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ORIGINAL ARTICLE

Dipeptidyl peptidase-4 inhibitors and the risk of community-acquired pneumonia in patients with type 2 diabetes

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Aims: To determine whether the use of dipeptidyl peptidase-4 (DPP-4) inhibitors is associated with an increased risk of community-acquired pneumonia.
Methods: The UK Clinical Practice Research Datalink and the Hospital Episodes Statistics database were used to conduct a nested case–control analysis within a cohort of new users of antidiabetic drugs between 2007 and 2012. Incident cases of hospitalization for community-acquired pneumonia were matched with up to 20 controls on age, duration of treated diabetes, calendar year and duration of follow-up. Conditional logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for hospitalization for community-acquired pneumonia associated with current use of DPP-4 inhibitors compared with current use of two or more oral antidiabetic drugs.
Results: The cohort included 49 653 patients, of whom 562 were hospitalized for community-acquired pneumonia during follow-up (incidence rate 5.2/1000 person-years). Compared with current use of two or more oral antidiabetic drugs, current use of DPP-4 inhibitors was not associated with an increased risk of hospitalized community-acquired pneumonia overall (adjusted OR 0.80, 95% CI 0.50–1.29) or according to duration of use (p for trend = 0.57).
Conclusions: The use of DPP-4 inhibitors was not associated with an increased risk of hospitalization for community-acquired pneumonia. Additional research is needed to assess the association between these drugs and other serious infections.
Keywords: database research, DPP-IV inhibitor, pharmaco-epidemiology, type 2 diabetes

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral hypoglycaemic agents used to treat type 2 diabetes. These drugs increase glucagon like peptide-1 (GLP-1) endogeneous levels by inhibiting the DPP-4 enzyme (also known as CD26), which in turn increases glucose-stimulated insulin secretion and decreases glucagon release [1]. In addition to its role in glucose regulation, the DPP-4 enzyme has been shown to have pleiotropic effects [2]. It is expressed on the surface of leukocytes and stimulates inflammatory immune responses by modifying the production of several cytokines [2–5]. Consequently, it is hypothesized that DPP-4 inhibitors could alter the immune response and thus may play a role in the occurrence of infections. This hypothesis is supported by meta-analyses of randomized controlled trials and an adverse event database analysis, which found an association between DPP-4 inhibitors and an increased risk of infections, such as those of the respiratory and urinary tracts [6–8]. In addition, a meta-analysis of eight randomized controlled trials found a 29% increased risk of any infection with the DPP-4 inhibitor sitagliptin [9].

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Lower respiratory tract infections, such as community-acquired pneumonia, are common in patients with diabetes [10], and are associated with a high mortality [11–14]. Although the association between DPP-4 inhibitors and infections in general has been studied previously, their effects on the risk of community-acquired pneumonia remain poorly understood. We therefore conducted a population-based study to determine, in a real-world setting, whether the use of DPP-4 inhibitors was associated with an increased risk of community-acquired pneumonia in a large population-based cohort of patients with type 2 diabetes.

Materials and Methods

Data Sources

The present nested case–control analysis was conducted by linking the UK Clinical Practice Research Datalink (CPRD) and the Hospital Episodes Statistics (HES) database. The CPRD is used to record demographic characteristics, diagnoses and drug prescriptions issued by general practictioners for >13 million individuals in 680 general practices [15]. Diagnoses and procedures recorded in the CPRD are based on the Read classification, and prescriptions written by general practitioners are based on the UK Prescription Pricing

Authority Dictionary. Data collected in the CPRD have been validated and are of high quality [16]. Since 1997, the English CPRD practices can be linked to the HES database, which collects information on dates of hospital admissions, procedures and discharge diagnoses [coded using the International Classification of Diseases, 10th revision (ICD-10)].

