RESEARCH ARTICLE

Diabetes Management

Short and long-term impact of influenza infection on individuals with type 2 diabetes: Effect on healthcare utilization and diabetes complications

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ABSTRACT

Objectives: Influenza is a common and often underestimated viral infection that has been shown to trigger severe complications in high-risk patients and can lead to loss of blood glucose control in individuals with Type 2 diabetes (T2D). However, the long-term impact of influenza on this population has not been assessed very well. This study aims to examine the long-term burden of influenza infection among those with T2D, including impact on healthcare utilization and chronic diabetes-related complications.

Methods: A retrospective cohort study was conducted using US commercial claims (2015-2018). T2D patients who had experienced an influenza infection were matched 1:5 with non-infected controls. The matched cohorts were followed for one year and compared at five different time periods (four quarters of 91 days, and at full-year) by healthcare utilization, including number of outpatient, Emergency Room (ER), and inpatient hospital visits and total medical expenses. Diabetes Complications Severity Index Score (DCSI) was used to measure diabetes complications at index date and after one year.

Results: A total of 7,776 T2D patients with influenza were matched with 38,880 control patients. The cohort post-influenza infection had significantly higher total medical expenses, number of ER and outpatient visits in each time period, and increased numbers of hospitalizations in time periods Q1, Q3, and full-year. The influenza cohort also had significantly higher increase in DCSI after one year.

Conclusion: The results from this study suggest that an influenza infection may have a significant long-term impact on T2D patient morbidity, including worsening of diabetes. When estimating the burden of influenza on this population and making treatment decisions, both short- and long-term impact should be considered.

KEYWORDS

- type 2 Diabetes
- influenza
- health resources utilization
- diabetes complications severity indexc
- diabetes complications
- burden of influenza

Introduction

Influenza is a contagious viral infection of the respiratory tract that can lead to serious complications such as pneumonia [1]. It is a widespread infectious disease and the Centers for Disease Control and Prevention (CDC) estimated the 2017-2018 influenza season alone to have caused 45 million illnesses, 810,000 hospitalizations, and 61,000 deaths [2] Patients with chronic diseases such as diabetes, cardiovascular disease (CVD), asthma, or Chronic Obstructive Pulmonary Disease (COPD) are considered to be at high risk for developing severe influenza complications that can result in hospitalization and sometimes death [3].

Among comorbidities that confer a higher risk for severe influenza complications, type 2 diabetes (T2D) is of particular concern with about 7% of the US population estimated to

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have a diabetes diagnosis [4] and about 34% estimated to show signs of prediabetes [4]. Patients suffering from diabetes are at a greater risk of becoming hospitalized following an influenza infection with a three times higher mortality risk [5]. According to the CDC, about 30% of adult influenza-related hospitalizations included diabetes as a comorbidity [5]. Among those at high risk, influenza infection can trigger CVD events leading to acute myocardial infarction (MI) [6,7]. In addition, during active viral infection among diabetic patients, the metabolic situation may be further destabilized causing glycemic variability and/or a loss of control of blood glucose levels, associated with other severe complications [8,9]. In addition, loss of blood glucose control further contributes to aggravation of chronic diabetes-related microvascular complications, promoting nephropathy, neuropathy, and retinopathy, and macrovascular complications, including heart failure, stroke, and MI [10]. A retrospective cohort study that followed patients with T2D found significant increases in abnormal glucose events and ischemic heart disease following, or immediately preceding, influenza diagnosis compared to a baseline period [11].

For diabetes patients, influenza vaccines are strongly recommended by the CDC and prompt antiviral treatment is recommended in those that are experiencing an influenza infection [5]. Among T2D patients, vaccination has been shown to reduce hospitalizations and mortality [12,13] and protect against associated cardiac events [14]. However, only an estimated 61.6% of adults with diabetes received a vaccination in 2015 [15].

