CoLab Network

Common Data Model Report

Safety Monitoring During Use of Ozempic in People With Diabetes

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Key Messages

There is a need for real-world safety outcome monitoring of Ozempic in people with diabetes as its use increases in Canada.

We conducted a cohort study in 4 Canadian provinces to demonstrate the feasibility of replicating a US FDA Sentinel TreeScan signal-detection analysis using Ozempic as the case study.

The study identified 92,428 new users of Ozempic and 46,266 new users of sitagliptin with diabetes in British Columbia, Manitoba, Ontario, and Saskatchewan. A secondary analysis in the Ontario public drug plan found 44,185 new users of empagliflozin.

Compared to new users of sitagliptin, new users of Ozempic were relatively younger; less likely to have Alzheimer disease and other dementias; more likely to have hyperlipidemia and depressive disorder; more likely to be living with obesity; and much more likely to be coprescribed insulin.

Compared to new users of empagliflozin, new users of Ozempic were relatively younger, less likely to have a prior myocardial infarction and hypertension, more likely to be living with obesity, and more likely to be coprescribed insulin.

New users of Ozempic were followed for a median of 43 days compared to 103 days for new users of sitagliptin. The primary reasons for the shorter follow-up time were drug discontinuation or switching.

The study demonstrated that it is feasible to successfully replicate a US FDA Sentinel TreeScan analysis with Canadian data, but with limitations.

This feasibility study is the first of its kind in Canada and highlights important lessons for use of Canadian data in TreeScan-based analyses in future.

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Abbreviations

AE	adverse event
ED	emergency department
ICD-9	*International Classification of Diseases, Ninth Edition*
ICD-10-CA	*International Classification of Diseases, Tenth Edition, Canada*
LLR	log-likelihood ratio
SCDM	Sentinel Common Data Model
SGLT2	sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus

Introduction and Rationale

Background

Semaglutide, a glucagon-like peptide 1 receptor agonist, is approved and marketed in Canada under 3 brand names: Ozempic (2018), Rybelsus (2020), and Wegovy (2024).[1] Ozempic is an injectable formulation of semaglutide. It was approved January 2018 for the once-weekly treatment of adults with type 2 diabetes mellitus (T2DM) to improve glucose levels in combination with diet, exercise, and other drug therapies for the treatment of diabetes.[2] Rybelsus, an oral form of semaglutide, was approved in March 2020.[3] Similar to Ozempic, Rybelsus is indicated as an adjunct to diet and exercise to improve glucose levels in adults living with T2DM, to be taken alone or in combination with other medications for the treatment of diabetes.[1] At the time of approval, Ozempic was found to significantly lower hemoglobin A1C and body weight in people living with T2DM.[4] The rapid uptake of Ozempic and Rybelsus has led Health Canada to closely monitor their use, both on- and off-label.[5] Guidance on the optimal prescribing of Ozempic and Rybelsus is needed to ensure that people with T2DM are benefiting from drug therapy treatment with minimal harm. However, data on the real-world safety of these drug therapies are limited.

In August 2022, the US FDA Sentinel Initiative undertook a safety signal identification analysis for Ozempic by investigating the nonpregnancy, noncancer outcomes of people newly using Ozempic for the treatment of T2DM compared to people newly using sitagliptin.[6,7] Statistical alerts generated during these signal identification analyses do not on their own represent safety signals, but opportunities for targeted pharmacoepidemiologic studies. The Sentinel signal identification analysis was undertaken as a propensity score–matched new-user cohort study with the dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, as the comparator reference exposure. Sitagliptin was selected as the reference exposure because sitagliptin and semaglutide have related mechanisms of action. In addition, sitagliptin was included in the Peptide Innovation for Early Diabetes Treatment (PIONEER) trial program that directly compared oral semaglutide with sitagliptin.[8] The overall incidence of adverse events (AEs) in the trial was similar between oral semaglutide and sitagliptin. The greatest percentage of overall events for oral semaglutide were gastrointestinal events (primarily nausea, vomiting, and diarrhea). The incidence of gastrointestinal AEs was higher for semaglutide, although most gastrointestinal AEs were mild to moderate in severity.[9] In the Sentinel signal identification analysis, nausea and vomiting were among the most frequently observed events in the hospital and emergency department (ED) setting, with a statistically significant relative risk among Ozempic users of 1.18;[6] relative risk was 1.21 if people who were coprescribed insulin were excluded.[7]

Main Take-Aways

Semaglutide is marketed in Canada under the brand names of Ozempic, Rybelsus, and Wegovy. It is used to improve glucose control in adults with T2DM. A recent safety signal identification study by the FDA compared Ozempic to sitagliptin for treating T2DM and found that the incidence of gastrointestinal AEs was higher for semaglutide, with nausea, vomiting, and diarrhea among the most frequently observed events.

Purpose of this Report

As 1 in a series of Sentinel Common Data Model (SCDM) demonstration projects, the purpose of this study was to explore the feasibility of replicating signal identification analyses in Canada, using the Sentinel Ozempic analysis[10] as a case study. As an extension to the Sentinel analysis, we added a secondary comparator, the most frequently prescribed sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin.

Policy Issue

As the use of Ozempic increases, there is a need for further real-world outcome monitoring of the drug in Canada. Guidance is needed on the optimal prescribing of Ozempic to ensure that patients are benefiting from treatment with minimal harm.

Policy Question

Are there potential safety signals associated with the use of Ozempic among adults with diabetes?

Main Take-Aways

As Ozempic use increases in Canada, there is a need for real-world safety outcome monitoring. This study aimed to replicate an FDA Sentinel signal-detection analysis using the tool, TreeScan, to compare Ozempic to sitagliptin and empagliflozin among adults with diabetes.

Research Question

Are there potential safety signals in the post-market space among adults with diabetes treated with Ozempic versus similar people treated with sitagliptin or empagliflozin?

Objectives

The objective of this project was to determine whether there are potential safety signals for Ozempic during the treatment of adults with diabetes using the safety signal identification tool, TreeScan.

More specifically, we aimed to:

- describe the characteristics of new users of Ozempic and sitagliptin before and after propensity score–based matching
- describe the frequency of treatment episodes and compare treatment episode length and reason for loss to follow-up during the study period
- describe the frequency and excess risk for TreeScan-identified outcome events in people using Ozempic versus a matched group exposed to sitagliptin
- describe the frequency and excess risk for TreeScan-identified outcome events in people using Ozempic versus a matched group exposed to empagliflozin.

Methods

Study Design, Setting, and Patients

This was a population-based cohort study in British Columbia, Manitoba, Ontario, and Saskatchewan of adults with diabetes who were newly treated with Ozempic or sitagliptin. People with evidence of cancer or end-stage kidney disease were excluded. Ontario analyses were limited to public drug plan beneficiaries. Because alternate forms of semaglutide (Rybelsus and Wegovy) were not covered by the provincial public drug plans during the study period, they were excluded from the study. Consistent with the FDA Sentinel protocol we sought to replicate, all exclusion criteria were examined in the 400 days preceding the first dispensing of Ozempic or sitagliptin during the accrual period, which ran from the date of the first dispensing of Ozempic in each province (British Columbia: March 7, 2018; Manitoba: April 6, 2018; Ontario: September 30, 2019; and Saskatchewan: March 29, 2018) to the latest date possible in each province (British Columbia: March 31, 2023**;** Manitoba: March 31, 2023; Ontario: March 31, 2023; Saskatchewan: December 31, 2022). In secondary analyses, we excluded patients who were coprescribed insulin, and substituted empagliflozin as the comparator instead of sitagliptin. The empagliflozin analysis included data from Ontario from September 30, 2019, to March 31, 2022.

The study entry criteria required all eligible persons to have continuous enrolment in their provincial health insurance plans for at least 400 days before or on the first date of dispensing Ozempic or sitagliptin, with a grace period of 45 days. All required 1 or more outpatient or inpatient diagnosis codes for diabetes (*International Classification of Diseases, Ninth Revision [ICD-9]*: 250; *ICD, Tenth Revision, Canada* [*ICD-10-CA*]: E10-E14) in the 400 days preceding or on the date of first dispensing of Ozempic or sitagliptin. Inpatient or ED diagnoses of type 1 diabetes were excluded. However, because outpatient diagnosis codes cannot differentiate type 1 from type 2 diabetes, we did not exclude persons with a type 1 diabetes diagnosis unless they presented to an acute care setting in the 400 days preceding cohort entry.

Study Data Sources

The study leveraged provincial administrative health care data transformed into the SCDM.[9] The data included information on demographics, health insurance status, and vital status from the provincial health insurance registry; outpatient (physician office, phone, virtual, ED) and hospital encounter data from physician claim databases and the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System; diagnoses and procedures associated with these encounters; and prescription drug claims from the provincial drug benefit databases. Importantly, because comprehensive drug claim data are not available for all residents of Ontario, ascertainment of drug exposures and outcomes were confined to Ontarians eligible for the provincial drug benefit program (i.e., persons aged 65 years and older and social assistance recipients).

Key Study Measures

Exposures

In the primary analysis we identified the first Ozempic and sitagliptin treatment episode during the accrual period for each user, with incident use defined as no use in the preceding 365 days. As a test of specificity, in a secondary analysis conducted in Ontario, the largest of the provincial cohorts, we substituted sitagliptin with empagliflozin. We chose empagliflozin over other potential comparators because we believed SGLT2 inhibitors to be the optimal contemporary alternative to Ozempic, and among the drugs in the class, empagliflozin had proven cardiovascular benefits similar to those of Ozempic and was the most frequently prescribed SGLT2 inhibitor in Ontario.

Outcomes

The main outcome was the occurrence of nonpregnancy, noncancer inpatient or ED discharge diagnoses among incident users of Ozempic compared with incident users of sitagliptin (or empagliflozin in the secondary analysis) during the 183 days following the index dispensing. To emulate the Sentinel study, follow-up began on the day after the index dispensing and continued until the date of the first occurrence of any of the following:

- death
- provincial health plan disenrolment
- end of the study accrual period
- end of the exposure episode
- dispensing of the comparator study drug
- dispensing of another semaglutide product (Rybelsus or Wegovy; retained for completeness, not applicable for the Ontario analysis)
- dispensing of another dipeptidyl peptidase-4 (SGLT2 inhibitor for the empagliflozin secondary analysis)
- dispensing of another glucagon-like peptide 1 receptor agonist
- 183 days following index dispensing.

We identified incident outcome events as the first inpatient or ED diagnosis to occur in the 183 days following the index dispensing, but not in the 400 days preceding dispensing (i.e., no outcome diagnoses with the same first 3 digits of the *ICD-10-CA* code in the preceding 400 days). We evaluated incident outcome events beginning 1 day after exposure initiation until the end of the exposure episode provided that both members of the matched pair were available to contribute at-risk time for the outcome of interest.