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 13_034RA2) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

Base Cohort. All patients aged ≥18 years and newly treated with a non-insulin antidiabetic drug (metformin, sulphonylureas, prandial glucose regulators, thiazolidinediones, acarbose, DPP-4 inhibitors and GLP-1 analogues) between 1 January 1988 and 31 March 2012 were identified. We excluded patients initially treated with insulin, as these represent patients with type 1 diabetes or an advanced type 2 diabetes. We also excluded patients with a history of polycystic ovarian syndrome, as this is another known indication for metformin. All patients were required to have at least 1 year of baseline medical history in the CPRD before their first non-insulin prescription.

Study Cohort. Within the base cohort defined above, we assembled a study cohort composed of all patients who began taking a new antidiabetic drug on or after 2007 (the year the first DPP-4 inhibitor, sitagliptin, was licensed in the UK). These patients included those newly treated with a non-insulin antidiabetic drug, as well as those who switched or added-on an antidiabetic drug not previously used in the patient's treatment history. Study cohort entry was defined by the date of this new prescription. We excluded all patients diagnosed with a lower respiratory tract infection, as well as those hospitalized for any cause (with a length of stay ≥2 days) in the 30 days before cohort entry, to ensure that cases of pneumonia were community-acquired. We also excluded patients with a history of any cancer (except non-melanoma skin cancer) at any time before cohort entry and those with prescriptions for antituberculosis drugs in the year before cohort entry.

All patients meeting the study inclusion criteria were followed until a hospitalization for community-acquired pneumonia or censoring attributable to any hospitalization lasting ≥2 days, death from any cause, end of registration with the general practice, end of HES linkage or end of the study period (31 March 2012), whichever came first.

Case–Control Selection

A nested case–control analysis was performed within the study cohort defined above. Cases consisted of patients hospitalized for community-acquired pneumonia, defined as a hospitalization for pneumonia (ICD-10 codes: B01.2, B05.2, B20.6, B25.0, J10.0, J11.0, J12-J18, J85.1, U04, U04.9) recorded in the HES database in primary or secondary position within the first 2 days of the admission. Our case definition was restricted to the first 2 days of admission to ensure that cases were community-acquired and not nosocomial pneumonia. Only hospitalizations with a length of stay >1 day were included as cases, except for patients who died on their admission date. The index date was defined as the case's date of hospital admission.

Each case was randomly matched, using risk-set sampling, with up to 20 control subjects selected from patients in the cohort [i.e. who at the time of the case's event (or index) date, were still at risk of developing the outcome]. Controls were matched to cases on age (±1 year), duration of treated diabetes (time from the first non-insulin antidiabetic prescription to cohort entry ±90 days), year of study cohort entry and duration of follow-up. For 17 cases, the matching criteria were relaxed using larger calipers for year of study cohort entry (±1 year), age (±5 years) and duration of treated diabetes (±90 days). The controls were assigned the index date of their respective case.

Exposure Definition

Exposure to antidiabetic drugs was assessed at the index date and defined hierarchically according to the following six mutually exclusive categories: (i) current use of a DPP-4 inhibitor, such as sitagliptin, saxagliptin, vildagliptin or linagliptin; (ii) current use of a GLP-1 analogue, such as exenatide or liraglutide; (iii) current use of insulin; (iv) current use of two or more oral antidiabetic drugs; (v) current use of an oral antidiabetic agent in monotherapy; and (vi) no current use of an antidiabetic agent at index date. For all categories above, current use was defined by a prescription duration plus a 30-day grace period that overlapped with the index date. The reference category for all analyses consisted of patients currently using two or more oral antidiabetic agents.

Potential Confounders

All models were adjusted for the following potential confounders measured at study cohort entry: sex, body mass index (BMI), glycated haemoglobin (HbA1c) concentration, excessive alcohol use (based on diagnoses for alcohol-related disorders, such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), smoking, number of physician visits in the previous year, history of pulmonary comorbidities (lower respiratory tract infection, asthma, chronic obstructive pulmonary disease, bronchiectasis; assessed in the year before cohort entry), diabetic arterial complications (retinopathy, neuropathy, nephropathy, peripheral arteriopathy, myocardial infarction, stroke), use of antidiabetic drugs (metformin, sulphonylureas, thiazolidinediones, insulins and other agents; assessed in the year before cohort entry), use of immunosuppressive agents, inhaled bronchodilators, inhaled corticosteroids, non-topical antibiotics, non-topical corticosteroids (assessed in the year before cohort entry), and use of influenza or pneumococcal vaccines (assessed in the year before cohort entry). Variables with missing information were coded as 'unknown' [17].

