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Original article

Depression and the risk of hospitalization in type 2 diabetes patients: A nested case-control study accounting for non-persistence to antidiabetic treatment

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ABSTRACT

Introduction: Depression is one of the most common comorbidities of type 2 diabetes. The relationship between these two diseases seems to be bidirectional. Both conditions separately lead to significant morbidity and mortality, including hospitalization. Moreover, depression is associated with non-persistence with antidiabetic drugs.

Objectives: To measure the effect of depression on morbidity and particularly on all-cause, diabetes-related, cardiovascular-related and major cardiovascular events-related hospitalization, adjusting for non-persistence to antidiabetic drugs and other confounders.

Methods: We performed a nested case-control study within a cohort of type 2 diabetic individuals initiating antidiabetic drugs. Using the health administrative data of the province of Quebec, Canada, we identified all-cause, diabetes-related, cardiovascular-related and major cardiovascular hospitalizations during a maximum follow-up of eight years after the initiation of antidiabetic drug treatment. A density sampling method matched all cases with up to 10 controls by age, sex, and the Elixhauser comorbidity index. The effect of depression on hospitalization was estimated using conditional logistic regressions adjusting for non-persistence to antidiabetic drug treatment and other variables.

Results: We identified 41,550 all-cause hospitalized cases, of which 34,437 were related to cardiovascular (CV) diseases, 29,584 to diabetes, and 13,867 to major CV events. Depression was diagnosed in 2.51% of all-cause hospitalizations and 1.16% of matched controls. 69.11% of cases and 72.59% of controls were on metformin monotherapy. The majority (71.62% vs 75.02%, respectively) stayed on metformin monotherapy without adding or switching drugs during follow-up. Non-persistence was at similar rates (about 30%) in both groups. In the multivariable analyses, depression was associated with an increased risk for all-cause hospitalizations, with odds ratios (ORs) ranging from 2.21 (95% CI: 2.07–2.37) to 1.32 (95% CI: 1.22–1.44) according to the model adjustment (from the univariate to the fully adhjusted).

Conclusion: Depression increased the risk of all-cause hospitalizations among patients treated for diabetes, even after accounting for non-persistence and other potentially confounding factors. These results stress the impact of depression on diabetic patients' use of health care resources.

Introduction

Depression is a frequent mental health problem with an estimated lifetime prevalence of 15 to 18%, and it is projected to become the first cause of burden disease worldwide by 2030 [1]. Chronic diseases, including type 2 diabetes, impose great adaptive stress predisposing to depression [2, 3].

Type 2 diabetes is a highly prevalent chronic disease that can lead to severe macrovascular and microvascular complications [4, 5]. Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes [4, 5]. All those complications increase the risk of hospitalization and contribute to the high economic burden related to diabetes [6]. Blood glucose control is the cornerstone of treatment to prevent such complications, often requiring complex regimens,

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including lifestyle changes and pharmacotherapy [7]. Adherence to medications, including antidiabetic drugs (ADs), is an important contributory factor in the optimal management of type 2 diabetes [8]. The negative impact of non-adherence on mortality and hospitalizations has been studied in diabetes patients [9, 10]. In the US, the first and second leading causes of non-adherence-related hospitalizations were, respectively, mental health disorders and diabetes [11].

Patients with type 2 diabetes are at higher risk of depression [3, 12]. The diagnosis of depression occurs more frequently in the first year after initiating type 2 diabetes pharmacological treatment [13]. In patients with type 2 diabetes, depression seems associated with an increased number of days of hospitalization, according to some studies [14, 15], but this association was non-significant in another study [16]. Moreover, depression is also associated with non-adherence to ADs [3, 8, 10, 17, 18], poor self-care behaviors [17] and mortality [19, 20]. In a large retrospective study of new ADs users, the median time to discontinue ADs was 1.81 years for patients on antidepressants and 3.23 years for those not taking them [21]. Nevertheless, even in non-depressed patients with diabetes, non-adherence seems to be high [8]. We can thus hypothesize that both depression and non-adherence would contribute to the increase of hospitalizations in type 2 diabetic patients.

To our knowledge, no studies have assessed the effect of depression on hospitalization in type 2 diabetes.

The objective of this study was thus to measure the effect of depression on hospitalizations and particularly on all-cause, diabetes-related and cardiovascular-related and major cardiovascular events-related hospitalization, adjusting for non-persistence to antidiabetic drugs and other confounders.