Analyses

Propensity Score Estimation and Matching

We assessed age, sex, and calendar year on the index exposure date and a list of covariates prespecified by the Sentinel project team (Appendix 1) in the 400 days preceding the index date. The covariates were defined

using I*CD-9* and *ICD-10-CA* diagnosis codes, Canadian Classification of Interventions (CCI) procedure codes, provincial physician fee codes, and Health Canada Drug Identification Numbers (DINs). We used these covariates and the Sentinel Propensity Score Analysis module to calculate propensity scores and identify 1:1 propensity score–matched cohorts using nearest-neighbour matching without replacement with a specified caliper width of 0.025. Covariates were considered balanced when they had a standardized mean difference of less than 0.1.

TreeScan Statistics

Outcome events were evaluated using TreeScan (v.2.0) to determine the presence of imbalances in outcome incidence that rise to the level of statistical significance. TreeScan is a data-mining program that uses tree-based scan statistics.[11] Under the null hypothesis, there is no position on the "tree" — in this case, diagnosis code category — when outcomes are expected to occur in a ratio other than that of the fixed ratio of the matched cohort (here 1:1).

By identifying outcomes coded on hospital and ED discharge abstracts, we could use the natural hierarchical structure of the *ICD-10-CA* classification system as the reference data source for TreeScan. *ICD-10-CA* codes move from 23 broad categories of diagnoses or chapters, such as diseases of the nervous system (i.e., G00-G99) to progressively more specific diagnosis categories, such as, G82193 (Spastic paraplegia, unspecified, at the lumbar level) (refer to Appendix 2). The *ICD-10-CA* classification system contains up to 6 levels of increasing specificity. We excluded 6 diagnosis chapters thought not to be relevant for this study: C00-D49 (Neoplasms), O00-O99 (Pregnancy, childbirth and the puerperium), P00-P96 (Certain conditions originating in the perinatal period), Q00-Q99 (Congenital malformations, deformations, and chromosomal abnormalities), V00-Y99 (External causes of morbidity), and Z00-Z99 (Factors influencing health status and contact with health services).

We used the unconditional Bernoulli tree–based scan statistic (refer to Appendix 3) by calculating the log-likelihood ratio (LLR) for every third through sixth diagnosis code level or node of the *ICD-10-CA* outcome tree. This statistic tests the null hypothesis of no difference in risk of AEs in any outcome node in the tree against a 1-sided alternative that there is at least 1 node in the tree where the risk of AEs is greater in the exposed group than in the comparator group. To control for false-positive alerts, TreeScan generates multiplicity-adjusted P values to adjust for inflated type I error rates due to multiple hypothesis testing. P values can be interpreted at face value as the probability of seeing an association of the observed magnitude or 1 more extreme if the null hypothesis were true. The distribution of the tree-based scan statistic is unknown and is therefore derived nonparametrically by generating distributions under the null hypothesis of no effect of exposure in any node via Monte Carlo simulation. The test statistics from 9,999 datasets simulated under the null and from the single observed dataset are ranked from largest to smallest. The multiple testing–adjusted P value is determined by the rank *R* of the observed test statistic divided by 10,000 (9,999 simulated + 1 observed dataset), so that P = R / (9,999 + 1).

Findings

Main Take-Aways

We identified 92,428 new users of Ozempic and 46,266 new users of sitagliptin.

In general, new users of Ozempic were younger, less likely to have Alzheimer disease and other dementias, more likely to be living with diabetes, more likely to have hyperlipidemia, and depressive disorder, and more likely to be living with obesity. They also received more health services and other medications.

The potential safety concerns in the Ozempic versus sitagliptin analysis included nausea, vomiting, obesity, polyneuropathy, and other nervous system disorders, although none reached a conventional level of statistical significance.

Patient Characteristics

After application of the study entry criteria, we identified 92,428 new users of Ozempic and 46,266 new users of sitagliptin (refer to Appendix 4, Table 2). Appendix 4, Table 3 presents the baseline characteristics of people included in the study before propensity score matching. Ozempic users were relatively younger and less likely to have fluid or electrolyte disorders, Alzheimer disease, and other dementias; they were more likely to have coded diabetes, hyperlipidemia, depressive disorder, and obesity. New users of Ozempic were also much more likely to be coprescribed insulin. Patients prescribed Ozempic also received more health services and other medications. Propensity score matching significantly reduced the size of the study cohort to 30,089 patients per group (representing a 67% reduction in the number prescribed Ozempic and 35% reduction in the number prescribed sitagliptin) but achieved good balance (refer to Appendix 4, Table 4). In the secondary analysis that excluded patients coprescribed insulin, the matched cohort was relatively smaller (25,445 patients per group) but was also well balanced (data not shown).

Appendix 4, Table 5 describes the relative contributions of the provinces to the pooled, propensity score–matched cohort. Ontarians comprised 75% of the overall study cohort. It comprised 77% females and 23% males. Also, because those who were living in Ontario received public drug plan benefits, they were significantly older than patients in other provinces, with a mean age of 69 years versus 57 years in Manitoba, for example.

Appendix 4, Tables 6 and 7 describe new users of Ozempic versus the secondary comparator, empagliflozin, in Ontario, before and after matching, respectively. After application of the study entry criteria, we identified 44,185 new users of empagliflozin (versus 35,562 for sitagliptin). When compared with empagliflozin, new users of Ozempic were relatively younger, less likely to have a prior myocardial infarction and hypertension, and more likely to be living with obesity (Table 6). Patients prescribed Ozempic also received relatively more health services and other medications, including insulin. Propensity score matching reduced the size of the study cohort to 17,810 patients per group but achieved good balance on potential confounders (Table 7).

Summary of Time To End and Reasons for End of At-Risk Period

The 92,428 new users of Ozempic and 46,266 new users of sitagliptin contributed 92,948 and 46,383 exposure episodes, respectively. Appendix 4, Tables 8 and 9 summarize the time to, and the reasons for, the end of the at-risk period according to drug exposure before matching. New users of Ozempic were followed for a median of 43 days versus 103 days for sitagliptin, with the most frequent reasons for the shorter follow-up time being drug discontinuation or switching (52% in the Ozempic group and 65% in the sitagliptin group).

TreeScan-Based Signals of Potential Adverse Events

Appendix 4, Table 10 lists the potential safety signals derived from ED and inpatient admissions for the matched Ozempic versus sitagliptin cohort, including those coprescribed insulin, presented according to the unconditional Bernoulli LLR and corresponding P value. Only potential signals with at least 6 observations are reported. None of the potential safety signals reached a conventional level of statistical significance. The greatest likelihood ratios were associated with diagnosis codes for nausea, vomiting, obesity, polyneuropathy, and other disorders of the nervous system. Diagnosis codes for nausea and vomiting were also among the list of candidate events.

Appendix 4, Table 11 lists the potential signals for the matched Ozempic versus sitagliptin cohort after excluding those who were coprescribed insulin. None of the potential safety signals reached statistical significance. The greatest likelihood ratios were associated with diagnosis codes for primary bilateral gonarthrosis (osteoarthritis of the knees), superficial injuries of the wrist and hand, and gastroenteritis and diarrhea.

Appendix 4, Table 12 presents the results for the matched Ozempic-empagliflozin cohort from Ontario, including those coprescribed insulin. Again, none of the potential safety signals reached statistical significance. Similar to the sitagliptin analysis, the most frequent observations were associated with gastrointestinal diagnoses, including nausea and vomiting, diarrhea, gastroenteritis, and other functional intestinal disorders. The diagnosis associated with the highest likelihood ratio was *ICD-10-CA* F32, depressive episode (LLR = 4.852; P value = 0.288). After excluding patients who were coprescribed insulin, the only new diagnoses that emerged were *ICD-10-CA* E10, type 1 diabetes (LLR = 5.545; P value = 0.1098) and *ICD-10-CA* B02, herpes zoster (LLR = 2.773; P value = 0.9804).

Strengths and Limitations

Main Take-Aways

We showed that it is feasible to successfully replicate an FDA Sentinel TreeScan signal-detection analysis with Canadian data, but with important considerations.

We were able to eliminate between-group differences in the characteristics of people in the study using the propensity score–matching method. However, this led to a significant loss in the number of patients

available for study, with a 67% reduction in the number of people treated with Ozempic. When we changed the comparison drug from sitagliptin to empagliflozin, a more contemporary alternative to Ozempic, we were able to achieve good balance and retain more people treated with Ozempic (25%). None of the potential safety signals we observed reached statistical significance due in part to the small sample size. However, the diagnosis codes for nausea and vomiting were similar to those observed in the prior FDA analyses.

Note that these analyses alone do not establish or confirm safety signals. Further focused studies are necessary to establish the presence of meaningful safety signals.

The main purpose of this project was to test the feasibility of replicating an FDA Sentinel TreeScan signal-detection analysis using Ozempic as the case study. Using Canadian administrative health care data transformed into the Sentinel CDM and an adaptation of FDA's original analytic program, we showed that it was feasible to replicate the Sentinel study methods, but with important limitations. None of the potential safety signals we observed reached statistical significance. However, the diagnosis codes associated with the largest LLRs — nausea and vomiting — were similar in both countries. We achieved good balance on potential confounders with propensity score matching, but with substantial loss in the number of patients available for study: 67% loss in the case of Ozempic. Switching the active comparator from sitagliptin to empagliflozin (a more likely contemporary alternative to Ozempic) achieved covariate balance with loss of considerably fewer people treated with Ozempic(25%). Although none of the potential safety signals reached statistical significance, the change in comparator from sitagliptin to empagliflozin identified different potential candidate signals that may suggest better control for confounding. For example, the diagnosis with the second-largest LLR in the sitagliptin analysis was obesity (most likely a result of confounding by indication), whereas for empagliflozin, the largest LLR was associated with the diagnosis code for depressive episode, which is more likely to be a potential treatment-related AE. As a feasibility analysis, and the first of its kind in Canada, our study highlights important lessons for the use of Canadian data in TreeScan-based analyses in the future.