Statistical Analysis

Primary Analysis. Descriptive statistics were used to summarize the characteristics of the cases and matched controls. A crude incidence rate, with 95% confidence intervals (CIs) based

on the Poisson distribution, was calculated by dividing the number of patients hospitalized for community-acquired pneumonia over the person-time at risk. Conditional logistic regression models were used to estimate odds ratios (ORs) with 95% CIs of hospitalized community-acquired pneumonia associated with current use of DPP-4 inhibitors, compared with current use of two or more oral antidiabetic agents. This analysis was considered to be the primary analysis.

Secondary Analyses. We performed three secondary analyses. First, we evaluated whether the risk varied with duration of treatment among current users of DPP-4 inhibitors. Patients were considered continuously exposed if the duration of one prescription overlapped the date of the subsequent prescription, allowing for a 30-day grace period between two successive, non-overlapping prescriptions. Second, we analysed the risk of hospitalized community-acquired pneumonia for each type of DPP-4 inhibitor. Third, we assessed whether duration of treated diabetes modified the association between current use of DPP-4 inhibitors and hospitalized community-acquired pneumonia. For that analysis, an interaction term between exposure and duration of treated diabetes was included in the regression model.

Sensitivity Analyses. We conducted seven sensitivity analyses. First, we repeated the primary analysis using grace periods of 0 and 90 days. Second, to assess the choice of our exposure groups, we compared the current use of DPP-4 inhibitors with all possible antidiabetic drug combinations that did not include a DPP-4 inhibitor. Third, we conducted analyses using a subcohort of patients who did not receive insulin (a marker of increased severity of diabetes) or thiazolininediones (which have previously been associated with pneumonia) [18] before cohort entry and for whom we also censored the follow-up time at the first prescription of insulin or thiazolininediones. Fourth, we repeated our primary analysis using the combination of metformin and sulphonylureas as the reference group. Fifth, the hierarchical classification of exposure was reordered, considering exposure to insulin first, thiazolininediones second and then DPP-4 inhibitors. Sixth, to assess the robustness of our outcome defintion, we repeated our analyses with our case series restricted to those identified in the HES database by an ICD-10 code in primary position only. Finally, to study the effect of the time of covariate measurement, we repeated our analyses with models adjusted for potential confounders measured at index date instead of cohort entry. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Primary Analysis

The study cohort included 49 653 new users of antidiabetic agents as of 2007 (Figure 1). The mean [standard deviation