Methods

Study design and data sources

We conducted four distinct nested case-control studies to evaluate the association between depression and four hospitalization-related outcomes. We used linked databases from the Quebec Public Health Insurance Board (*Régie de l'assurance maladie du Québec* - RAMQ), the Quebec hospitalization archives (MedEcho) and the Quebec Statistics Database (*Institut de la Statistique du Québec* - ISQ) as the sources of information. These databases include information on patient sociodemographics, vital status, diagnosis (in-hospital and outpatient), medical procedures and prescribed drugs claimed (drug name, supply date, days' supply) for all Quebec residents covered by the public drug insurance group plan (about 46% of the Quebec population and virtually all people 65 years old and above) [22]. RAMQ databases are considered accurate and valid for research purposes [23].

Population: base cohort

Nested case-control studies are conducted within well-defined cohorts. To this end, our base cohort consisted of all Quebec residents insured by the public drug plan, claiming their first oral antidiabetic drug (OAD) between January 1, 2000, and December 31, 2004. The date of first dispensation (claim) of an OAD was thus the cohort entry. In all the text, we will refer to this date as the cohort entry. We excluded patients who, at the cohort entry date, were under 18 years, claiming only insulin or had been diagnosed with depression or suspected with depression in the year before. To ensure the exclusion of virtually all the patients with a history of depression, those with even a single ICD-9 or ICD-10 [International Classification of Diseases, Ninth or tenth revision] inpatient or outpatient code for depression (ICD-9 codes: 296.2, 296.3, 300.4, 311; ICD-10 codes: F32, F33, F34.1, F38.1) or a claim for an antidepressant drug were excluded.

Definition of cases and control selection

Four distinct nested case-controls studies were conducted within our cohort of newly treated diabetic subjects. In the first study, cases were all the patients hospitalized for any cause. Thus, we started by identifying all the patients who were hospitalized for any reason and assessed the duration of follow-up from the initiation of antidiabetic drug treatment (cohort entry) until they were hospitalized (index date). We also assessed the follow-up duration for the remaining patients in the cohort (until December 31, 2008). Next, for each case, we identified all the patients who had at least the same follow-up duration as the case and were not cases at the time the individual became a case. This group of non-cases is known as the individuals who are in the risk set of that case and are eligible to be selected as controls to be matched with that case. Finally, according to the density sampling approach, each case was matched with up to 10 controls randomly selected from the case-specific risk set. The date the case occurred was the case index date. An index date was thus assigned to the matched controls ensuring a similar follow-up (namely, the time between the cohort entry [first OAD claim] and the index [hospitalization] dates) for each matched case-controls pair. The design thus imposes a matching on the duration of follow-up (further description is provided in Fig. 1). In addition to matching on the duration of follow-up, cases and controls were also matched on sex, age (+/- 5 years), and the Elixhauser comorbidity index [24]. The Elixhauser comorbidity index is calculated with administrative health database diagnoses and has demonstrated a higher ability to predict mortality over other indexes [25]. It includes 31 different comorbidities and was originally developed to predict in-hospital mortality, hospital charges and length of stay [24]. Even if initially developed to predict mortality, the Elixhauser index has been validated to predict hospital readmission [26]. It is also commonly used as a summary of patients' comorbidities - instead of using individual comorbidity variables - in health research [27]. Moreover, it is used as a prognosis factor for outcomes of several diseases, like burn patients [28] and acute coronary syndrome [29].

We used the approach described above to create nested case-controls samples for three other outcomes (specific hospitalizations). Theses outcomes (cases) included individuals hospitalized with a diagnostic code related to: 1) diabetes complications (ICD-10 codes: E11.0; E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.8, E16.0, E16.1, E16.2, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, M14.2, M14.6, T38.3, N08.3); 2) cardiovascular (CV) diseases (ICD-10 codes: I05-I99); and 3) major CV events (ICD-10 codes: I20.x, I21.x, I24.x, I46.x, I50.x, I60.x, I61.x, I62.x, I63.x, I64.x, R57.0).

Exposure assessment

Depression was the primary exposure studied. It was assessed before each patient index date using a modified version of the algorithm developed by Alaghehbandan [30] :

- at least one hospitalization or one psychiatric consultation with diagnostic depression code (ICD-9 codes: 296.2, 296.3, 300.4, 311; or ICD-10 codes: F32, F33, F34.1, F38.1), or
- at least two medical consultations, in 24 months with a diagnostic depression code, or
- at least one medical consultation and one claim for an antidepressant drug within 24 months.