First, the absolute and relative number of events was markedly smaller in the Canadian data. The Sentinel analysis, which was based upon a matched cohort of 134,007 incident users of the study drugs, observed 1,862 inpatient or ED encounters with a diagnosis of, for example, nausea or vomiting (1.4%).[6] In contrast, the Canadian cohort comprised just 30,089 matched patients and observed 68 such encounters (0.2%). This reduction in sample size and event rate limited our ability to detect a statistically significant signal, if present, and coincided with smaller LLR test statistics. In the Sentinel study, LLR test statistics that exceeded a value of 9 reached statistical significance. In a separate US study using similar methods to evaluate signals associated with new exposure to the SGLT2-inhibitor, canagliflozin, LLR test statistics exceeding 8 reached statistical significance.[12] The largest LLR test statistic in our study was 5.5 (with a corresponding P value of 0.28) (refer to Appendix 4, Table 11). The Ontario cohort comprised older adults and those receiving social assistance (rather than the more diverse composition of the Sentinel Distributed Database and other provincial databases) and this may have contributed to relatively lower event rates in Ontario, which comprised 75% of the overall study cohort. Ontario cohort members were approximately 10 years older than those in the other study provinces.

A second related challenge of Canadian data is our use of *ICD-8* and *ICD-9* (rather than *ICD-10*) diagnosis codes to identify the main reason for physician office visits. Consequently, in contrast to studies undertaken in the US Sentinel Distributed Database, it is not currently possible to use data from outpatient physician office visits as a data source for potential drug safety signals in Canada, which is the setting where patients with AEs, such as nausea and vomiting, are most likely to present. In the Sentinel study, for example, adding physician service claims to inpatient and ED encounters increased the number of "nausea and vomiting" outcome events from 1,862 (1.4%) to 4,909 (3.7%). This equated to corresponding increases in the relative risk, LLR test statistic, and P value from relative risk = 1.18 (LLR = 32.0; P = 0.001) to relative risk = 1.30 (LLR = 219.5; P = 0.0001).[6] One strategy to potentially overcome this limitation of Canadian data is development of a diagnosis code classification scheme ("tree") that integrates *ICD-9* with *ICD-10*. Development of such a scheme could be expedited, and the analytic efficiency of signal detection improved, by initially focusing on the subset of diagnosis codes or code categories of greatest importance to regulators, together with information regarding the codes or categories that are most reliably coded in administrative data. Even without this integration, further statistical efficiency could be achieved by limiting analyses to fewer and perhaps higher, less-specific levels of the *ICD-10-CA* diagnosis tree (e.g., limiting analysis to levels 3 and 4 as opposed to levels 3 to 6) (refer to Appendix 2).

Third, another limitation of Canadian physician service claims for signal-detection studies is the limited number of diagnosis codes permitted with each encounter. In Ontario, for example, physicians are permitted to enter just 1 diagnosis code — the main reason — for each encounter. In contrast, US claim standards permit up to 12 diagnosis codes on an outpatient service claim.[13] This results in considerably more diagnostic information available for both characterizing patients and detecting outcomes. For signal-detection studies, both are important. Proper and complete characterization of patients at baseline ensures that exposure groups are well balanced, and that any subsequent safety signals that emerge are less likely to represent preexisting conditions. For example, Table 10 shows that obesity was the diagnosis with the second-highest LLR test statistic. However, Table 4 shows that just 3% of study patients were characterized as living with obesity at baseline. This suggests that the potential safety signal may be at least partially a consequence of residual confounding by incomplete characterization at baseline, meaning patients receiving Ozempic were more likely to be living with obesity before drug exposure, but this was not captured in the data available to us at baseline nor was it reflected in the historical inpatient and ED data used to identify the incident safety signal. This contrasts the Sentinel study, in which 55% of the matched cohort were characterized as living with obesity and the outpatient physician service claims could be used for signal detection. That other potential signals in our analysis included gonarthrosis (osteoarthritis of the knee) may provide further support for this idea (Table 11).

Fourth, because our aim was to demonstrate that we could replicate the Sentinel analysis, the parameters we used for establishing the baseline characteristics, propensity scores, censoring criteria, and time horizon for detecting events were identical to those used in the original study. The maximum duration of follow-up,183 days, may make sense for diabetes medication starts in general.[14] However, we now know that the median follow-up time for new Ozempic starts is considerably shorter than that for sitagliptin. Given what we now

know from this study, the lookback period, covariates, time horizon, and other parameters could be altered to better suit the specific therapies studied here.

Fifth, although the "days supplied" field on a prescription drug claim is a reasonably accurate proxy for prescription duration for most oral medications, we do not know whether it is reliable for injectable medications that are administered with varying dosages. For example, a patient could receive two 2 mg pens with 56 days supplied (assuming 0.5 mg weekly). However, if the patient is taking 0.25 mg weekly, the prescription would last 112 days, and what appears as a gap of 56 days is continuous use. This may contribute to differential misclassification of exposure time across the study groups. We are unaware of validation work for varying dose injectables.

Finally, as in any analyses for identification of potential safety signals, such analyses on their own do not establish or confirm safety signals. Subsequent focused studies are needed to confirm the presence of meaningful safety signals.

Conclusions and Implications for Decision- or Policy-Making

We set out to evaluate the feasibility of replicating an FDA Sentinel TreeScan safety signal-detection analysis using Ozempic as the case study. Using Canadian administrative health data transformed into the Sentinel CDM and an adaptation of FDA's original analytic program, we demonstrated that it was feasible to replicate FDA's study methods, but with important limitations. Our study has important lessons for use of Canadian data in TreeScan-based analyses in future.

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Clinical Review

Michael Paterson drafted the scientific protocol, contributed to review and interpretation of the study results, and drafted, reviewed, and approved the report.

Fangyun Wu contributed to drafting of the scientific protocol, conducted analyses at the Ontario site and quality checks of results, contributed to the review and interpretation of the study results, and reviewed and approved the report.

Baiju Shah reviewed the scientific protocol, provided clinical expertise, and reviewed and approved the report.

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Matthew Dahl, Data Analyst, contributed to drafting the scientific protocol, conducted analyses at the Manitoba site and quality checks of results, contributed to the review and interpretation of the study results, and reviewed and approved the report.

Sean Burnett contributed to drafting of the scientific protocol, conducted analyses at the British Columbia site and quality checks of results, contributed to the review and interpretation of the study results, and reviewed and approved the report.

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Conflicts of Interest

Donica Janzen disclosed the following:

Travel funding or payment

CNODES — Not related to a specific drug, technology, or topic. Student travel award.

Robert Platt disclosed the following:

Since 2019, served as a consultant for 7 companies, some as a consulting expert for Analysis Group, an economics consulting company.

Payment as Advisor or Consultant

- Biogen — Multiple drugs, 2017 to 2023. Advice on general methodological issues regarding multiple drugs including Tysabri and Tecfidera (multiple sclerosis) and Aduhelm (Alzheimer disease). This work terminated in December 2023.
- Boehringer Ingelheim — Endowed Chair 2016 to present; consultant on patient issues July 2022 to September 2022.
- Merck — Vaccines (MMR, Zostavax), Singulair asthma treatment 2018 to present. Expert witness in 3 legal matters, ongoing. Advisor on study design for observational studies in reproductive medicine.
- Nant Pharma — Abraxane, 2020 to 2021. Expert in arbitration case, terminated 2021.
- Vanda Pharma — Hetlioz. Study steering committee in pediatric observational studies of latanoprost.
- Viatris (purchased from Pfizer) — Latanoprost, 2014 to present. Advised on arbitration hearing.
- Finsbury — Medical device. Expert reports in litigation, terminated summer 2019.

Payment for academic appointments (endowed chairs)

- Boehringer Ingelheim — Endowed Chair 2016 to present; consultant July 2022 to September 2022.

Precision Analytics — Serving as Scientific/strategic advisor for a small consulting company developed by former students. No compensation received for this work.

No other conflicts of interest were declared.

Appendix 1: Candidate Covariates for Inclusion in the Propensity Score

Note that this appendix has not been copy-edited.

Healthcare service utilization, Combined Comorbidity Score, < Gagne 2011, Sun 2017 > acute myocardial infarction; ADHD, conduct disorder, Hyperkinetic Syndrome; alcohol use disorders, anemia, anxiety disorders, arrhythmia, asthma, autism spectrum disorders, autoimmune disease, bacterial infection, benign prostatic hyperplasia, cataracts, chronic kidney disease, coagulopathy, colonoscopy, COPD; cystic fibrosis and other metabolic developmental disorders, degenerative diseases of CNS; depression, bipolar, or other depressive mood disorders; diabetes, drug use disorders,, epilepsy, ; fibromyalgia, chronic pain, and fatigue, fluid and electrolyte disorder, gallstones, glaucoma, heart failure and non-ischemic heart disease, hip/pelvic fracture, HIV/AIDS, hyperparathyroidism, hyperlipidemia, hypertension, hypothyroidism, ischemic heart disease, leukemias and lymphomas; liver disease, cirrhosis, and other liver conditions; mammogram, medicines for gout, mental and physical impairments, migraine and chronic headache, muscular dystrophy, obesity, opioid disorder, organ transplant, osteoporosis with or without pathological fracture, other developmental delays, other infections, Parkinson's disease and secondary parkinsonism, peripheral vascular disease, personality disorders, pneumonia, PTSD, pressure and chronic ulcers, psychosis, pulmonary circulation disorders, pulmonary disease, renal failure, rheumatoid arthritis/osteoarthritis, schizophrenia and other psychotic disorders, sertraline, spina bifida and other congenital anomalies of the nervous system, spinal cord injury, stroke/transient ischemic attack, sulfa antibiotics, tobacco use, traumatic brain injury and nonpsychotic mental disorders, viral hepatitis, weight loss, and insulin dispensings.

Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A Combined Comorbidity Score Predicted Mortality in Elderly Patients Better Than Existing Scores. *J Clin Epidemiol.* 2011;64(7):749-759. PubMed

Sun JW, Rogers JR, Her Q, Welch EC, Panozzo CA, Toh S, Gagne JJ. Adaptation and Validation of the Combined Comorbidity Score for ICD-10-CM. *Med Care.* 2017;55(12):1046-1051. PubMed

Appendix 2: Example of Hierarchical Organization of *ICD-10-CA* Classification System and List of *ICD-10-CA* Chapters

Note that this appendix has not been copy-edited.