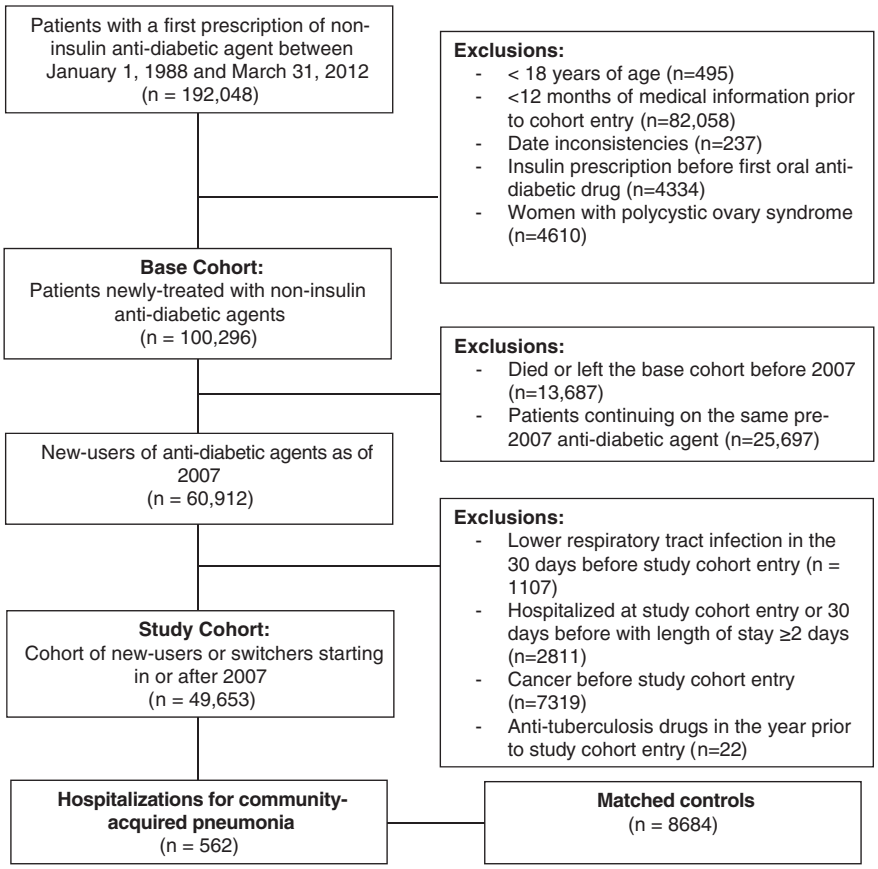

Figure 1. Study flow chart.

Table 1. Baseline characteristics of cases of hospitalized community-acquired pneumonia and matched controls.

Baseline characteristics	Cases n = 562	Controls n = 8684
Age, years, mean (s.d.)	68.4 (13.1)	68.4 (13.1)
Males, n (%)	319 (56.8)	4725 (54.1)
Duration of treated diabetes, years, mean (s.d.)	1.9 (3.3)	1.9 (3.3)
Year of cohort entry, n (%)		
2007	183 (32.6)	2821 (32.2)
2008	146 (26.0)	2172 (27.0)
2009	110 (19.6)	1718 (19.0)
2010	80 (14.2)	1282 (14.3)
2011	S	671 (7.3)
2012	S	20 (0.2)
Body mass index, n (%)		
≤25 kg/m^2	106 (18.9)	1209 (15.3)
26–30 kg/m^2	173 (30.8)	2885 (33.1)
>30 kg/m^2	265 (47.2)	4364 (49.5)
Unknown	18 (3.2)	226 (2.2)
Excessive alcohol use, n (%)	111 (19.8)	1021 (11.8)
Smoking status, n (%)		
Ever	415 (73.8)	5242 (59.9)
Never	S	3394 (39.7)
Unknown	S	48 (0.4)
>4 physician visits in the year before cohort entry, n (%)	556 (98.9)	8366 (97.1)
HbA1c categories, n (%)		
≤7% (53 mmol/mol)	78 (13.9)	1207 (12.9)
7.1–8% (54–64 mmol/mol)	150 (26.7)	2677 (31.2)
>8% (64 mmol/mol)	240 (42.7)	3345 (42.7)
Unknown	94 (16.7)	1455 (13.3)

HbA1c, glycated haemoglobin; S, suppressed as at least one cell has a count <5; s.d., standard deviation.

(s.d.)] age of the study subjects was 59.6 (13.3) years, 58.2% were males, and the mean (s.d.) duration of treated diabetes before entry to the study cohort was 1.5 (3.0) years. The baseline characteristics of the study cohort are summarized in Table S1. The study cohort was followed for a mean (s.d.) of 2.2 (1.5) years, generating a total of 106 718 person-years of follow-up. Overall, a total of 562 patients were hospitalized for community-acquired pneumonia during follow-up, generating an incidence rate of 5.2/1000 (95% CI 4.9–5.7) person-years.