Influenza infection constitutes a definite morbidity burden on diabetic patients, as shown by an increased risk of death, frequent hospitalization and influenza-related complications, as compared to non-diabetic patients [5,12,16,17]. However, these studies have examined the burden of influenza on diabetic patients based on short-term outcomes during the acute influenza episode, while the long-term impact of influenza on diabetic patients has not been well-studied [16,17]. Additionally, current understanding of the risk of diabetes-associated complications following influenza infection is limited to case studies [8,9]. Therefore, to inform best practices for the prevention, treatment and management of diabetes following influenza infection, there is a need to further examine the burden of influenza on these patients over a long-term period.

The objective of the current study was to measure the short- and long-term burden of influenza infection among T2D patients. This study examines the impact of influenza infection on healthcare utilization and diabetes-related complications among T2D patients over one year.

Methods

Study design

IBM MarketScan® US commercial claims database was used to conduct a retrospective cohort study of T2D patients with influenza during the 2016-2017 influenza season compared to a propensity score matched population of similar T2D patients without influenza. Health resource utilization outcomes, including diabetes-related complications, were compared over the year following influenza infection. The MarketScan® database includes over 250 million de-identified patients with medical and drug claims from more than 300 large self-insured US employers and 25 US health plans [18].

Patients included in the study were age 18 or older at study start date, had continuous enrollment data 12 months before study start date and 12 months after the index influenza episode, and had a diagnosis of T2D prior to study start date. The study start date was October 1, 2016. T2D patients were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes [19,20]. Diagnosis of T2D was defined using a previously validated algorithm as those with at least two outpatient claims within two years or one inpatient claim that included a diagnosis of T2D, and at least one prescribed antihyperglycemic drug during the 12 months prior to the start of the study [21]. Patients with a type 1 diabetes diagnosis code were excluded.

Patients with T2D that were diagnosed with influenza between October 2016 to April 2017 were propensity-score-matched with similar T2D patients that were not diagnosed with influenza (see below for matching covariates). Propensity score matching was used to adjust for covariates, with a one-year look back period of October 1, 2015 to October 1, 2016. The

index date was assigned after matching. For the influenza cohort, each patient's index date was defined to be the date of their influenza diagnosis. Matched controls were assigned the same index date as their corresponding influenza patient. Outcomes were collected for one year following the index date.

Study variables

A propensity score model was developed using a number of covariates that predict risk of receiving an influenza diagnosis, including age, number of conditions considered to be high risk for severe influenza complications, diabetes complications severity index (DCSI) score, sex, region, health plan type, reported to receive influenza vaccine, diabetes drug classification, prior-year hospitalization, and prior-year Emergency Room (ER) visit. A comorbidity index was not used because of overlap with the DCSI and number of conditions considered to be at high risk for severe influenza complications.

Conditions considered to be high risk for severe influenza complications (in addition to endocrine disorders) was based on the CDC definition that included neurologic disorders, blood disorders, liver disease, pulmonary disorders, heart disease, kidney disease, and obesity [3]. DCSI is a 14-level metric quantifying the severity of diabetes complications, including scores for cardiovascular, retinopathy, nephropathy, neuropathy, cerebrovascular, peripheral vascular disease, and metabolic complications. The DCSI has been previously validated for utilization in claims analysis to quantify severity of diabetes and updated using ICD-10 codes [22,23].

Diabetes drug classification is a metric to gauge the severity of diabetes based on the class of diabetes drug the patient is taking, according to the American Diabetes Association diabetes pharmacologic step-therapy guidelines [24]. Patients taking only metformin and no other anti-hyperglycemic drugs were considered to be Category one. Patients on antihyperglycemics other than or in addition to metformin were considered to be Category two, and patients using insulin were considered to be Category three regardless of other comedications. Drugs were identified using National Drug Codes (NDC) [25].