Table 1: Example of Hierarchical Organization of *ICD-10-CA* Classification System

Level	Chapter or Code Range	Description
1	G00-G99	Diseases of the nervous system
2	G81-G83	Paralytic syndromes
3	G82	Paraplegia and tetraplegia
4	G820	Flaccid paraplegia
5	G8201	Flaccid paraplegia, complete
6	G82011	Flaccid paraplegia, complete, at cervical level

ICD-10-CA Chapters

1. Certain infectious and parasitic diseases - (A00-B99)
2. Neoplasms (Cancer) - (C00-D49)
3. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism - (D50-D59)
4. Endocrine, nutritional and metabolic diseases - (E00-E99)
5. Mental and behavioural disorders - (F00-F99)
6. Diseases of the nervous system - (G00-G99)
7. Diseases of the eye and adnexa - (H00-H59)
8. Diseases of the ear and mastoid process - (H60-H99)
9. Diseases of the circulatory system - (I00-I99)
10. Diseases of the respiratory system - (J00-J99)
11. Diseases of the digestive system - (K00-K99)
12. Diseases of the skin and subcutaneous tissue - (L00-L99)
13. Diseases of the musculoskeletal system and connective tissue - (M00-M99)
14. Diseases of the genitourinary system - (N00-N99)
15. Pregnancy, childbirth and the puerperium - (O00-O99)

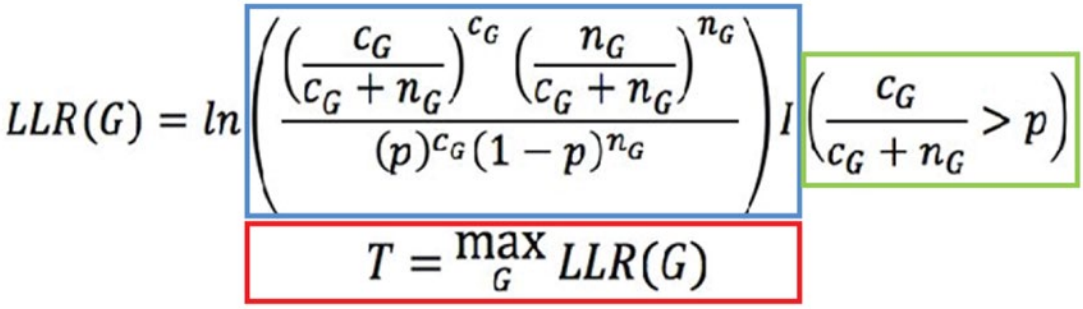
16. Certain conditions originating in the perinatal period - (P00-P99)
17. Congenital malformations, deformations, and chromosomal abnormalities - (Q00-Q99)
18. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)
19. Injury, poisoning and certain other consequences of external causes (S00-T99)
20. Provisional codes for temporary assignments of new disease of uncertain etiology (U00-U99)
21. External causes of morbidity and mortality (V00-Y99)
22. Factors influencing health status and contact with health services (Z00-Z99)
23. Morphology of neoplasms (800-998)

Appendix 3: Calculation of the Test Statistic for an Unconditional Bernoulli Probability

Note that this appendix has not been copy-edited.

The log likelihood ratio (LLR) based test statistic *T* can be calculated as follows.

Figure 1: Calculation of the Test Statistic for an Unconditional Bernoulli Probability



$$LLR(G) = ln\left(\frac{\left(\frac{c_G}{c_G + n_G}\right)^{c_G}\left(\frac{n_G}{c_G + n_G}\right)^{n_G}}{(p)^{c_G}(1-p)^{n_G}}\right) I\left(\frac{c_G}{c_G + n_G} > p\right)$$

$$T = \max_G LLR(G)$$

C_G = cases in the treatment group for a given node G; LLR = log-likelihood ratio; n_G = cases in the reference group for a given node G; T = unconditional Bernoulli tree-based scan statistic; p = probability of being in the treatment group.

Notes: Expression in blue: This is the maximum likelihood estimation. It takes the form of a Bernoulli probability model. The numerator of the equation is based on the observed data. The denominator of the equation is based on the expectation under the null hypothesis. If the observed data "fit" the pattern of the null hypothesis, then this expression would be 1. The "log" of the function is for mathematical convenience. The ln (1) = 0.

Expression in green: This is an indication function. It means that an LLR is ONLY recorded if there are more cases in the treatment group than expected. So, an LLR is only calculated among nodes on the tree when the LLR would normally exceed 0 (or the likelihood ratio would exceed 1).

Expression in red: The log likelihood ratio is calculated for every position (node) on the tree including each individual diagnosis code and groupings of codes. For any dataset (i.e., across all nodes of the tree), the test statistic for that dataset is the maximum across all the nodes.

Appendix 4: Main Findings

Table 2: Cohort Attrition

Entry criteria	Ozempic		Sitagliptin	
	Remaining	Excluded	Remaining	Excluded
Members meeting enrolment and demographic requirements				
Enrolled at any point during the query period	31,497,703	N/A	31,497,703	N/A
Had required coverage type (medical and/or drug coverage)	19,306,506	12,191,197	19,306,506	12,191,197
Enrolled during specified age range	16,372,293	2,934,213	16,372,293	2,934,213
Had requestable medical charts	16,372,293	0	16,372,293	0
Met demographic requirements (sex)	16,372,197	96	16,372,197	96
Members with a valid index event				
Had any cohort-defining claim during the query period	299,109	16,073,088	329,668	16,042,529
Claim recorded during specified age range	299,054	55	329,648	20
Episode defining index claim recorded during the query period	297,585	1,469	118,608	211,040
Members with required pre-index history				
Had sufficient pre-index continuous enrolment	265,112	32,473	76,799	41,809
Met inclusion and exclusion criteria[a]	92,948	172,164	46,383	30,416
Evidence of cancer	N/A	49,315	N/A	14,544
Evidence of end-stage renal disease	N/A	21,231	N/A	4,059
Evidence of rybelsus	N/A	555	N/A	19
Evidence of semaglutide	N/A	N/A	N/A	3,689
Evidence of sitagliptin	N/A	64,954	N/A	N/A
Evidence of t1dm_aved	N/A	14,488	N/A	5,513
Evidence of t1dm_ip	N/A	4,359	N/A	2,103

Entry criteria	Ozempic		Sitagliptin	
	Remaining	Excluded	Remaining	Excluded
No evidence of t2dm_aved	N/A	70,043	N/A	9,050
No evidence of t2dm_ip	N/A	156,425	N/A	24,212
Met event incidence criteria	92,948	0	46,383	0
Members with required post-index follow-up				
Had sufficient post-index continuous enrolment	91,641	1,307	46,296	87
Had minimum days' supply on index date	91,641	0	46,296	0
Had index episode of minimal required length	91,641	0	46,296	0
Had index episode longer than blackout period	91,641	0	46,296	0
Did not have an event during blackout period	91,641	0	46,296	0
Final cohort				
Number of members	91,641	0	46,296	0
Number of episodes	91,641	0	46,296	0
Members meeting comparative cohort eligibility requirements				
Excluded due to same-day initiation of both exposure groups	92,948	0	46,383	0
Excluded due to prior initiation of other exposure group	**92,428**	520	**46,266**	117
Included in propensity score-matched comparative analysis	**30,089**	62,339	**30,089**	16,177

Note: This table has not been copy-edited.

Table 3: Baseline Characteristics of Study Patients Before Propensity Score Matching — Ozempic Versus Sitagliptin

Patient characteristics[a]	Ozempic		Sitagliptin		Covariate balance	
	Number/mean	Percent/standard deviation[b]	Number/mean	Percent/standard deviation[b]	Absolute difference	Standardized difference
Unique patients	92,428	100.0%	46,266	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	62.4	11.5	68.1	11.1	−5.754	**−0.509**
18 to 39 years	5,494	5.9%	1,375	3.0%	2.972	**0.144**
40 to 64 years	39,603	42.8%	11,535	24.9%	17.915	**0.385**
≥ 65 years	47,331	51.2%	33,356	72.1%	−20.888	**−0.440**
Sex						
Female	47,625	51.5%	21,884	47.3%	4.226	0.085
Male	44,803	48.5%	24,382	52.7%	−4.226	−0.085
Year						
2018	3,004	6.6%	2,484	26.3%	−19.732	**−0.553**
2019	10,678	12.2%	6,409	14.2%	−2.063	−0.061
2020	13,496	14.6%	12,119	26.2%	−11.593	**−0.291**
2021	22,989	24.9%	12,516	27.1%	−2.180	−0.050
2022	31,577	34.2%	10,388	22.5%	11.711	**0.262**
2023	10,684	12.2%	2,350	5.2%	6.961	**0.249**
Health Characteristics						
Charlson/Elixhauser combined comorbidity score[c]	0.4	0.9	0.4	1.0	0.014	0.015
Anemia	4,451	4.8%	2,132	4.6%	0.208	0.010
Arrhythmia	7,303	7.9%	2,970	6.4%	1.482	0.057

Patient characteristics[a]	Ozempic		Sitagliptin		Covariate balance	
	Number/mean	Percent/standard deviation[b]	Number/mean	Percent/standard deviation[b]	Absolute difference	Standardized difference
Autoimmune disease	5,060	5.5%	1,831	4.0%	1.517	0.072
Bacterial infection	2,180	2.4%	1,338	2.9%	−0.533	−0.033
Coagulopathy	399	0.4%	186	0.4%	0.030	0.005
Colonoscopy	3,616	3.9%	2,157	4.7%	−0.750	−0.037
Degenerative disease of central nervous system	863	0.9%	591	1.3%	−0.344	−0.033
Fluid and electrolyte disorder	696	0.8%	1,065	2.3%	−1.549	**−0.127**
Gallstones	349	0.4%	193	0.4%	−0.040	−0.006
Hyperparathyroidism	20	0.0%	18	0.0%	−0.017	−0.010
Mammogram	12,639	13.7%	8,771	19.0%	−5.283	**−0.143**
Organ transplant	10	0.0%	7	0.0%	−0.004	−0.004
Other infections	514	0.6%	498	1.1%	−0.520	−0.058
Psychosis	3,017	3.3%	1,351	2.9%	0.344	0.020
Pulmonary circulation disorders	70	0.1%	40	0.1%	−0.011	−0.004
Pulmonary disease	7,855	8.5%	2,925	6.3%	2.176	0.083
Renal failure	38	0.0%	31	0.1%	−0.026	−0.011
Weight loss	5,320	5.8%	1,975	4.3%	1.487	0.068
Gout medications	3,151	3.4%	1,126	2.4%	0.975	0.058
Sertraline	2,942	3.2%	1,242	2.7%	0.499	0.030
Sulfa antibiotic	1,061	1.1%	554	1.2%	−0.050	−0.005
AMI	3,616	3.9%	2,157	4.7%	−0.750	−0.037
Alzheimer's disease[d]	1,295	1.4%	1,713	3.7%	−2.301	**−0.146**