The characteristics of the cases and matched controls are shown in Table 1. Other baseline conditions and medications are shown in Table S2. Cases and controls were similar in terms of BMI, HbA1c concentration, use of oral antidiabetic agents and microangiopathic complications of type 2 diabetes (retinopathy, neuropathy and nephropathy). By contrast, compared with controls, cases were more likely to have smoked, to have used alcohol excessively, and to have a history of myocardial infarction, stroke, peripheral arteriopathy and pulmonary comorbidities (lower respiratory tract infection, asthma, chronic obstructive pulmonary disease, bronchiectasis). For both cases and matched controls, the mean (s.d.) duration of follow-up was 1.5 (1.2) years.

The results of the primary and secondary analyses are shown in Table 2. After adjustment for potential confounders, current use of DPP-4 inhibitors was not associated with an increased risk of hospitalized community-acquired pneumonia, when compared with current use of two or more oral antidiabetic agents (adjusted OR 0.80, 95% CI 0.50–1.29). There was no evidence of a duration–response relationship, with no OR found to be statistically significant and all ORs under the null value (p for trend = 0.57). In terms of individual DDP-4 inhibitor types, no single agent was associated with an increased risk of hospitalized community-acquired pneumonia. Finally, there was no evidence that the association varied with duration of treated diabetes (<5 years, adjusted OR 0.79, 95% CI 0.44–1.41; ≥5 years, adjusted OR 0.91, 95% CI 0.40–2.09; p for interaction = 0.17).

Sensitivity Analyses

As with our primary analyses, none of the sensitivity analyses revealed an association between the use of DPP-4 inhibitors and the risk of hospitalized community-acquired pneumonia (Tables S3–S9).

Discussion

The results of this large population-based study indicate that the use of DPP-4 inhibitors when compared with the use of other oral antidiabetic agents is not associated with an increased risk of hospitalized community-acquired pneumonia. Similar null findings were observed in secondary analyses, and the results remained robust in a number of sensitivity analyses. To date, our study is the first observational study using a large population-based cohort to assess the association between DPP-4 inhibitors and the risk of community-acquired pneumonia.

Our null findings contrast with experimental data suggesting an immunomodulatory effect of DPP-4 inhibitors. Indeed, in addition to the GLP-1, other regulatory peptides, including cytokines and chemokines, are substrates of DPP-4/CD26 [2–4]. Thus, DPP-4/CD26 is thought to enhance T-cell activation [19], and studies have suggested that DPP-4 inhibition suppresses DNA synthesis of mononucleocytes and T-cells *in vitro* [4]. This leads to the upregulation of the immunosuppressive cytokine transforming growth factor-β1 and the inhibition of T-cells in mice [5]; however, these findings are not supported by a recent *in vitro* and *in vivo* study [20]. In addition, there are mechanistic differences between sitagliptin and vildagliptin with regard to markers of oxidative stress and systemic inflammation [20–22], such that differential modification of immune responses within the class of DPP-4 inhibitors cannot be excluded. In the present study, with 22 of 25 cases exposed to sitagliptin, there were insufficient data to conclusively examine the risk of hospitalized community-acquired pneumonia by type of DPP-4 inhibitor.

Within the World Health Organization pharmacovigilance database (VigiBase), the reporting of infections was higher for patients using DPP-4 inhibitors than for users of metformin (reporting OR 2.3, 95% CI 1.9–2.7), with a stronger association for upper respiratory tract infections (reporting OR 12.3, 95% CI 8.6–17.5) [8]; however, given the numerous biases

Table 2. Risk of hospitalization for community-acquired pneumonia according to current exposure to antidiabetic agents.

Current exposure*	Cases n = 562	Controls† n = 8684	Crude OR (95% CI)	Adjusted OR‡(95% CI)
≥2 oral anti-diabetic agents, n (%)	149 (26.5)	1708 (19.7)	1.00 (reference)	1.00 (reference)
DPP-4 inhibitors, n (%)	25 (4.5)	336 (3.9)	0.77 (0.49–1.23)	0.80 (0.50–1.29)
Duration of DPP-4 inhibitor use§ n (%)				
1–107 days	9 (1.6)	111 (1.3)	0.83 (0.40–1.75)	0.95 (0.44–2.04)
108–304 days	8 (1.4)	111 (1.3)	0.88 (0.40–1.94)	0.79 (0.35–1.77)
≥305 days	8 (1.4)	114 (1.3)	0.64 (0.30–1.39)	0.70 (0.32–1.55)
				p for trend = 0.57
Types of DPP-4 inhibitors, n (%)				
Sitagliptin	22 (3.9)	281 (3.2)	0.83 (0.51–1.36)	0.88 (0.53–1.46)
Vildagliptin	S	39 (0.5)	0.43 (0.10–1.90)	0.45 (0.10–2.00)
Saxagliptin	S	S	0.83 (0.11–6.54)	0.57 (0.06–5.02)
Linagliptin	0 (0.0)	S	—	—