Study outcomes

Outcomes of interest included metrics of healthcare utilization and changes in chronic diabetes-related complications throughout the year following influenza infection. Healthcare utilization consisted of number of hospitalizations, number of outpatient visits, number of ER visits, and total medical costs. Each of these four metrics were captured in total for the year and in each of the four quarters (91 days, Q1-Q4) following diagnosis of influenza. Total medical costs was defined as total costs of all outpatient, inpatient, and ER visit claims, adjusted to 2018 dollars. The change in chronic diabetes-related complications was captured by calculating the difference between the DCSI at baseline and one-year after influenza diagnosis. Individual components of the DCSI were also compared between the cohorts using the average number of new or exacerbated complications. A new complication was defined as the presence of a DCSI-classified complication category after a year of follow-up that was absent at index date. Similarly, exacerbations were defined to be an increase in the severity of the complication at one year of follow-up compared to baseline using the DCSI definitions [22].

Statistical analysis

Cases and controls were matched by propensity scores to adjust for potential confounding. The propensity model was developed predicting the propensity for diagnosis of influenza. After propensity scores were obtained, caliper matching method was used with the caliper set to 0.2 standard deviation of the logit of the propensity score. Patients with influenza were matched with patients without influenza at a one to five ratio. Following matching, the cohort balance was compared using standardized differences, with a standardized difference of less than 0.10 considered to indicate negligible correlation [26]. The pre- and post-match variables were also compared using t-tests for continuous variables and chi-squared tests for categorical variables to further assess cohort differences.

Outcomes for each time period (Q1, Q2, Q3, Q4, and full-year) were compared across the matched cohorts using t-tests. Analyses were conducted with SAS® version 9.4 (SAS Institute Inc., Cary, NC), with statistical significance set at 0.05.

Results

Population characteristics

A total of 436,550 patients met the inclusion criteria and were eligible for propensity score

matching. Of the sample, 7,776 patients had a diagnosis of influenza. Table 1 compares the influenza cohort (those that were diagnosed with influenza from October 1, 2016 to April 30, 2017) to the non-influenza cohort (those with no influenza diagnosis in the same time period). Using the standardized difference metric, characteristics that were significantly different between the cohorts were age, number of conditions considered high risk for severe influenza complications, sex, region, health plan type, and presence of a prior-year ER visit.

Propensity score model

The 7,776 diabetes patients identified with a diagnosis of influenza were matched at a one to five ratio to 38,880 diabetes patients without influenza. Because all patients in the influenza cohort were successfully matched, no influenza cases were excluded. Table 2 shows the comparison of post-match characteristics of the cohorts. After matching, no standardized differences exceeded the 0.10 threshold, indicating the cohorts were balanced.

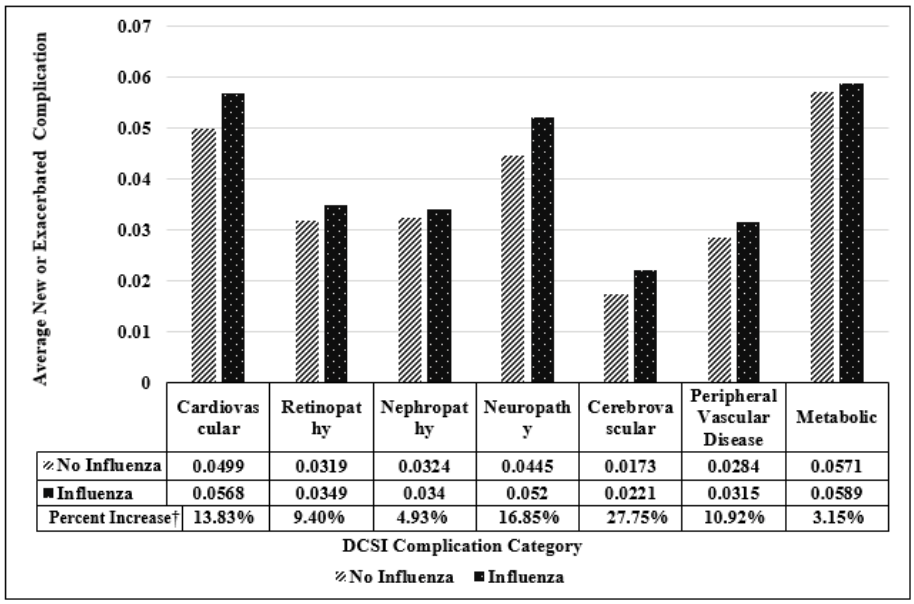
Outcomes

Following propensity score matching, healthcare utilization and change in chronic diabetes-related complications in the year following influenza infection were compared between the two cohorts. Table 3 compares the outcomes for each of the cohorts and displays the percent increase for the influenza cohort for each metric.