Patient characteristics[a]	Ozempic		Sitagliptin		Covariate balance	
	Number/mean	Percent/standard deviation[b]	Number/mean	Percent/standard deviation[b]	Absolute difference	Standardized difference
Asthma	4,415	4.8%	1,558	3.4%	1.409	0.071
Benign prostatic hypertrophy	2,349	2.5%	1,537	3.3%	−0.781	−0.046
Cataract	7,310	7.9%	3,280	7.1%	0.819	0.031
COPD	2,560	2.8%	1,163	2.5%	0.256	0.016
Depressive bipolar disorder	2,257	2.4%	798	1.7%	0.717	0.050
Diabetes	89,571	96.9%	42,746	92.4%	4.517	**0.202**
Glaucoma	9,305	10.1%	3,562	7.7%	2.368	0.083
Heart failure	4,368	4.7%	1,654	3.6%	1.151	0.058
Hip fracture	220	0.2%	235	0.5%	−0.270	−0.044
Hyperlipidemia	10,065	10.9%	3,084	6.7%	4.224	**0.150**
Hypertension	29,244	31.6%	14,711	31.8%	−0.157	−0.003
Hypothyroid	3,000	3.2%	1,209	2.6%	0.633	0.038
Ischemic heart disease	6,775	7.3%	3,414	7.4%	−0.049	−0.002
Non-Alzheimer dementia[d]	108	0.1%	377	0.8%	−0.698	**−0.103**
Osteoporosis	1,272	1.4%	936	2.0%	−0.647	−0.050
Parkinson	360	0.4%	291	0.6%	−0.239	−0.034
Pneumonia	1,667	1.8%	1,338	2.9%	−1.088	−0.072
Rheumatoid arthritis	1,689	1.8%	643	1.4%	0.438	0.035
Stroke (Transient ischemic attack)	1,471	1.6%	1,210	2.6%	−1.024	−0.071
Alcohol use	303	0.3%	160	0.3%	−0.018	−0.003
Anxiety disorder	10,832	11.7%	4,782	10.3%	1.384	0.044

Patient characteristics[a]	Ozempic		Sitagliptin		Covariate balance	
	Number/mean	Percent/standard deviation[b]	Number/mean	Percent/standard deviation[b]	Absolute difference	Standardized difference
Bipolar disorder[d]	2,073	2.2%	634	1.4%	0.872	0.066
Cerebral palsy[d]	19	0.0%	11	0.0%	−0.003	−0.002
Depressive disorder[d]	6,063	6.6%	1,655	3.6%	2.983	**0.136**
Drug use disorder	1,458	1.6%	730	1.6%	−0.000	−0.000
Epilepsy	377	0.4%	274	0.6%	−0.184	−0.026
Fibromyalgia (chronic pain)	1,185	1.3%	1,057	2.3%	−1.003	−0.076
HIV	225	0.2%	95	0.2%	0.038	0.008
Intellectual disability[d]	47	0.1%	45	0.1%	−0.046	−0.017
Learning disability[d]	13	0.0%	9	0.0%	−0.005	−0.004
Leukemia (lymphoma)	26	0.0%	32	0.1%	−0.041	−0.019
Liver disease	3,822	4.1%	1,093	2.4%	1.773	0.100
Migraine	1,382	1.5%	378	0.8%	0.678	0.063
Mobility impairment[d]	52	0.1%	79	0.2%	−0.114	−0.034
Muscular dystrophy	71	0.1%	21	0.0%	0.031	0.013
Multiple sclerosis[d]	264	0.3%	83	0.2%	0.106	0.022
Obesity	8,932	9.7%	854	1.8%	7.818	**0.341**
Opioid disorder	68	0.1%	45	0.1%	−0.024	−0.008
Developmental delay	18	0.0%	12	0.0%	−0.006	−0.004
Peripheral vascular disease	1,681	1.8%	699	1.5%	0.308	0.024
Personality disorder	51	0.1%	43	0.1%	−0.038	−0.014
Posttraumatic stress disorder	147	0.2%	97	0.2%	−0.051	−0.012

Patient characteristics[a]	Ozempic		Sitagliptin		Covariate balance	
	Number/mean	Percent/standard deviation[b]	Number/mean	Percent/standard deviation[b]	Absolute difference	Standardized difference
Present chronic ulcer	1,023	1.1%	421	0.9%	0.197	0.020
Schizophrenia[d]	900	1.0%	575	1.2%	−0.269	−0.026
Schizophrenic psychotic disorder	105	0.1%	122	0.3%	−0.150	−0.035
Blind/visual impairment[d]	216	0.2%	134	0.3%	−0.056	−0.011
Deaf/hearing impairment[d]	1,561	1.7%	870	1.9%	−0.192	−0.014
Spinal injury	224	0.2%	178	0.4%	−0.142	−0.025
Tobacco use	737	0.8%	342	0.7%	0.058	0.007
Traumatic brain injury	609	0.7%	326	0.7%	−0.046	−0.006
Viral hepatitis	430	0.5%	254	0.5%	−0.084	−0.012
Mental/physical impairment	1,874	2.0%	1,122	2.4%	−0.398	−0.027
Insulin	33,071	35.8%	4,602	9.9%	25.833	**0.646**
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	16.1	11.8	10.6	8.7	5.511	**0.532**
Mean number of emergency room encounters	0.4	1.6	0.4	1.2	−0.015	−0.011
Mean number of inpatient hospital encounters	0.1	0.4	0.1	0.5	−0.037	−0.079
Mean number of filled prescriptions	81.0	179.4	63.4	126.2	17.580	**0.113**
Mean number of generics dispensed	10.3	5.3	8.3	5.1	2.063	**0.398**

Patient characteristics[a]	Ozempic		Sitagliptin		Covariate balance	
	Number/mean	Percent/standard deviation[b]	Number/mean	Percent/standard deviation[b]	Absolute difference	Standardized difference
Mean number of unique drug classes dispensed	10.2	5.0	8.2	4.9	1.984	**0.402**

Note: This table has not been copy-edited.

[a]Covariates in bold show a standardized difference greater than 0.1.

[b]Value represents standard deviation where no % follows the value

[c]The Charlson/Elixhauser Combined Comorbidity Score is calculated based on comorbidities observed during a requester-defined window around the exposure episode start date. (Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-759).

[d]These covariates were not included in the propensity score logistic regression model.

Table 4: Baseline Characteristics of Study Patients After Propensity Score Matching — Ozempic Versus Sitagliptin

Patient Characteristics	Ozempic		Sitagliptin		Covariate Balance	
	Number/Mean	Percent/Standard Deviation[a]	Number/Mean	Percent/Standard Deviation[a]	Absolute Difference	Standardized Difference
Unique patients	30,089	32.6%	30,089	65.0%	N/A	N/A
Demographic Characteristics						
Age (years)	66.6	10.1	66.5	11.5	0.078	0.007
18 to 39 years	840	2.8%	1,124	3.7%	−0.944	−0.053
40 to 64 years	8,124	27.0%	8,811	29.3%	−2.283	−0.051
≥ 65 years	21,125	70.2%	20,154	67.0%	3.227	0.070
Sex						
Female	14,623	48.6%	14,546	48.3%	0.256	0.005
Male	15,466	51.4%	15,543	51.7%	−0.256	−0.005
Year						
2018	1,214	19.2%	1,170	18.5%	0.697	0.018
2019	3,935	13.6%	3,989	13.8%	−0.187	−0.005

Patient Characteristics	Ozempic		Sitagliptin		Covariate Balance	
	Number/Mean	Percent/Standard Deviation[a]	Number/Mean	Percent/Standard Deviation[a]	Absolute Difference	Standardized Difference
2020	6,418	21.3%	6,333	21.0%	0.282	0.007
2021	8,051	26.8%	8,098	26.9%	−0.156	−0.004
2022	8,378	27.8%	8,394	27.9%	−0.053	−0.001
2023	2,093	7.2%	2,105	7.3%	−0.042	−0.002
Health Characteristics						
Charlson/Elixhauser combined comorbidity score[b]	0.3	0.9	0.3	0.9	0.010	0.012
Anemia	1,287	4.3%	1,266	4.2%	0.070	0.003
Arrhythmia	2,073	6.9%	2,044	6.8%	0.096	0.004
Autoimmune disease	1,322	4.4%	1,334	4.4%	−0.040	−0.002
Bacterial infection	781	2.6%	770	2.6%	0.037	0.002
Coagulopathy	110	0.4%	101	0.3%	0.030	0.005
Colonoscopy	1,626	5.4%	1,592	5.3%	0.113	0.005
Degenerative disease of central nervous system	326	1.1%	301	1.0%	0.083	0.008
Fluid and electrolyte disorder	396	1.3%	375	1.2%	0.070	0.006
Gallstones	117	0.4%	127	0.4%	−0.033	−0.005
Hyperparathyroidism	8	0.0%	9	0.0%	−0.003	−0.002
Mammogram	6,095	20.3%	6,066	20.2%	0.096	0.002
Other infections	243	0.8%	225	0.7%	0.060	0.007
Psychosis	812	2.7%	784	2.6%	0.093	0.006

Patient Characteristics	Ozempic		Sitagliptin		Covariate Balance	
	Number/Mean	Percent/Standard Deviation[a]	Number/Mean	Percent/Standard Deviation[a]	Absolute Difference	Standardized Difference
Pulmonary circulation disorders	26	0.1%	25	0.1%	0.003	0.001
Pulmonary disease	2,067	6.9%	2,022	6.7%	0.150	0.006
Renal failure	17	0.1%	18	0.1%	−0.003	−0.001
Gout medications	1,539	5.1%	1,550	5.2%	−0.037	−0.002
Sertraline	818	2.7%	821	2.7%	−0.010	−0.001
Sulfa antibiotic	817	2.7%	792	2.6%	0.083	0.005
AMI	317	1.1%	324	1.1%	−0.023	−0.002
Alzheimer disease[c]	618	2.1%	725	2.4%	−0.356	−0.024
Asthma	1,112	3.7%	1,102	3.7%	0.033	0.002
Benign prostatic hypertrophy	946	3.1%	939	3.1%	0.023	0.001
Cataract	2,163	7.2%	2,211	7.3%	−0.160	−0.006
COPD	790	2.6%	777	2.6%	0.043	0.003
Depressive bipolar disorder	552	1.8%	514	1.7%	0.126	0.010
Diabetes	28,496	94.7%	28,609	95.1%	−0.376	−0.017
Glaucoma	2,345	7.8%	2,403	8.0%	−0.193	−0.007
Heart failure	1,146	3.8%	1,146	3.8%	0.000	0.000
Hip fracture	109	0.4%	105	0.3%	0.013	0.002
Hyperlipidemia	1,905	6.3%	1,896	6.3%	0.030	0.001
Hypertension	8,765	29.1%	8,641	28.7%	0.412	0.009
Hypothyroid	744	2.5%	761	2.5%	−0.056	−0.004
Ischemic heart disease	2,566	8.5%	2,555	8.5%	0.037	0.001