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; OR, odds ratio; S, suppressed as at least one cell has a count <5.
*Current users of glucagon-like peptide 1 analogues, insulins, single oral antidiabetic drugs, and non-current users of antidiabetic drugs are not shown in the table, but were considered in the regression model for proper estimation of treatment effects (representing 388 cases and 6640 controls).
†Cases and controls were matched on age, duration of treated diabetes, calendar year of study cohort entry, and duration of follow-up.
‡Adjusted for sex, body mass index, number of antidiabetic drugs ever used, glycated haemoglobin concentration, excessive alcohol use, smoking, history of lower respiratory tract infections, use of antidiabetic drugs (metformin, sulphonylureas, thiazolidinediones, insulins and other agents), more than four physician visits in the year before cohort entry, asthma, chronic obstructive pulmonary disease or bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled corticosteroids, non-topical antibiotics, oral corticosteroids, influenza or pneumococcal vaccines.
§Duration categories based on the tertile distribution among controls.

involved in reporting adverse events, the conclusions that can be drawn from adverse events databases are limited [23]. To date, no other pharmacoepidemiological study has investigated pneumonia as an adverse outcome. A population-based cohort study of 72 738 new users of oral antidiabetic drugs between 2004 and 2009 retrieved from a large US insurance claims database, did not find any significant association between sitagliptin and upper respiratory tract infections; lower respiratory tract infections were not examined [24]. Interestingly, another recent cohort study using US insurance claims data from 2005 to 2012 provided evidence of an immunomodulating effect of DPP-4 inhibitors: the risks of incident rheumatoid arthritis and other autoimmune diseases were lower in users of DPP-4 inhibitors compared with non-users [25]. In 2008, a meta-analysis of randomized controlled trials performed by the Cochrane Collaboration, which included 3589 patients, showed a statistically significant 29% increase in all-cause infections associated with sitagliptin (no association was found for vildagliptin) [9]. In addition, two meta-analyses reported an increased risk of nasopharyngitis and of urinary tract infection [6,7]. By contrast, several recent meta-analysis of randomized controlled trials concluded that there was no increased risk of pneumonia with sitagliptin when compared with placebo or active comparators [26–28]. DPP-4 inhibitor use was not associated with an increased incidence of respiratory infections in three pooled safety analyses of randomized clinical trials (generally <2 years in duration) of sitagliptin, saxagliptin and linagliptin, which included 10 246, 9156 and 3572 patients, respectively [29–31].

The strengths of the present study include the use of a large population-based cohort for which data sources have been shown to be of high quality and provide the necessary information to account for important potential confounders (BMI, excessive alcohol use, HbA1c). The use of a base cohort of patients with diabetes followed for up to 25 years allows a comparison of patients at similar points in the natural history of the disease. We chose to focus on hospitalized community-acquired pneumonia because it is common, is associated with significant morbidity and mortality [32] and has been previously used in the HES database [33,34]. Another strength was our choice of comparator. Because DPP-4 inhibitors are used as second-/third-line therapy and as there is no pharmaceutical class available or suitable for a direct comparison, we considered the group of patients who were prescribed two or more oral antidiabetic agents as the most clinically relevant comparator group, limiting potential confounding by indication.