Table 1: Comparison of baseline demographics and characteristics between the non- influenza and influenza cohorts, among patients with type 2 diabetes.

	Non-Influenza (n=428,774)	Influenza (n=7,776)	P value*	Standardized difference†
Age (Mean, SD)	53.34 (7.62)	52.06 (8.00)	<.0001	0.163
Number of conditions considered high risk for severe influenza complications (Mean, SD)	1.27 (1.20)	1.48 (1.29)	<.0001	0.1669
Diabetes Complications Severity Score (DCSI) (Mean, SD)	1.60 (1.89)	1.62 (1.93)	0.0062	0.0311
Sex, n (%)			<.0001	0.1282
Male	222,567 (51.9%)	3,539 (45.5%)		
Female	206,207 (48.1%)	4,237 (54.5%)		
Region, n (%)			<.0001	0.3165
South	63273 (14.8%)	862 (11.1%)		
North Central	82146 (19.2%)	983 (12.6%)		
Northeast	232291 (54.2%)	5385 (69.3%)		
West	50487 (11.8%)	525 (6.8%)		
Unknown	577 (0.13%)	21 (0.27%)		
Health plan type, n (%)			<.0001	0.1064
Preferred Provider Organization (PPO)	108620 (25.3%)	1724 (22.2%)		
Health Maintenance Organization (HMO)	50327 (11.7%)	816 (10.5%)		
Other health plan / unknown	269827(62.9%)	5236 (67.3%)		
Received influenza vaccine, n (%)			0.0003	0.0413
No reported influenza vaccine	283987 (66.2%)	5301 (68.2%)		
Yes	144787 (33.8%)	2475 (31.8%)		
Drug category, n (%)			0.0968	0
Metformin only	167842 (39.1%)	2999 (38.6%)		
Other anti-hyperglycemic drugs	163092 (38.0%)	2922 (37.6%)		
Insulin	97840 (22.8%)	1855 (23.9%)		
Prior-year hospitalization, n (%)			<0.0001	0.0503
No	398284 (92.9%)	7131 (91.7%)		
Yes	30490 (7.1%)	645 (8.3%)		
Prior-year ER visit, n (%)			<0.0001	0.1629
No	348741 (81.3%)	5767 (74.2%)		
Yes	80030 (18.7%)	2009 (25.8%)		

*P value calculated using t-tests for continuous variables and Chi-squared test for categorical.
†A threshold of 0.1 was used to indicate significant differences in the mean value of the characteristic between groups.
ER: Emergency Room.



	Cardiovascular	Retinopathy	Nephropathy	Neuropathy	Cerebrovascular	Peripheral Vascular Disease	Metabolic
No Influenza	0.0499	0.0319	0.0324	0.0445	0.0173	0.0284	0.0571
Influenza	0.0568	0.0349	0.034	0.052	0.0221	0.0315	0.0589
Percent Increase†	13.83%	9.40%	4.93%	16.85%	27.75%	10.92%	3.15%

Figure 1: Average number of new or exacerbated complications for each component category of the DCSI for the influenza cohort, compared to the non-influenza cohort, after one year*

*Cohorts compared using t-test comparisons were not significant at the 0.05 level.

†Percent increase of the influenza cohort compared to the non-influenza cohort.

DCSI: Diabetes Complications Severity Index.

The influenza cohort had significantly higher average number of outpatient visits for each time period, ranging from a 41.19% increase in Q1 to a 17.23% increase in Q4. Similarly, this cohort had significantly higher number of average ER visits in each time period, ranging from a 165.77% increase in Q1 to a 28.21% increase in Q4. The influenza cohort also had a significantly higher number of average hospitalizations in Q1, Q3, and full-year time periods with an increase of 140.91%, 34.78%, and 52.22%, respectively. Additionally, this cohort had significantly higher total medical expenses in each of the time periods, ranging from a 53.16% increase in Q1 to a 14.29% increase in Q4 as shown in Figure 1.