Patient Characteristics	Ozempic		Sitagliptin		Covariate Balance	
	Number/Mean	Percent/Standard Deviation[a]	Number/Mean	Percent/Standard Deviation[a]	Absolute Difference	Standardized Difference
Non-Alzheimers dementia[c]	76	0.3%	123	0.4%	−0.156	−0.027
Osteoporosis	502	1.7%	481	1.6%	0.070	0.006
Parkinson	166	0.6%	150	0.5%	0.053	0.007
Pneumonia	692	2.3%	644	2.1%	0.160	0.011
Rheumatoid arthritis	460	1.5%	470	1.6%	−0.033	−0.003
Stroke (Transient ischemic attack)	585	1.9%	586	1.9%	−0.003	−0.000
Alcohol use	82	0.3%	83	0.3%	−0.003	−0.001
Anxiety disorder	3,277	10.9%	3,221	10.7%	0.186	0.006
Bipolar disorder[c]	475	1.6%	427	1.4%	0.160	0.013
Cerebral palsy[c]	9	0.0%	10	0.0%	−0.003	−0.002
Depressive disorder[c]	1,222	4.1%	1,173	3.9%	0.163	0.008
Drug use disorder	446	1.5%	435	1.4%	0.037	0.003
Epilepsy	135	0.4%	134	0.4%	0.003	0.000
Fibromyalgia chronic pain	592	2.0%	575	1.9%	0.056	0.004
HIV	63	0.2%	56	0.2%	0.023	0.005
Intellectual disability[c]	22	0.1%	35	0.1%	−0.043	−0.014
Leukemia lymphoma	16	0.1%	13	0.0%	0.010	0.005
Liver disease	781	2.6%	788	2.6%	−0.023	−0.001
Migraine	294	1.0%	285	0.9%	0.030	0.003
Mobility impairment[c]	25	0.1%	26	0.1%	−0.003	−0.001
Muscular dystrophy	14	0.0%	14	0.0%	0.000	0.000

Patient Characteristics	Ozempic		Sitagliptin		Covariate Balance	
	Number/Mean	Percent/Standard Deviation[a]	Number/Mean	Percent/Standard Deviation[a]	Absolute Difference	Standardized Difference
Multiple sclerosis[c]	79	0.3%	58	0.2%	0.070	0.015
Obesity	844	2.8%	752	2.5%	0.306	0.019
Opioid disorder	27	0.1%	35	0.1%	−0.027	−0.008
Peripheral vascular disease	504	1.7%	490	1.6%	0.047	0.004
Personality disorder	18	0.1%	24	0.1%	−0.020	−0.008
Posttraumatic stress disorder	63	0.2%	62	0.2%	0.003	0.001
Present chronic ulcer	231	0.8%	230	0.8%	0.003	0.000
Schizophrenia[c]	287	1.0%	334	1.1%	−0.156	−0.015
Schizophrenia psychotic	50	0.2%	50	0.2%	0.000	0.000
Blind/visual impairment[c]	69	0.2%	87	0.3%	−0.060	−0.012
Deaf/hearing impairment[c]	580	1.9%	551	1.8%	0.096	0.007
Spinal injury	97	0.3%	100	0.3%	−0.010	−0.002
Tobacco use	215	0.7%	214	0.7%	0.003	0.000
Traumatic brain injury	190	0.6%	186	0.6%	0.013	0.002
Viral hepatitis	148	0.5%	137	0.5%	0.037	0.005
Mental physical impairment	693	2.3%	695	2.3%	−0.007	−0.000
Insulin	4,506	15.0%	4,372	14.5%	0.445	0.013
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	11.4	8.7	11.4	8.9	0.047	0.005
Mean number of emergency room encounters	0.4	2.1	0.4	1.2	0.002	0.001

Patient Characteristics	Ozempic		Sitagliptin		Covariate Balance	
	Number/Mean	Percent/Standard Deviation[a]	Number/Mean	Percent/Standard Deviation[a]	Absolute Difference	Standardized Difference
Mean number of inpatient hospital encounters	0.1	0.4	0.1	0.4	0.004	0.010
Mean number of filled prescriptions	70.4	141.4	69.6	126.4	0.823	0.006
Mean number of generics dispensed[c]	9.1	4.5	9.2	5.1	−0.009	−0.002
Mean number of unique drug classes dispensed	9.1	4.3	9.1	4.9	0.011	0.002

Note: This table has not been copy-edited.

[a]Value represents standard deviation where no % follows the value.

[b]The Charlson/Elixhauser Combined Comorbidity Score is calculated based on comorbidities observed during a requester-defined window around the exposure episode start date. (Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011;64(7):749-759).

[c]These covariates were not included in the propensity score logistic regression model.

Table 5: Contribution of Study Provinces to the Pooled, PS-Matched Cohort

Patient Characteristics	British Columbia		Manitoba		Ontario		Saskatchewan	
	Number/Mean	Percent/ Standard Deviation	Number/Mean	Percent/ Standard Deviation	Number/Mean	Percent/ Standard Deviation	Number/Mean	Percent/ Standard Deviation
Unique patients								
Ozempic (N = 30,089)	4,156	13.8%	2,154	7.2%	22,592	75.1%	1,187	3.9%
Sitagliptin (N = 30,089)	4,156	13.8%	2,154	7.2%	22,592	75.1%	1,187	3.9%
Age (mean years)								
Ozempic	60.2	10.9	57.0	12.2	69.0	9.6	60.4	11.7
Sitagliptin	59.9	12.2	56.8	13.6	69.0	11.1	60.3	13.1
Sex (female)								

Patient Characteristics	British Columbia		Manitoba		Ontario		Saskatchewan	
	Number/Mean	Percent/ Standard Deviation	Number/Mean	Percent/ Standard Deviation	Number/Mean	Percent/ Standard Deviation	Number/Mean	Percent/ Standard Deviation
Ozempic (N = 14,623)	1,771	12.1%	1,064	7.3%	11,270	77.1%	518	3.5%
Sitagliptin (N = 14,546)	1,737	11.9%	1,076	7.4%	11,193	76.9%	540	3.7%

Note: This table has not been copy-edited.

Table 6: Baseline Characteristics of Study Patients Before Propensity Score Matching — Ozempic Versus Empagliflozin (in Ontario)

Patient Characteristics[a]	Ozempic		Empagliflozin		Covariate Balance	
	Number/Mean	Percent/ Standard Deviation[b]	Number/Mean	Percent/ Standard Deviation[b]	Absolute Difference	Standardized Difference
Unique patients	23,857	100.0%	44,185	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	67.9	9.6	71.1	9.5	−3.140	**−0.329**
18 to 39 years	402	1.7%	498	1.1%	0.558	0.047
40 to 64 years	5,273	22.1%	6,137	13.9%	8.213	**0.215**
≥ 65 years	18,182	76.2%	37,550	85.0%	−8.771	**−0.223**
Sex						
Female	10,730	45.0%	19,151	43.3%	1.634	0.033
Male	13,127	55.0%	25,034	56.7%	−1.634	−0.033
Year						
2019	6,066	25.4%	4,878	11.0%	14.387	**0.379**
2020	8,692	36.4%	15,373	34.8%	1.641	0.034

Patient Characteristics[a]	Ozempic		Empagliflozin		Covariate Balance	
	Number/Mean	Percent/ Standard Deviation[b]	Number/Mean	Percent/ Standard Deviation[b]	Absolute Difference	Standardized Difference
2021	7,494	31.4%	19,436	44.0%	−12.576	**−0.262**
2022	1,605	6.7%	4,498	10.2%	−3.452	**−0.124**
Health Characteristics						
Charlson/Elixhauser combined comorbidity score[c]	0.4	0.9	0.5	1.1	−0.123	**−0.125**
Anemia	1,181	5.0%	2,383	5.4%	−0.443	−0.020
Arrhythmia	1,833	7.7%	4,234	9.6%	−1.899	−0.068
Autoimmune disease	1,170	4.9%	1,795	4.1%	0.842	0.041
Bacterial infection	661	2.8%	1,297	2.9%	−0.165	−0.010
Coagulopathy	83	0.3%	226	0.5%	−0.164	−0.025
Colonoscopy	1,704	7.1%	2,688	6.1%	1.059	0.043
Degenerative disease of central nervous system	208	0.9%	473	1.1%	−0.199	−0.020
Fluid and electrolyte disorder	270	1.1%	1,004	2.3%	−1.141	−0.088
Gallstones	93	0.4%	189	0.4%	−0.038	−0.006
Hyperparathyroidism	6	0.0%	11	0.0%	0.000	0.000
Mammogram	5,786	24.3%	9,987	22.6%	1.650	0.039
Other infections	201	0.8%	468	1.1%	−0.217	−0.022
Psychosis	567	2.4%	1,049	2.4%	0.003	0.000
Pulmonary circulation disorders	18	0.1%	55	0.1%	−0.049	−0.016
Pulmonary disease	1,595	6.7%	2,999	6.8%	−0.102	−0.004
Renal failure	12	0.1%	33	0.1%	−0.024	−0.010

Patient Characteristics[a]	Ozempic		Empagliflozin		Covariate Balance	
	Number/Mean	Percent/ Standard Deviation[b]	Number/Mean	Percent/ Standard Deviation[b]	Absolute Difference	Standardized Difference
Weight loss	< 6	0.0%	13	0.0%	−0.025	−0.019
Gout medications	1,166	4.9%	2,335	5.3%	−0.397	−0.018
Sertraline	709	3.0%	1,074	2.4%	0.541	0.033
Sulfa antibiotics	591	2.5%	843	1.9%	0.569	0.039
AMI	304	1.3%	1,326	3.0%	−1.727	**−0.120**
Alzheimer's disease[d]	502	2.1%	1,478	3.3%	−1.241	−0.076
Asthma	862	3.6%	1,484	3.4%	0.255	0.014
Benign prostatic hypertrophy	1,001	4.2%	1,798	4.1%	0.127	0.006
Cataract	1,938	8.1%	3,418	7.7%	0.388	0.014
Chronic obstructive pulmonary disease	644	2.7%	1,352	3.1%	−0.360	−0.022
Depressive bipolar disorder	375	1.6%	628	1.4%	0.151	0.012
Diabetes	23,421	98.2%	41,477	93.9%	4.301	**0.221**
Glaucoma	2,031	8.5%	3,604	8.2%	0.357	0.013
Heart failure	1,222	5.1%	3,328	7.5%	−2.410	−0.099
Hip fracture	72	0.3%	208	0.5%	−0.169	−0.027
Hyperlipidemia	1,132	4.7%	2,946	6.7%	−1.922	−0.083
Hypertension	5,620	23.6%	13,861	31.4%	−7.813	**−0.176**
Hypothyroid	388	1.6%	1,015	2.3%	−0.671	−0.048
Ischemic heart disorder	3,783	15.9%	7,404	16.8%	−0.900	−0.024
Non-Alzheimer dementia[d]	43	0.2%	231	0.5%	−0.343	−0.058
Osteoporosis	384	1.6%	1,001	2.3%	−0.656	−0.048