The beginning date of the depression episode (depression date) was the first date of hospitalization, medical consultation or antidepressant claim, whichever came first.

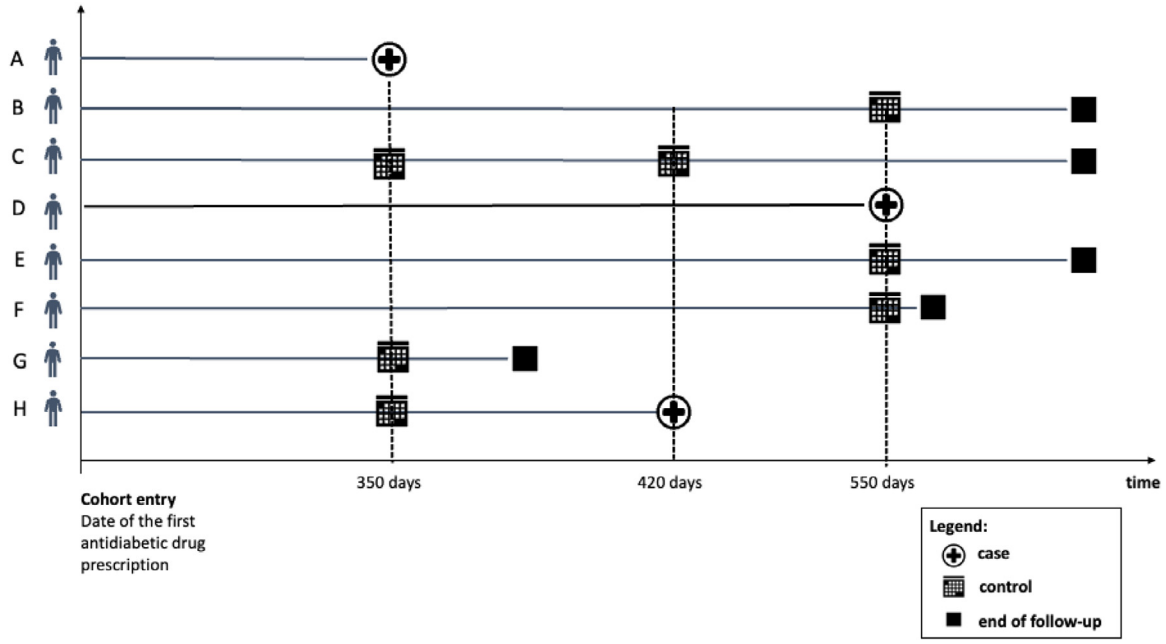

Fig. 1. Representation of the selection of controls for cases (hospitalizations) within the cohort of newly treated type 2 diabetic patients. In the figure, each line represents the follow-up for each cohort patient. Crosses represent cases, who are patients A, D and H. Patient A was hospitalized 350 days after the initiation of the antidiabetic drug (cohort entry). According to the density sampling method principle, patients B to H were all eligible to be selected as controls for patient A as they had all a follow-up greater than 350. In this example, patients C, G and H were randomly matched to patient A. The date the hospitalization occurred for patient A is the case index date. The same index date is thus assigned to the matched controls ensuring the same follow-up duration of 350 days for those controls. Exposure to depression is therefore assessed for this matched pair case-controls before their index date. Patient D was hospitalized on day 550. At that moment, patients B, C, E and F had follow-ups greater or equal to 550 days and were eligible as controls for patient D. Patients B, E and F were randomly matched to patient D. The index date of this matched pair ensures a pre-index date follow-up of 550 days. The same matching process is used for patient H, who became a case on day 420. Patient H was already randomly selected as a control for patient A at day 350 because he became a case afterwards, at day 420 when he was hospitalized. In this example, patient C was randomly matched as a control to patient H. Patient C was thus selected as a control for both patient A and patient H at different times (day 350 and day 420, respectively).