A year after the index date, patients that had been infected with influenza had a significantly higher average DCSI score compared to the non-influenza group (increase of 6.22%) and a significantly higher average DCSI score change from baseline over patients without history of influenza (increase of 10.87%).

Discussion

To our knowledge, this is the first report examining the long-term impact of influenza on individuals with T2D. Among T2D patients, those who were diagnosed with influenza had significantly higher healthcare utilization both in the short-term after the event and also up to one year following infection compared to those that did not have influenza. These results suggest that influenza has a sustained impact on individuals with T2D beyond the initial infection and recovery period, suggesting a worsening of the underlying metabolic disease state.

The influenza cohort showed consistent increases in healthcare utilization compared to the uninfected cohort over multiple time periods. While it is known that influenza will lead to a higher healthcare utilization for individuals with T2D after infection due to increased direct medical costs and hospitalizations, the results of this study suggests augmentation of healthcare utilization extend beyond the initial infection phase for at least up to a year [5,13,17,27]. Among Q1-Q4, the largest healthcare utilization increase for the influenza cohort compared to the non-influenza cohort was the average number of ER visits, with a 36% increase in Q2 and Q3 and a 28% increase in Q4. Comparatively, average number of hospitalizations was the only healthcare utilization measure that was not significantly higher in all time periods assessed. While Q1 and Q3 showed individually statistically significant increases, Q2 and Q4 did not. A possible explanation may be that the effect size of the sustained burden of influenza is less for hospitalizations compared to outpatient and

Table 2: Comparison of post-match demographics and characteristics between the no influenza and influenza cohorts, among patients with type 2 diabetes.

	No influenza (n=38,880)	Influenza (n=7,776)	P value*	Standardized difference†
Age (Mean, SD)	52.44 (8.05)	52.06 (8.00)	0.0002	0.0472
Number of conditions considered high risk for severe influenza complications (Mean, SD)	1.450 (1.25)	1.48 (1.29)	0.0432	0.0248
Diabetes Complications Severity Score (DCSI) (Mean, SD)	1.60 (1.84)	1.62 (1.93)	0.0042	0.0349
Sex, n (%)			0.6805	0.0051
Male	17596 (45.3%)	3539 (16.7%)		
Female	21284 (54.7%)	4237 (16.6%)		
Region, n (%)			0.3617	0.041
South	4166 (10.7%)	862 (11.1%)		
North Central	4886 (12.6%)	983 (12.6%)		
Northeast	27226 (70.0%)	5385 (69.3%)		
West	2530 (6.51%)	525 (6.8%)		
Unknown	72 (0.19%)	21 (0.27%)		
Health plan type, n (%)			0.433	0
Preferred Provider Organization (PPO)	8654 (22.3%)	1724 (22.2%)		
Health Maintenance Organization (HMO)	3892 (10.0%)	816 (10.5%)		
Other health plan/unknown	26334 (67.7%)	5236 (67.3%)		
Received influenza vaccine, n (%)			0.7453	0.0413
No reported influenza vaccine	26578 (68.4%)	5301 (68.2%)		
Yes	12302 (31.6%)	2475 (31.8%)		
Drug category, n (%)			0.719	0
Metformin only	15112 (38.9%)	2999 (38.6%)		
Other anti-hyperglycemic drugs	14656 (37.7%)	2922 (37.6%)		
Insulin	9112 (23.4%)	1855 (23.9%)		
Prior-year hospitalization, n (%)			0.0084	0.0346
No	35992 (92.6%)	7131 (91.7%)		
Yes	2888 (7.4%)	645 (8.3%)		
Prior-year ER visit, n (%)			0.3817	0.0628
No	29019 (74.6%)	5767 (74.2%)		
Yes	9861 (25.4%)	2009 (25.8%)		

*P value calculated using t-tests for continuous variables and Chi-squared test for categorical.
†A threshold of 0.1 was used to indicate significant differences in the mean value of the characteristic between groups.
ER, Emergency Room.

