CoLab Network

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Drugs Health Technologies Health Systems

Common Data Model Report

# Utilization of Antidiabetic Drugs During Pregnancy

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This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

# Key Messages

**There is a need for current data on the use of antidiabetic drugs (ADDs)** during pregnancy in Canada.

**We conducted a cohort study in 3 Canadian provinces to demonstrate the feasibility** of replicating a US FDA Sentinel study of ADD use during pregnancy. We used Canadian data that were transformed into the Sentinel Common Data Model (CDM).

**Between 2012 and 2022, we identified 249,063 unique pregnancies** among 166,529 individuals across Manitoba, Ontario, and Saskatchewan. Of these, 3,308 individuals (2.0%) had pre-existing diabetes and 21,031 (12.6%) had gestational diabetes mellitus (GDM).

**Overall, 3.8% of live birth and stillbirth pregnancies were exposed to** insulin, 3.1% to metformin, and 0.3% to a sulfonylurea. Insulin use increased from 1.3% in the first trimester to 3.7% in the third trimester.

**Among the 4,058 pregnancies with pre-existing diabetes,** 86.0% were exposed to insulin, 50.4% to metformin, and 15.4% to a sulfonylurea, with the use of insulin increasing throughout pregnancy.

**Among the 24,448 pregnancies with GDM,** 23.4% were exposed to insulin and 18.9% to metformin, with use increasing throughout pregnancy and over the study period.

**To our knowledge, this is the first multiprovincial, population-based study of ADD use during pregnancy in Canada**, and the first Canadian project to use the Sentinel CDM to study drug use during pregnancy. We successfully demonstrated the feasibility of replicating the FDA Sentinel analysis using Canadian data transformed into the Sentinel CDM.

**Our findings confirm that a growing percentage of pregnancies are exposed to ADDs** in Canada. This highlights the importance of ongoing surveillance of the real-world use and safety of ADDs during pregnancy.

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# Abbreviations

| | |
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| **ADD** | antidiabetic drug |
| **CDM** | Common Data Model |
| **CNODES** | Canadian Network for Observational Drug Effect Studies |
| **DPP4** | dipeptidyl peptidase 4 |
| **GDM** | gestational diabetes mellitus |
| **GLP-1** | glucagon-like peptide 1 |
| ICD-9 | *International Classification of Diseases, Ninth Revision* |
| ICD-10-CA | *International Classification of Diseases, Tenth Revision, Canada* |
| **SGLT-2** | sodium-glucose cotransporter-2 |
| **TZD** | thiazolidinedione |

# Introduction and Rationale

## Background

The prevalence of diabetes and GDM have increased over the past 2 decades, leading to increasing exposure to ADDs during pregnancy.[1,2] Insulin is the first-line medication for the treatment of both pre-existing diabetes during pregnancy and GDM. Second-line medications are biguanides, such as metformin, and sulfonylureas, such as glyburide.[3] Metformin is the only oral ADD recommended during pregnancy; glyburide is typically reserved for patients who are unable to use insulin and for whom metformin is insufficient to maintain optimal glycemic control. As the prevalence of type 2 diabetes mellitus increases, there is increasing need to monitor the real-world use and safety of ADDs during pregnancy.

In January 2020, the US FDA Sentinel Initiative published a study of ADD use during pregnancy across multiple US health insurers leveraging the Sentinel CDM. This report covered the period 2001 to 2013 and demonstrated important trends in ADD therapy during pregnancy among persons with and without pre-existing diabetes.[1,4] A search for relevant Canadian studies identified a retrospective cohort study of 16,857 Alberta residents who were pregnant with GDM covering the period 2009 to 2014.[5] By 2014, the percentage prescribed an ADD had increased from 25% to 31.4%. Persons receiving insulin had increased to 28.3% and those receiving metformin had increased to 3.2%. Infants born large for gestational age were more common among pregnancies during which GDM was treated with insulin or metformin (17%) than when GDM was untreated (13%). The accrual periods of these studies are quite dated, particularly given the rapid increase in the prevalence of diabetes during pregnancy and the evolution of clinical practice guidelines for treatment with ADDs during pregnancy, particularly treatment for GDM.[6,7]

**Main Take-Aways**

The prevalence of diabetes and GDM have increased over the past 2 decades, leading to increasing exposure to ADDs during pregnancy.