Patient Characteristics[a]	Ozempic		Empagliflozin		Covariate Balance	
	Number/Mean	Percent/ Standard Deviation[b]	Number/Mean	Percent/ Standard Deviation[b]	Absolute Difference	Standardized Difference
Parkinson	123	0.5%	276	0.6%	−0.109	−0.014
Pneumonia	612	2.6%	1,296	2.9%	−0.368	−0.022
Rheumatoid arthritis	409	1.7%	682	1.5%	0.171	0.013
Stroke (transient ischemic attack)	519	2.2%	1,319	3.0%	−0.810	−0.051
Attention-deficit/hyperactivity disorder	< 6	0.0%	7	0.0%	−0.007	−0.007
Alcohol use	39	0.2%	125	0.3%	−0.119	−0.025
Anxiety disorder	2,694	11.3%	4,455	10.1%	1.210	0.039
Bipolar[d]	340	1.4%	498	1.1%	0.298	0.027
Cerebral palsy[d]	< 6	0.0%	13	0.0%	−0.021	−0.015
Cystic fibrosis	< 6	0.0%	< 6	0.0%	−0.005	−0.006
Depressive disorder[d]	864	3.6%	1,154	2.6%	1.010	0.058
Drug use disorder	311	1.3%	630	1.4%	−0.122	−0.011
Epilepsy	97	0.4%	219	0.5%	−0.089	−0.013
Fibromyalgia chronic pain	492	2.1%	996	2.3%	−0.192	−0.013
HIV	64	0.3%	92	0.2%	0.060	0.012
Intellectual disability[d]	12	0.1%	30	0.1%	−0.018	−0.007
Learning disability[d]	< 6	0.0%	< 6	0.0%	−0.003	−0.003
Leukemia lymphoma	8	0.0%	27	0.1%	−0.028	−0.013
Liver disease	624	2.6%	980	2.2%	0.398	0.026
Migraine	206	0.9%	317	0.7%	0.146	0.016
Mobility impairment[d]	17	0.1%	83	0.2%	−0.117	−0.032

Patient Characteristics[a]	Ozempic		Empagliflozin		Covariate Balance	
	Number/Mean	Percent/ Standard Deviation[b]	Number/Mean	Percent/ Standard Deviation[b]	Absolute Difference	Standardized Difference
Muscular Dystrophy	8	0.0%	18	0.0%	−0.007	−0.004
Multiple sclerosis[d]	41	0.2%	60	0.1%	0.036	0.009
Obesity	935	3.9%	696	1.6%	2.344	**0.144**
Opioid disorder	17	0.1%	50	0.1%	−0.042	−0.014
Developmental delays	< 6	0.0%	< 6	0.0%	−0.003	−0.003
Peripheral vascular disease	667	2.8%	1,012	2.3%	0.505	0.032
Personality disorder	18	0.1%	25	0.1%	0.019	0.007
Posttraumatic stress disorder	50	0.2%	105	0.2%	−0.028	−0.006
Pressure chronic ulcer	193	0.8%	295	0.7%	0.141	0.017
Schizophrenia[d]	219	0.9%	486	1.1%	−0.182	−0.018
Schizophrenic psychotic	34	0.1%	107	0.2%	−0.100	−0.023
Blind (visual impairment)[d]	65	0.3%	142	0.3%	−0.049	−0.009
Deaf (hearing impairment)[d]	566	2.4%	1,012	2.3%	0.082	0.005
Spinal bifida	< 6	0.0%	6	0.0%	−0.005	−0.005
Spinal injury	85	0.4%	190	0.4%	−0.074	−0.012
Tobacco use	179	0.8%	355	0.8%	−0.053	−0.006
Traumatic brain injury	163	0.7%	320	0.7%	−0.041	−0.005
Viral hepatitis	105	0.4%	221	0.5%	−0.060	−0.009
Mental physical impairment	655	2.7%	1,258	2.8%	−0.102	−0.006
Insulin	11,667	48.9%	6,893	15.6%	33.304	**0.762**

Patient Characteristics[a]	Ozempic		Empagliflozin		Covariate Balance	
	Number/Mean	Percent/ Standard Deviation[b]	Number/Mean	Percent/ Standard Deviation[b]	Absolute Difference	Standardized Difference
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	12.0	8.8	10.4	8.2	1.606	**0.189**
Mean number of emergency room encounters	0.4	1.3	0.5	1.5	−0.073	−0.052
Mean number of inpatient hospital encounters	0.1	0.4	0.2	0.5	−0.069	**−0.150**
Mean number of filled prescriptions	111.6	165.3	78.2	140.6	33.340	**0.217**
Mean number of generics dispensed[d]	12.1	5.3	9.2	4.9	2.826	**0.558**
Mean number of unique drug classes dispensed	11.8	4.9	9.1	4.6	2.656	**0.555**

Notes: This table has not been copy-edited.

For Ozempic vs. empagliflozin, the Ontario data are available from September 30, 2019, to March 31, 2022.

[a]Covariates in bold show a standardized difference greater than 0.1.

[b]Value represents standard deviation where no % follows the value

[c]The Charlson/Elixhauser Combined Comorbidity Score is calculated based on comorbidities observed during a requester-defined window around the exposure episode start date. (Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-759).

[d]These covariates were not included in the propensity score logistic regression model.

Table 7: Baseline Characteristics of Study Patients After Propensity Score Matching — Ozempic Versus Empagliflozin (in Ontario)

Patient characteristics	Ozempic		Empagliflozin		Covariate Balance	
	Number/mean	Percent/standard deviation[a]	Number/mean	Percent/standard deviation[a]	Absolute difference	Standardized difference
Unique patients	17,810	74.7%	17,810	40.3%	N/A	N/A
Demographic Characteristics						
Age (years)	68.9	9.1	68.9	10.5	0.022	0.002
18 to 39 years	229	1.3%	379	2.1%	−0.842	−0.065
40 to 64 years	3,240	18.2%	3,685	20.7%	−2.499	−0.063
≥ 65 years	14,341	80.5%	13,746	77.2%	3.341	0.082
Sex						
Female	7,888	44.3%	7,896	44.3%	−0.045	−0.001
Male	9,922	55.7%	9,914	55.7%	0.045	0.001
Year						
2019	3,346	18.8%	3,379	19.0%	−0.185	−0.005
2020	6,644	37.3%	6,671	37.5%	−0.152	−0.003
2021	6,430	36.1%	6,396	35.9%	0.191	0.004
2022	1,390	7.8%	1,364	7.7%	0.146	0.005
Health Characteristics						
Charlson/Elixhauser combined comorbidity score[b]	0.4	0.9	0.4	0.9	−0.003	−0.004
Anemia	888	5.0%	878	4.9%	0.056	0.003
Arrhythmia	1,424	8.0%	1,433	8.0%	−0.051	−0.002
Autoimmune disease	809	4.5%	809	4.5%	0.000	0.000

Patient characteristics	Ozempic		Empagliflozin		Covariate Balance	
	Number/mean	Percent/standard deviation[a]	Number/mean	Percent/standard deviation[a]	Absolute difference	Standardized difference
Bacterial infection	467	2.6%	459	2.6%	0.045	0.003
Coagulopathy	70	0.4%	65	0.4%	0.028	0.005
Colonoscopy	1,204	6.8%	1,253	7.0%	−0.275	−0.011
Degenerative disease of central nervous system	167	0.9%	160	0.9%	0.039	0.004
Fluid and electrolyte disorder	230	1.3%	241	1.4%	−0.062	−0.005
Gallstones	72	0.4%	82	0.5%	−0.056	−0.009
Hyperparathyroidism	6	0.0%	6	0.0%	0.000	0.000
Mammogram	4,217	23.7%	4,171	23.4%	0.258	0.006
Organ transplant	0	0.0%	< 6	0.0%	NaN	NaN
Other infections	153	0.9%	162	0.9%	−0.051	−0.005
Psychosis	420	2.4%	413	2.3%	0.039	0.003
Pulmonary circulation disorders	13	0.1%	12	0.1%	0.006	0.002
Pulmonary disease	1,134	6.4%	1,133	6.4%	0.006	0.000
Renal failure	10	0.1%	8	0.0%	0.011	0.005
Weight loss	< 6	0.0%	< 6	0.0%	−0.011	−0.011
Gout medications	881	4.9%	887	5.0%	−0.034	−0.002
Sertraline	504	2.8%	489	2.7%	0.084	0.005
Sulfa antibiotics	400	2.2%	417	2.3%	−0.095	−0.006
AMI	265	1.5%	254	1.4%	0.062	0.005
Alzheimer's disease[c]	409	2.3%	500	2.8%	−0.511	−0.032
Asthma	601	3.4%	611	3.4%	−0.056	−0.003

Patient characteristics	Ozempic		Empagliflozin		Covariate Balance	
	Number/mean	Percent/standard deviation[a]	Number/mean	Percent/standard deviation[a]	Absolute difference	Standardized difference
Benign prostatic hypertrophy	723	4.1%	744	4.2%	−0.118	−0.006
Cataract	1,413	7.9%	1,391	7.8%	0.124	0.005
COPD	465	2.6%	475	2.7%	−0.056	−0.004
Depressive bipolar disorder	264	1.5%	259	1.5%	0.028	0.002
Diabetes	17,384	97.6%	17,421	97.8%	−0.208	−0.014
Glaucoma	1,473	8.3%	1,472	8.3%	0.006	0.000
Heart failure	960	5.4%	957	5.4%	0.017	0.001
Hip fracture	62	0.3%	62	0.3%	0.000	0.000
Hyperlipidemia	892	5.0%	870	4.9%	0.124	0.006
Hypertension	4,495	25.2%	4,419	24.8%	0.427	0.010
Hypothyroid	312	1.8%	309	1.7%	0.017	0.001
Ischemic heart disorder	2,778	15.6%	2,762	15.5%	0.090	0.002
Non-Alzheimer dementia[c]	43	0.2%	53	0.3%	−0.056	−0.011
Osteoporosis	311	1.7%	293	1.6%	0.101	0.008
Parkinson	99	0.6%	95	0.5%	0.022	0.003
Pneumonia	454	2.5%	472	2.7%	−0.101	−0.006
Rheumatoid arthritis	291	1.6%	300	1.7%	−0.051	−0.004
Stroke (transient ischemic attack)	397	2.2%	402	2.3%	−0.028	−0.002
ADHD[d]	< 6	0.0%	< 6	0.0%	0.000	0.000
Alcohol use disorder	37	0.2%	38	0.2%	−0.006	−0.001
Anxiety disorder	1,904	10.7%	1,949	10.9%	−0.253	−0.008
Bipolar[c]	239	1.3%	219	1.2%	0.112	0.010