ER visits. Another possibility is that the sample size was not large enough to achieve significance of hospitalization increases for Q2 and Q4, given that the outcome of hospitalization was rarer than ER visits and outpatient visits. An in-depth investigation of the underlying reason for hospitalizations and ER visits may reveal specific types of complications.

This study also found that T2D patients with influenza had significantly higher prevalence of new or exacerbated complications after a year of follow-up compared to T2D patients without influenza. This could be an indicator that influenza infection can result in a worsening of the underlying metabolic disease state. The increased risk of new or worsening complications is a concern for this population because individuals with type 2 diabetes are at a much greater risk of dying from cardiovascular complications compared to the general population [28]. Our data suggests that there may be a need to increase the proportion of adults with T2D receiving influenza vaccination each year. However, it is also important to note that adjusted overall seasonal influenza vaccine effectiveness is variable and ranged from 10% to 60% for seasons 2004-2018 based on CDC estimations [29]. Therefore, prompt treatment with antivirals may have additional importance in reducing the long-term risk of developing

Table 3: Comparison of the health care utilization and increase in chronic diabetes-related complications of the matched cohorts (no influenza versus influenza) in 91-day intervals (Q1-Q4), following influenza infection, among patients with type 2 diabetes.

	No influenza (n=38880)*	Influenza (n=7776)*	P value†	Percent increase for influenza cohort
Average outpatient visits: full-year	15.35 (17.04)	19.03 (18.49)	<.0001	23.97%
Average outpatient visits: Q1	3.850 (5.033)	5.436 (5.437)	<.0001	41.19%
Average outpatient visits: Q2	3.762 (5.033)	4.448 (5.498)	<.0001	18.23%
Average outpatient visits: Q3	3.904 (5.160)	4.671 (5.605)	<.0001	19.65%
Average outpatient visits: Q4	3.820 (5.005)	4.478 (5.320)	<.0001	17.23%
Average ER visits: full-year	0.448 (1.22)	0.747 (1.75)	<.0001	66.74%
Average ER visits: Q1	0.111 (0.470)	0.295 (0.751)	<.0001	165.77%
Average ER visits: Q2	0.111 (0.451)	0.151 (0.555)	<.0001	36.04%
Average ER visits: Q3	0.111 (0.457)	0.151 (0.546)	<.0001	36.04%
Average ER visits: Q4	0.117 (0.457)	0.15 (0.618)	<.0001	28.21%
Average hospitalizations: full-year	0.090 (0.421)	0.137 (0.524)	<.0001	52.22%
Average hospitalizations: Q1	0.022 (0.174)	0.053 (0.268)	<.0001	140.91%
Average hospitalizations: Q2	0.021 (0.171)	0.024 (0.173)	0.1349	14.29%
Average hospitalizations: Q3	0.023 (0.172)	0.031 (0.216)	<.0001	34.78%
Average hospitalizations: Q4	0.024 (0.183)	0.028 (0.200)	0.0626	16.67%
Average total Expenditure: full-year‡	10864 (32569)	13820 (37681)	<.0001	27.21%
Average total Expenditure: Q1‡	2607 (11193)	3993 (14429)	<.0001	53.16%
Average total Expenditure: Q2‡	2635 (12017)	3181 (12294)	0.0003	20.72%
Average total Expenditure: Q3‡	2725 (10921)	3336 (12881)	<.0001	22.42%
Average total Expenditure: Q4‡	2897 (13636)	3311 (14136)	0.0151	14.29%
DCSI one year after index date	2.136 (2.149)	2.269 (2.239)	<.0001	6.22%
DCSI change one year after index date	0.353 (0.807)	0.392 (0.853)	0.0001	10.87%

*Data presented as mean (SD).
†P value calculated using t-tests, statistical significance is indicated by P < 0.05.
‡ Total Expenditure includes Inpatient + Outpatient + ER visits in 2018 dollars.
Q, Quarter; ER, Emergency Room; DCSI, Diabetes Complications Severity Index.

chronic complications. While assessing the effect of antivirals on the mitigation of long-term impact of influenza was outside the scope of the current study, benefits of antiviral treatment for diabetes patients infected with influenza have recently been documented for short-term outcomes [30]. Additional studies are needed to examine the long-term effect of antivirald on the complications following an influenza infection.