The present study has some potential limitations. First, as we used prescriptions by general practitioners to define drug exposure, we may have underestimated the exposure to DPP-4 inhibitors because prescriptions written by specialists were not included; however, all patients entered the study cohort based on a prescription issued by their general practitioner, and both our exposure and comparison groups consisted of patients currently exposed to antidiabetic drugs prescribed by general practitioners, suggesting that this was unlikely to have biased our results. Some misclassification of exposure is also possible as the CPRD records prescriptions that are written rather than filled and does not contain information regarding patient adherence, although there is no reason to believe that any potential lack of adherence was different between the exposure groups. Our outcome definition, restricted to hospitalized community-acquired pneumonia, underestimated the overall incidence of community-acquired pneumonia because of the exclusion of non-hospitalized patients or those with only 1 day of hospitalization. Our overall incidence rate of hospitalized

community-acquired pneumonia of 5.22/1000 person-years is less than that found in another study of patients with diabetes using the CPRD [10]. In the latter study, the rate of community-acquired pneumonia was 10.3/1000 person-years, and up to 81.4% of the cases were hospitalized. The difference is probably attributable to the fact that this previous study only included patients aged ≥65 years and also included patients with type 1 diabetes [10]. Another previous study of an administrative database from Ontario, Canada found a much higher rate of pneumonia in patients with diabetes (49.2/1000 person-years), but was based on an older population, where the outcome definition also included hospital-acquired pneumonia as well as outpatient claims for pneumonia (which could possibly include other respiratory tract infections, such as bronchitis) [35]. Although respiratory tract infections are relatively frequent in patients with diabetes, hospitalization for community-acquired pneumonia is much less common, limiting our statistical power for secondary analyses. Overall, the present study cannot exclude a modest increase (up to 29%) as well as a 50% decrease in the incidence of pneumonia. Finally, because of the observational nature of the present study and despite the adjustment for important risk factors, the possible effects of residual confounding must be considered when interpreting our results.

In summary, the present study does not support an increased risk of hospitalization for community-acquired pneumonia with the use of DPP-4 inhibitors among patients with type 2 diabetes. Nevertheless, more research is needed to determine whether DPP-4 inhibitors are associated with the risk of other serious infections.

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Conflict of Interest

The authors have no conflict of interest to declare.

J.-L. F. contributed to the study conception and design, drafted the manuscript, and contributed to the interpretation of data, and critical revision of the manuscript for important intellectual content. K. B. F., P. E. and L. A. contributed to the study conception and design, the conduct of the statistical analyses, interpretation of data and critical revision of the manuscript for important intellectual content. V. P. contributed to the statistical analyses, interpretation of data and critical revision of the manuscript for important intellectual content. L. A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of the study cohort population.

Table S2. Baseline conditions and medications of cases hospitalized for community-acquired pneumonia and matched controls.

Table S3. Risk of hospitalization for community-acquired pneumonia with current exposure to antidiabetic agents, according to varying grace period durations.

Table S4. Risk of hospitalization for community-acquired pneumonia with current exposure to antidiabetic agents in the subcohort of patients who did not receive insulin or thiazolinediones before cohort entry and censoring those who received insulin or thiazolinediones during follow-up.

Table S5. Risk of hospitalization for community-acquired pneumonia with current exposure to dipeptidyl peptidase-4 (DPP-4) inhibitors compared with all other possible antidiabetic combinations which did not include a DPP-4 inhibitor.

Table S6. Risk of hospitalization for community-acquired pneumonia with current exposure to dipeptidyl peptidase-4 inhibitor compared with the combination of metformin and sulfonylureas.

Table S7. Risk of hospitalization for community-acquired pneumonia with current exposure to antidiabetic agents when changing the hierarchical classification of exposure considering exposure to insulin first, thiazolinediones second, and then dipeptidyl peptidase-4 inhibitors.

Table S8. Risk of hospitalization for community-acquired pneumonia with current exposure to antidiabetic agents when hospitalization for community-acquired pneumonia was defined in the Hospital Episode Statistics database by a ICD-10 in primary position only.

Table S9. Risk of hospitalization for community-acquired pneumonia with current exposure to antidiabetic agents when covariates were measured at index date instead of cohort entry.

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