Covariables

Covariables were chosen among those present in the RAMQ databases based on previous studies [13, 16, 18-20, 31] and our clinical judgment. Non-persistence with antidiabetic drugs was assessed by the refill-gap method. Persistence is a component of medication adherence and refers to the act of continuously refilling prescriptions for the recommended length of time [32]. While adherence is the thoroughness to which a person's behavior conforms with the health care provider's recommendations, such as taking medications [11]. Subjects were classified as non-persistent when the refill-gap (between two consecutive antidiabetic drug claims) was superior to 90 days. This length of time was chosen because the standard days' supply for one prescription is 30 days for most of our population, leading to a corresponding interruption of 60 days. The end of day's supply for their last antidiabetic drug claim was the date of treatment discontinuation for subjects deemed non-persistent. Since the RAMQ database does not provide information about drug use during hospital stays, hospitalization days were excluded from the refill-gap calculation, assuming that individuals were appropriately treated while hospitalized.

Moreover, switching from one antidiabetic drug to another within the allowed time gap was accepted because it may occur in clinical practice to reach optimal therapeutic management. Other covariables were measured at different times. At the cohort entry date, we estimated the socioeconomic status according to the presence and amount of a guaranteed income supplement (GIS) or the presence of employment assistance (high = no GIS, medium = partial GIS, and low = maximum GIS or employment assistance); we also assessed the area of residence (urban, rural, unknown), using the first three postal code digits; the treatment regimen of first antidiabetic drug prescription (metformin, other monotherapy, insulin-free combination therapy or insulin combination therapy); and the specialty of the first antidiabetic drug prescriber (general practitioner, specialist or unknown).

In the year preceding the cohort entry, we measured: the number of physician visits, the number of different medications claimed, the occurrence of an anxiety disorder (ICD-9 codes: 300.0, 300.2, 300.3; or ICD-10 codes: F40, F41, except F41.2), and of cognitive impairment (ICD-9 codes: 290.x; or ICD-10 codes: F01, F02, F03). From the cohort entry to the index date (i.e., the first hospitalization for cases and the assigned index date for matched controls), we assessed: non-persistence with antidiabetic drugs, the Elixhauser comorbidity index and the modification of the antidiabetic drug treatment (no change, OAD only addition, insulin addition, OAD and insulin addition). Supplemental Figure 1 (see supplementary materials associated with this article on line) shows all the variable used in the study and their possible relations with the exposure and the outcome.

Statistical analyses

Data were analyzed using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA) with bilateral tests and results were considered significant when P-value ≤ 0.05. Depression exposure and all identified covariates stratified by case or control status were processed for descriptive statistics (number of patients and percentage). To measure the association between depression and hospitalization, we used conditional univariate and multivariable logistic regressions adjusting for potential confounding factors and calculated crude odds ratios (ORs) and adjusted odds ratios (aOR) with their 95% confidence intervals (CIs). For every case-control subgroup, three different models were performed (one univariate and two multivariable models) with distinct adjusting variables. As detailed in Table 1, a first adjusted model (model A) included variables measured before antidiabetic drug treatment initiation. A second adjusted model (model B) also included the Elixhauser comorbidity index during follow-up

Table 1
Univariate and multivariable conditional logistic regression analyses of the association between depression and all-cause and specific-cause hospitalization.

	Unadjusted			Model A*			Model B*		
	OR	**95% CI**	***P*-value**	**aOR**	**95% CI**	***P*-value**	**aOR**	**95% CI**	***P*-value**
All-cause hospitalization (41,550 cases and 414,782 controls)									
Depression (yes vs no)	2.21	2.07–2.37	<0.0001	1.70	1.59–1.83	<0.0001	1.32	1.22–1.44	<0.0001
Diabetes-related hospitalization (29,584 cases and 295,548 controls)									
Depression (yes vs no)	1.04	0.96–1.13	0.35	1.01	0.92–1.10	0.90	0.99	0.91–1.08	0.81
Cardiovascular-related hospitalization (34,437 cases and 344,041 controls)									
Depression (yes vs no)	1.29	1.18–1.40	<0.0001	1.13	1.03–1.23	0.01	0.94	0.86–1.03	0.18
Major cardiovascular event hospitalization (13,867 cases and 138,560 controls)									
Depression (yes vs no)	1.49	1.33–1.66	<0.0001	1.23	1.09–1.38	0.00	1.04	0.92–1.17	0.54

OR: odds ratio; aOR: adjusted odds ratio; CI: confident interval. *Model A: adjusted for socioeconomic status; area of residence; treatment regimen of first antidiabetic drug prescription; specialty of the first antidiabetic drug prescriber; modification of the antidiabetic drug treatment during follow-up; non-persistence with antidiabetic drugs; number of physician visits in the year before cohort entry; number of different drugs in the year before cohort entry; diagnosis of anxiety disorder during follow-up; diagnosis of cognitive impairment during follow-up. Model B: adjusted for the same variables as Model A, plus the Elixhauser comorbidity index during follow-up.

since the subject's physical health may vary during follow-up, independently of the presence of depression.