The influenza cohort had a greater number of new or exacerbated complications in each of the DCSI categories compared to the non-influenza cohort one year after the index date. None of the differences were statistically significant for each DCSI category individually, but this may be due to sample size. It is notable that all seven categories showed a marked numerical increase for the influenza cohort, and when the categories were combined into a single metric (total number of new or exacerbated complications), its result is statistically significant. Using a larger sample size, or a longer time period may reveal significant differences for some of these individual complications. The three largest increases seen in the influenza cohort compared to the non-influenza cohort were cardiovascular, cerebrovascular, and neuropathy. It has been previously established that influenza is linked to and may trigger cardiovascular disease so it is not surprising that two of the highest increases in complications for the influenza cohort compared to the non-influenza cohort were in the vascular categories [6,7]. The second highest increase of new complications in the influenza cohort compared to the non-influenza cohort was in neuropathy, which suggests that influenza infection may also contribute to exacerbating microvascular complications in the long-term. Further study of the impact of influenza on microvascular events in this population may be warranted.

▪ Study limitations

There are several potential limitations and possible sources of bias in the current study. Because claims are collected for billing purposes, data

may be incomplete or inaccurate, and diagnoses may also be miscoded. Given that continuous enrollment is an inclusion criterion, patients who died or were otherwise lost to follow-up are not included, leading to selection bias. Additionally, some individuals in the non-influenza cohort may have had influenza but were not diagnosed. It should also be noted that this study utilized data from US commercial insurance plans and results may not be generalizable to populations not represented, such as patients older than 65 years of age covered by Medicare.

An additional source of bias is that influenza infection could lead patients to seek medical services, which could increase the likelihood that an existing or new complication is diagnosed and in a larger number of new complications in the influenza cohort. However, because new complications were measured after one year, it is likely that individuals would have seen a healthcare provider at least once during the timeframe regardless of influenza infection, thus mitigating this bias. Bias could be decreased further by examining the difference in complications after two years, which could be a potential add-on for future studies.

- **Future studies**

There are several areas that can be expanded on and questions that arise following the study results. For example, the long-term clinical outcomes of influenza-infected T2D patients that received antivirals should be evaluated. It is important to understand if antiviral treatment could mitigate some of the sustained burden of influenza on this population. Another assessment to consider would be an analysis of blood glucose levels in the year following influenza infection. Each influenza season is unique and may vary greatly in severity so the results may not be representative across multiple influenza seasons, Additional studies of different influenza seasons would help in understanding and supporting the results of the present study.

The present study showed that the influenza cohort had significantly higher outpatient, inpatient, and ER visits in multiple time periods, and additional research should examine the specific causes of these visits. Knowing the specific causes could aid clinicians in advance to manage the sustained burden of influenza in the T2D population.

Conclusion

The results from this study indicate an influenza infection does constitute a significant long-term health burden on T2D patients and may worsen the underlying metabolic disease state, as indicated through an increase in diabetes-related chronic complications. These findings also stress the importance of preventing and treating influenza in this population. When estimating the impact of influenza on diabetes patients, both the short and long-term impact should be considered.

Acknowledgement

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Conflict of Interest

Authors BDL, CW, TMT, HM, PD, and ST were employed by Genentech, Inc. at the time of the study. SWK was employed by Roche at the time of the study.

Author Contributions

All authors contributed to the design of the study. B.D.L analyzed the data, and all authors interpreted the results. B.D.L. prepared the first draft of the manuscript, and all authors reviewed and approved the manuscript. C.W. supervised the study. B.D.L. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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