive symptoms could be emotionally distressed due to their diabetes, rather than being clinically depressed.[51]

Our study also has some limitations, especially due to the use of administrative data. In the RAMQ databases, there is no information about patients aged under 65 years who are covered by a private drug insurance group plan, which results in a sample where employed patients are under-represented. The impact of this under-representation on our observed incidence is difficult to assess. On average, publicly insured patients have a lower socioeconomic status. Because depression is more prevalent in low-income groups,[40] the incidence we observed could be higher than a representative sample of the diabetic population of Quebec. Contrarily, depression is more frequent in younger individuals than in the older population.[30] In our cohort, patients were, on average, older than the general diabetic population, meaning that the incidence we observed could be lower than a representative sample. Nevertheless, this under-representation of younger patients should not have a large impact on the results because the prevalence of diabetes sharply increases with age.[52] We cannot establish how our results apply to other populations in other healthcare contexts. We used claims data rather than a structured diagnostic interview to assess depression. The algorithm used to identify patients with depression had a sensitivity of 78% and a specificity of 93%.[27] Furthermore, since depression is likely underdiagnosed and undertreated in primary care, especially among the older population,[31–33] it is thus possible that we have underestimated the incidence of depression. In the literature, no perfect algorithms for the detection of depression in the administrative data exist.[53] Moreover, different diagnostic codes are currently being used for depression diagnosis, but there is no consensus on which codes to include in an algorithm to detect depressed patients.[53] In addition, as we were not able to accurately determine the exact date for both the onset of depression and the diagnosis of type 2 diabetes, we cannot rule out the fact that some depressions may have occurred before the oral antidiabetic drug treatment was initiated. Finally, certain characteristics and clinical data known for being associated with the occurrence of depression, such as severity of diabetes,[54] smoking habits,[41,55] body mass index,[56] ethnicity,[56] or self-perception of health status,[55] are also not available in the RAMQ databases and therefore could not be assessed.

CONCLUSIONS

Diabetes is a chronic condition requiring long-term, continuous management. Psychological distress can negatively influence the achievement of glycemic control required for preventing diabetes complications. Our results suggest that the incidence of diagnosed depression is low compared with available data on the incidence of symptoms of depression for the diabetic population of Quebec. Our results also suggest that being a woman, of a younger age, of low socioeconomic status, and having a history of mental disorders, such as anxiety or dementia, are important risk factors for the occurrence of depression in this population.

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