Sensitivity analyses were performed by changing definitions of non-persistence and depression. First, a refill gap of 180 days between two consecutive claims was allowed. Second, the allowed time between the medical consultation and the antidepressant claim (point 3 of the algorithm) was moved from 24 months to 12 months. The 24 months might indeed be considered too large since antidepressant drugs can be used for several other indications than depression (e.g., anxiety disorders, chronic pain, etc.) [33]. Finally, separate analyses were performed on subjects 65 years old or older at cohort entry. Indeed, in Quebec, virtually all individuals turning 65 years become insured by the public drug plan and have their drug claims recorded in the RAMQ database.

Results

Of the 79,513 patients newly treated with an antidiabetic medication, 41,550 were hospitalized for any causes during their follow-up. There were 34,437 patients hospitalized for cardiovascular (CV) diseases, 29,584 for diabetes, and 13,867 for major CV events.

These cases were matched to 414,782, 344,041, 295,548 and 138,560 controls, respectively. The characteristics of all-cause hospitalization cases and matched controls are presented in Table 2. For the all-cause hospitalization group, most of the cases and matched controls (36.40% and 36.46%) were in the 70–79 years age group, 53.17% of cases and 53.15% of matched controls were men and 30.89% of cases and 30.92% of controls had no comorbidity at cohort entry or in the 365 days before, 69.11% of cases vs 72.59% of controls were on metformin monotherapy, and the majority (71.62% vs 75.02%, respectively) did not add or change antidiabetic drug during follow-up.

Depression was diagnosed in 2.5% of patients hospitalized for any cause (all-cause hospitalizations cases) and 1.2% of matched controls. Non-persistence was similar in cases and controls (30.1% and 29.6%, respectively). Associations between depression and all-cause hospitalizations were significant regardless of the adjustment level of the model (Table 1). In the multivariable analysis, depression was associated with an increased risk for all-cause hospitalizations, with adjusted odds ratios (ORs) of 1.32 (95% CI: 1.22–1.44) or 1.70 (95% CI: 1.59–1.83) according to the model adjustment (Table 1). Results were consistent in sensitivity analyses changing depression definition, non-persistence definition (results not shown), or in older individuals' subgroup (Table 3).

Specific hospitalization results are also presented in Table 1. Briefly, we found statistically significant results in the univariate model for major CV events hospitalization and any CV-related hospitalizations with an OR of 1.49 (95% CI: 1.33–1.66) and 1.29 (95% CI: 1.18–1.40), respectively. When we adjusted for sociodemographic and medical conditions that occurred in the year before antidiabetic drug initiation (model A), we obtained an OR of 1.23 (95% CI: 1.09–1.38) for major CV hospitalizations and 1.13 (95% CI: 1.03–1.23) for CV-related hospitalizations. The results were no longer significant in the model adjusted for the Elixhauser comorbidity index during follow-up (model B). Similar results were obtained in the sensitivity analyses, except for any CV-related hospitalizations, for the 65 years and above, where significance was not reached (Table 3 for all-cause and specific-cause hospitalizations for those having 65 years and above). Depression was not associated with diabetes-related hospitalizations, neither in univariate nor in multivariable analysis. The lack of association was consistent in different models and the sensitivity analyses (results not shown).

Discussion

The main result of this large nested-case control study is that depression is independently associated with an increased likelihood of all-cause hospitalizations even when adjusting for non-persistence with antidiabetic drugs and other medical conditions. Moreover, we found that depression is also associated with an increased likelihood of CV-related hospitalizations and major CV event hospitalizations. Dissimilarly, we did not find associations between depression and diabetes-related hospitalizations. These results are in line with those in people with diabetes and bipolar disorder, for which the presence of these conditions increases the risk of rehospitalization regardless of the hospitalization-cause [34]. Therefore, it is not surprising that depression has the same effect. To our knowledge, no other studies have assessed the impact of depression on hospitalization in type 2 diabetes. Still, some studies have evaluated the impact of depressive symptoms on specific diseases that can lead to hospitalization. In Japanese patients with type 2 diabetes, the severity of depressive symptoms was significantly associated with severe hypoglycemia, ischemic heart disease and stroke after adjusting for confounding factors [35]. Those conditions often lead to hospitalization, but this information was not explicitly reported in the study [35]. In another study conducted in China, in patients with type 2 diabetes, more depressive symptoms were associated with hospitalizations [31], which is in line with our results on all-cause hospitalizations.