Patient characteristics	Ozempic		Empagliflozin		Covariate Balance	
	Number/mean	Percent/standard deviation[a]	Number/mean	Percent/standard deviation[a]	Absolute difference	Standardized difference
Depressive disorder[c]	564	3.2%	571	3.2%	−0.039	−0.002
Drug use disorder	235	1.3%	227	1.3%	0.045	0.004
Epilepsy	74	0.4%	92	0.5%	−0.101	−0.015
Fibromyalgia chronic pain	354	2.0%	361	2.0%	−0.039	−0.003
HIV	42	0.2%	42	0.2%	0.000	0.000
Intellectual disability[c]	10	0.1%	11	0.1%	−0.006	−0.002
Leukemia lymphoma	7	0.0%	< 6	0.0%	0.011	0.006
Liver disease	440	2.5%	429	2.4%	0.062	0.004
Migraine	139	0.8%	135	0.8%	0.022	0.003
Mobility impairment[c]	13	0.1%	23	0.1%	−0.056	−0.018
Muscular dystrophy	7	0.0%	7	0.0%	0.000	0.000
Multiple sclerosis[c]	31	0.2%	27	0.2%	0.022	0.006
Obesity	466	2.6%	476	2.7%	−0.056	−0.003
Opioid disorder	15	0.1%	15	0.1%	0.000	0.000
Developmental delays	< 6	0.0%	< 6	0.0%	0.011	0.011
Peripheral vascular disease	445	2.5%	426	2.4%	0.107	0.007
Personality disorder	8	0.0%	11	0.1%	−0.017	−0.007
Posttraumatic stress disorder	32	0.2%	31	0.2%	0.006	0.001
Pressure chronic ulcer	123	0.7%	122	0.7%	0.006	0.001
Schizophrenia[c]	166	0.9%	191	1.1%	−0.140	−0.014
Schizophrenic psychotic	28	0.2%	32	0.2%	−0.022	−0.005
Blindness (visual impairment)[c]	45	0.3%	65	0.4%	−0.112	−0.020

Patient characteristics	Ozempic		Empagliflozin		Covariate Balance	
	Number/mean	Percent/standard deviation[a]	Number/mean	Percent/standard deviation[a]	Absolute difference	Standardized difference
Deaf (hearing impairment)[c]	422	2.4%	389	2.2%	0.185	0.012
Spinal injury	66	0.4%	66	0.4%	0.000	0.000
Tobacco use	129	0.7%	135	0.8%	−0.034	−0.004
Traumatic brain injury	119	0.7%	116	0.7%	0.017	0.002
Viral hepatitis	84	0.5%	90	0.5%	−0.034	−0.005
Mental physical impairment	485	2.7%	484	2.7%	0.006	0.000
Insulin	6,156	34.6%	6,069	34.1%	0.488	0.010
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters	11.3	8.1	11.3	8.7	0.009	0.001
Mean number of emergency room encounters	0.4	1.4	0.5	1.6	−0.031	−0.020
Mean number of inpatient hospital encounters	0.1	0.4	0.1	0.4	−0.002	−0.005
Mean number of filled prescriptions	98.2	154.6	98.5	163.1	−0.292	−0.002
Mean number of generics dispensed[c]	11.0	4.6	11.0	5.2	−0.028	−0.006
Mean number of unique drug classes dispensed	10.8	4.4	10.8	4.9	−0.031	−0.007

Notes: This table has not been copy-edited.

For Ozempic vs. empagliflozin, the Ontario data are available from September 30, 2019, to March 31, 2022.

[a]Value represents standard deviation where no % follows the value.

[b]The Charlson/Elixhauser Combined Comorbidity Score is calculated based on comorbidities observed during a requester-defined window around the exposure episode start date. (Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-759).

[c]Covariates in italics were not included in the propensity score logistic regression model.

Table 8: Summary of Time to End of At-Risk Period According to Exposure Group

Exposure		Distribution of At-Risk Time in Days						
Drug	Total Number of Episodes	Minimum	Q1	Median	Q3	Maximum	Mean	Standard Deviation
Ozempic	92,948	0	22	43	103	182	69.5	62.5
Sitagliptin	46,383	0	43	103	182	182	102.1	71.2

Note: This table has not been copy-edited.

Table 9: Summary of Reasons for End of At-Risk Period According to Exposure Group[a]

Exposure		Censoring Reason									
		End of exposure episode[b]		Occurrence of User-Defined censoring criteria[c]		Death[d]		Disenrolment[e]		End of data/study period[f]	
Drug	Total Number of Episodes	Number	%	Number	%	Number	%	Number	%	Number	%
Ozempic	92,948	47,823	51.5%	34,834	37.5%	92	0.1%	5,222	5.6%	5,037/10,310	5.4/11.1%
Sitagliptin	46,383	30,235	65.2%	13,150	28.4%	296	0.6%	2,962	6.4%	2,545/2,661	5.5/5.7%

Note: This table has not been copy-edited.

[a]An episode may be censored due to more than one reason if they occur on the same date. Therefore, the sum of the reasons for censoring may be greater than the total number of episodes.

[b]Represents episodes censored due to end of the exposure episode. In as-treated analyses, exposure episodes are defined using days supplied as recorded in outpatient pharmacy dispensing records, and episodes end after days supplied are exhausted or a predetermined maximum episode duration is met.

[c]Represents episodes censored due to occurrence of user-defined criteria using drug, procedure, diagnosis, and/or laboratory codes.

[d]Represents episodes censored due to death.

[e]Represents episodes censored due to disenrolment from health plan. Data Partners often artificially assign a "disenrolment" date equal to data end date for members still enrolled on that date. Therefore, a patient may have dual reasons for censoring as "disenrolment" and "end of data" on the same day - this can be interpreted as right-censoring in most cases.

[f]Represents episodes censored due to Data Partner data end date or user-specified study end date.

Table 10: Signal Identification Outcome Assessment[a] Derived From Emergency Department and Inpatient *ICD-10-CA* Discharge Diagnoses Using an Unconditional Bernoulli Tree-Based Scan Statistic[b] Among Matched Ozempic and Sitagliptin Initiators (Including Insulin)

ICD-10-CA node description	Node	Node parent	Tree level	Number of observations	Observed cases	Expected cases	Relative risk	LLR[b]	P value
Nausea *with* vomiting	R113grp	R11grp	4	38	27	19	1.42	3.476	0.926
Nausea *and* vomiting	R11grp	R10_R19	3	68	44	34	1.29	2.985	0.998
Nausea alone	R111grp	R11grp	4	7	6	3.5	1.71	—	—
Vomiting alone	R112grp	R11grp	4	23	11	11.5	0.96	—	—
Other obesity	E668ngrp	E668grp	5	16	13	8	1.63	3.369	0.996
Polyneuropathy in diseases classified elsewhere	G63grp	G60_G65	3	21	16	10.5	1.52	3.030	0.998
Other disorders of nervous system in diseases classified elsewhere	G9 grp	G89_G99	3	26	19	13	1.46	2.877	0.999

LLR = unconditional Bernoulli log likelihood ratio-based test statistic

Note: This table has not been copy-edited.

[a]Outcomes were assessed at the third through sixth level with a 400-day washout using the hierarchical ICD-10-CA tree structure.

[b]Refer to Appendix 3 for details on the calculation of the unconditional Bernoulli log likelihood ratio (LLR) based test statistic.

Table 11: Signal Identification Outcome Assessment[a] Derived From Emergency Department and Inpatient *ICD-10-CA* Discharge Diagnoses Using an Unconditional Bernoulli Tree-Based Scan Statistic[b] Among Matched Ozempic and Sitagliptin Initiators (Excluding Insulin)

ICD-10-CA node description	Node	Node parent	Tree level	Number of observations	Observed cases	Expected cases	Relative risk	LLR[b]	P value
Primary gonarthrosis, bilateral	M170grp	M17grp	4	13	12	6.5	1.85	5.485	0.282
Gonarthrosis [arthrosis of knee]	M17grp	M15_M19	3	47	34	23.5	1.45	4.862	0.359
Gonarthrosis, unspecified	M179grp	M17grp	4	26	16	13	1.23		
Superficial injury of wrist and hand	S60grp	S60_S69	3	12	11	6	1.83	4.876	0.358
Unspecified superficial injury of wrist and hand	S609grp	S60grp	4	7	6	3.5	1.71		
Gastroenteritis and colitis of unspecified origin	A099grp	A09grp	4	55	37	27.5	1.35	3.350	0.989
Diarrhea and gastroenteritis of presumed infectious origin	A09grp	A00_A09	3	59	39	29.5	1.32	3.114	0.990

LLR = unconditional Bernoulli log likelihood ratio-based test statistic

Note: This table has not been copy-edited.

[a]Outcomes were assessed at the third through sixth level with a 400-day washout using the hierarchical ICD-10-CA tree structure.

[b]Refer to Appendix 3 for details on the calculation of the unconditional Bernoulli log likelihood ratio (LLR) based test statistic.

Table 12: Signal Identification Outcome Assessment[a] Derived From Emergency Department and Inpatient *ICD-10-CA* Discharge Diagnoses Using an Unconditional Bernoulli Tree-Based Scan Statistic[b] Among Matched Ozempic and Empagliflozin Initiators In Ontario (Including Insulin)

ICD-10-CA description	Node	Parent node	Tree level	Number of observations	Observed cases	Expected cases	Relative risk	LLR[b]	P value
Depressive episode	F32grp	F30_F39	3	7	7	3.5	2.00	4.852	0.288
Other functional intestinal disorders	K59grp	K55_K64	3	25	19	12.5	1.52	3.552	0.698
Gastroenteritis and colitis of unspecified origin	A099grp	A09grp	4	29	21	14.5	1.45	3.020	0.948
Nausea and vomiting	R11grp	R10_R19	3	26	19	13	1.46	2.877	0.958
Diarrhea and gastroenteritis of presumed infectious origin	A09grp	A00_A09	3	31	22	15.5	1.42	2.812	0.958

LLR = unconditional Bernoulli log likelihood ratio-based test statistic

Note: This table has not been copy-edited.

[a]Outcomes were assessed at the third through sixth level with a 400-day washout using the hierarchical ICD-10-CA tree structure.

[b]Refer to Appendix 3 for details on the calculation of the unconditional Bernoulli log likelihood ratio (LLR) based test statistic.

For more information on CoLab and its work visit **colab.cadth.ca**

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