Table 2
Characteristics of all-cause hospitalization cases and matched controls .

Characteristics	Cases No (%)		Controls No (%)	
	n = 41,550		*n* = 414,782	
Age				
18–24 years	132	(0.3)	1231	(0.3)
25–29 years	227	(0.6)	2202	(0.5)
30–34 years	338	(0.8)	3321	(0.8)
35–39 years	524	(1.3)	5200	(1.3)
40–44 years	823	(2.0)	8175	(2.0)
45–49 years	1259	(3.0)	12,583	(3.0)
50–54 years	1983	(4.8)	19,817	(4.8)
55–59 years	2968	(7.1)	29,674	(7.2)
60–64 years	4185	(10)	41,841	(10)
65–69 years	7341	(18)	73,404	(18)
70–74 years	8346	(20)	83,451	(20)
75–79 years	6776	(16)	67,755	(16)
80–84 years	4146	(10)	41,429	(10)
85–89 years	1896	(4.6)	18,850	(4.5)
90 years and above	606	(1.5)	5849	(1.4)
Sex				
Men	22,091	(53)	220,453	(53)
Elixhauser comorbidity index in the 1-year before cohort entry				
0 comorbidity	12,834	(31)	128,256	(31)
1 comorbidity	14,158	(34)	141,492	(34)
2 comorbidities	6892	(17)	68,738	(17)
>= 3 comorbidities	7666	(18)	76,296	(18)
Socioeconomic status at cohort entry				
High	21,451	(52)	228,425	(55)
Medium	13,150	(33)	124,074	(30)
Low	6949	(17)	62,283	(15)
Area of residence at cohort entry				
Rural	8906	(21)	82,198	(20)
Urban	32,545	(78)	331,843	(80)
Unknown	99	(0.2)	741	(0.2)
Number of different drugs claimed in the 1-year before cohort entry				
0 – 3	10,969	(26)	125,315	(30)
4 – 7	13,252	(32)	144,396	(35)
8 – 48	17,329	(42)	145,071	(35)
Number of physician visits in the 1-year before cohort entry				
0	10,622	(25)	135,189	(33)
1 – 3	13,065	(31)	133,165	(32)
4 – 192	17,863	(43)	146,428	(35)
Anxiety disorders during follow-up				
Yes	4684	(11)	34,112	(8.2)
Cognitive impairment during follow-up				
Yes	2663	(6.4)	6852	(1.7)
Depression during follow-up				
Yes	1043	(2.5)	4796	(1.2)
Non-Persistence with antidiabetic drugs				
Yes	12,500	(30)	122,605	(30)
Treatment regimen at cohort entry				
Metformin monotherapy	28,716	(69)	301,084	(73)
Monotherapy other than metformin	10,370	(25)	93,837	(23)
Combination therapy without insulin	2295	(5.5)	18,560	(4.5)
Combination therapy with insulin	169	(0.4)	1301	(0.3)
Specialty of the first antidiabetic drug prescriber				
General practitioner	34,720	(84)	356,032	(86)
Specialist	6745	(16)	57,434	(14)
Unknown	85	(0.2)	1316	(0.3)
Modification of the antidiabetic drug treatment during follow-up				
No additions	29,758	(72)	311,183	(75)
Adding OAD only	10,955	(26)	99,164	(24)
Adding insulin only	296	(0.7)	1269	(0.3)
Addition of OAD and insulin	541	(1.3)	3166	(0.8)
Elixhauser comorbidity index during follow-up				
0 comorbidity	2502	(6.0)	160,677	(39)
1 comorbidity	6953	(17)	140,252	(34)
2 comorbidities	9194	(22)	69,856	(17)
>= 3 comorbidities	22,901	(55)	43,997	(11)

Cohort entry: date of the first antidiabetic drug prescription.

Table 3
Univariate and multivariable conditional logistic regression analyses of the association between depression and all-cause and specific-cause hospitalization among patients 65 years and above.

	Unadjusted			Model A*			Model B*		
	OR	95% CI	*P*-value	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
All-cause hospitalization (29,111 cases and 290,738 controls)									
Depression (yes vs no)	2.18	1.99–2.38	<0.0001	1.61	1.46–1.77	<0.0001	1.22	1.10–1.36	0.00
Diabetes-related hospitalization (16,238 cases and 162,363 controls)									
Depression (yes vs no)	0.89	0.79–1.01	0.07	0.89	0.78–1.01	0.06	0.88	0.77–1.00	0.05
Cardiovascular-related hospitalization (24,418 cases and 243,965 controls)									
Depression (yes vs no)	1.27	1.13–1.42	<0.0001	1.11	0.99–1.24	0.08	0.93	0.83–1.04	0.22
Major cardiovascular event hospitalization (10,404 cases and 103,968 controls)									
Depression (yes vs no)	1.57	1.38–1.80	<0.0001	1.28	1.11–1.46	0.00	1.10	0.96–1.27	0.17

OR: odds ratio; aOR: adjusted odds ratio; CI: confident interval. *Model A: adjusted for socioeconomic status; area of residence; treatment regimen of first antidiabetic drug prescription; specialty of the first antidiabetic drug prescriber; modification of the antidiabetic drug treatment; non-persistence with antidiabetic drugs; number of physician visits in the year before cohort entry; number of different drugs in the year before cohort entry; diagnosis of anxiety disorder during follow-up; diagnosis of cognitive impairment during follow-up. Model B: adjusted for the same variables as Model A, plus the Elixhauser comorbidity index during follow-up.

Depression was also associated with a 2–3-fold increase in the risk of incident CV disease, especially stroke [36], and with more hospitalization days per year [36]. In patients with diabetes, comorbid depression is associated with an increased all-cause and cardiovascular mortality [19, 37]. The increased risk of all-cause and cardiovascular-related hospitalization we found follows a similar path, and our results on cardiovascular-related and major CV events-related hospitalizations are thus in line with these studies. The co-occurrence of type 2 diabetes and depression is indeed associated with an increased risk of coronary heart disease and stroke [38]. Nevertheless, we did not find any significant association between depression and diabetes-related hospitalizations. The ORs for the increased risk of hospitalizations are in the same order of magnitude as those for increased risks of mortality in diabetic patients with depression found in a previous study [19]. When specific mortality causes were assessed in that study, only diabetes-related mortality was not significantly associated with mortality [19]. We found the same non-significant results with diabetes-related hospitalizations. In a recent meta-analysis, depression was associated with an increased risk of diabetes macrovascular and microvascular complications [39]. However, in that review, five studies were unsuitable for the meta-analysis. Of these studies, two failed to find an association between depression and microvascular complications [39]. Since macrovascular complications (e.g., stroke, myocardial infarction) are at higher risk to require hospitalization than microvascular ones (e.g., retinopathy, neuropathy, diabetic foot), our results on diabetes-related hospitalization may be explained by these different risks. Indeed, among the ICD-10 diabetic complications included in this study, E11.0 (coma) is the one with the highest risk of requiring hospitalization but is also the less frequent one. Anyway, the reasons for this lack of association with diabetes-related hospitalizations remain uncertain, and further studies will be needed to elucidate this association. However, we cannot exclude that the lack of association in specific-cause hospitalization could be partly explained by a possible over-fitting of the models (especially Model B). Some covariables may indeed have acted as intermediate variables driving the association toward the null [40].

When limiting the analysis to the 65 years and above in assessing specific-cause hospitalizations, we found that, for CV-related hospitalizations, the results were no more significant in the fully adjusted model (model B, Table 3). Since cardiovascular disease prevalence increases with age [41], other factors than depression (i.e., other psychological factors or cardiovascular risk factors) may drive the risk of hospitalizations in this specific subgroup of patients.

Our results raise the question of how to prevent hospitalizations and improve care. A randomized controlled trial on Chinese subjects with type 2 diabetes showed that improving negative emotions and peer support reduced hospitalization, partly mediated by improving treatment adherence [31]. Nevertheless, in our study, adjusting for non-persistence to antidiabetic drugs did not change the association between depression and hospitalization as instead hypothesized. In a previous study, we found that depression was associated with an increased likelihood of non-persistence with antidiabetic drugs [18]. Still, non-persistence rates were noticeably high also in diabetic patients without depression [18]. Likewise, non-persistence to antidiabetic drugs was similar between cases and controls in the current study, suggesting that depression contributes to hospitalization through a pathway only marginally related to non-persistence to antidiabetic drugs. The increase in hospitalizations among type 2 diabetes patients with depression could be reduced with appropriate interventions targeting depressive symptoms [42, 43]. A 12-week intervention of integrated management of depression and diabetes to increase adherence was effective in improving HbA1c, with 61% of patients receiving the intervention achieving an HbA1c < 7% (vs. 36% of those in the control group) [44]. The intervention was also effective on depressive symptoms and medication adherence, but mortality and hospitalizations were not reported [44]. Moreover, studies on non-pharmacological treatment like cognitive behavioral therapy (CBT) and physical exercises suggest these interventions are the most promising since they can help manage both depression and blood glucose [45].

Strengths and limitations

Our study has several strengths, including a large and representative cohort of subjects newly treated with antidiabetic drugs and having experienced an hospitalization during the 8-year follow-up period. The population represents all publicly insured citizens, which corresponds to about 46% of Quebec's population. The subgroup results on patients having 65 years and above are also highly generalizable since the public drug plan automatically includes all Quebec residents at the age of 65. This means that the public drug plan covers virtually all seniors. Another strength is the design, a case-control study nested in a cohort, including all the eligible cases. This choice minimized the risk of immortal time bias, as suggested by methodological studies [46, 47], and permitted to estimate adjusted ORs that could be interpreted as rate ratios [48] because of the use of a risk-set which randomly assigned up to 10 matched controls to every case.

Lastly, the exposure variable, depression, was objectively measured. This avoided bias due to nonresponse, selection of controls in classical case-control studies, or recall bias. We also performed different sensitivity analyses, which confirmed the robustness of the results. Finally, we used the diagnostic codes of depression in the RAMQ databases, which are accurate and valid and are frequently used for research purposes [23, 49].

Nevertheless, this study also has some caveats. Even if the measure of depression was objective, we did not use the structured clinical interview for diagnosis but a validated algorithm [30]. This means that people need to 1) seek consultation for their depressive symptoms and 2) receive a diagnosis or treatment to be considered affected by depression. People are not always consulting for their symptoms, and depression is possibly underdiagnosed in primary care settings [50]. Moreover, our database does not capture psychotherapy, which is part of the first-line treatment of depression [43]. We could have thus missed some cases of depression and misclassified some people exposed to depression as not exposed because of the lack of diagnosis or treatment. Indeed, past studies in type 2 diabetes patients reported similar incidence rates of diagnosed depression [13, 51], and only one study in Quebec reported a higher incidence, but it considered symptoms instead of a formal diagnosis and identified both minor and major depressed patients [52]. Therefore, the individuals classified as exposed to depression could be more severe cases. Besides, when assessing non-persistence, we assumed that all antidiabetic medications claimed were consumed, thus probably overestimating real persistence. Nevertheless, persistence rates did not differ between case and controls. Because of the nature of the administrative data, it was not possible to account for some cardiovascular risk factors such as lipid levels, blood pressure, body mass index, smoking status, physical inactivity, or social status, which could be confounding or modifying variables. Finally, we identified patients with type 2 diabetes by medication use. This may limit the generalizability of the results only to newly pharmacologically treated diabetic patients.

Conclusion

Depression was associated with an increased risk of all-cause and CV-related hospitalizations in type 2 diabetes patients despite adjusting for non-persistence, age, and other potential confounders. These results stress the impact of depression on diabetic patients' use of health care resources. Clinicians should be aware of the increased risk of depression in patients with type 2 diabetes and its effects on health outcomes such as hospitalization. Depression is a treatable disease, and its treatment could reduce hospitalizations in type 2 diabetes [1, 39], especially by decreasing cardiovascular morbidity, but further studies are needed. Clinicians should regularly screen for depression [45] and make appropriate interventions to reduce these risks as recommended by guidelines. These include psychotherapy [43], pharmacotherapy [42], and monitoring blood glucose levels cautiously [53] during the depression episode and thereafter without neglecting prevention related to cardiovascular disease [54]. Further studies are needed to clarify the link between depression and hospitalizations and the effectiveness of depression treatment on diabetic and mental health outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was approved by the Ethics Review Board of the CHU de Québec-Université Laval Research Center. The Quebec Information access commissioner (*Commission d'accès à l'information du Québec*) agreed on our request to the RAMQ to use the data of the current study.

Supplementary materials

Supplementary material associated with this article (Fig. S1) can be found, in the online version, at http://www.scincedirect.com at doi:10.1016/j.diabet.2022.101334.

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