The US FDA Sentinel Initiative conducted a national study on ADD use during pregnancy from 2001 to 2013. However, similar data for Canada are not available.

## Purpose of This Report

As 1 in a series of Sentinel CDM demonstration projects, the purpose of this study was to demonstrate the feasibility of replicating the Sentinel CDM–based analysis in Canada, extending the accrual period over a more contemporary time horizon using the most recent Canadian data transformed into the Sentinel CDM.

## Policy Issue

Given the rapid increase in the prevalence of diabetes during pregnancy and the evolution of recommendations for treatment, contemporary data are needed on the use of ADDs during pregnancy in Canada.

**Main Take-Aways**

As the prevalence of diabetes during pregnancy increases and treatment guidelines evolve, contemporary data are needed on the use of ADDs during pregnancy. This study aimed to replicate a US FDA Sentinel study of ADD use during pregnancy using Canadian data that was transformed into the Sentinel CDM.

### Policy Question

What is the utilization of ADDs during pregnancy in Canada?

### Research Question

Which ADDs were prescribed for the treatment of diabetes during pregnancy in Canada from 2012 to 2022, and were those drugs changing over time?

## Objectives

The objective of this project is to document the utilization of ADD among pregnant persons in Canada using data transformed into the Sentinel CDM.

Specifically, we aimed to:

- describe the baseline characteristics of pregnant persons at the time of conception
- describe the prevalence of use of specific ADDs overall and according to maternal characteristics and over time.

## Methods

### Study Design, Setting, and Membership

This was a multiprovincial, population-based cohort study of pregnant persons, aged 10 to 54 years, with a hospital discharge record of stillbirth or live birth between January 1, 2012, and December 31, 2022 (or the most recent data available at the time of study) in Manitoba, Ontario, and Saskatchewan. Since the study required prescription drug claims and the Ontario public drug plan only covers those receiving social assistance, the Ontario study was limited to these patients who otherwise met the study entry criteria. In Saskatchewan, drug claims with the required data elements were available only from January 1, 2017, onward. Consequently, the Saskatchewan study accrual period began January 2017.

We constructed 3 cohorts. The first was a base cohort of all eligible live birth or stillbirth pregnancies. The second comprised the subset of pregnancies among persons with pre-existing diabetes, identified as any pregnancy associated with the dispensing of a non-metformin ADD or dispensing of metformin with

a diabetes diagnosis code (*International Classification of Diseases, Ninth Revision* [*ICD-9*] 250x, *ICD-10 Canadian Modification* [*ICD-10-CA*] E10x-E14x) at any time in the 183 days preceding the estimated date of conception. We required that claims for metformin have an accompanying diabetes diagnosis because metformin may be used to treat other conditions, such as polycystic ovary syndrome. For the purposes of describing ADD therapy among those with GDM, the third cohort comprised the subset of pregnancies without an ADD dispensing or a diabetes diagnosis code in the 183 days preceding the estimated conception date who either had diagnosis code for GDM or were dispensed an ADD (including metformin) during the second or third trimester.

Live births and stillbirths were identified using a claims-based algorithm. The algorithm included *ICD10-CA* diagnosis codes specifying the gestational week of delivery, preterm delivery, or postterm delivery, which allowed us to estimate the duration of the pregnancy episode. In the case that specific pregnancy duration or preterm or postterm codes were missing, the pregnancy duration was set to 273 days for live births and 196 days for stillbirths. Pregnancies were excluded from the cohort if there was a delivery record in the 182 days preceding the delivery date of interest. Trimesters were defined as days 0 to 97, days 98 to 195, and day 196 to the delivery date.

The study entry criteria required that all cohort members had continuous enrolment in their provincial health insurance plan for at least 183 days preceding the estimated date of conception. Insurance coverage gaps of up to 30 days were deemed permissible. Persons were permitted to contribute multiple pregnancy episodes during the accrual period as long as the study entry criteria were satisfied.

## Study Data Sources

The study leveraged provincial administrative health care data transformed into the Sentinel CDM. The underlying data sources included information on demographic characteristics, health insurance status, and vital status from the provincial health insurance registry; outpatient and hospital encounter data from physician service claim databases and the Canadian Institute for Health Information Discharge Abstract Database, respectively; emergency department records captured in the National Ambulatory Care Reporting System (where available); and prescription drug claims from the provincial drug benefit claim databases.

## Study Measures

### ADD Exposures

To simplify reporting, we combined ADDs into the 9 therapeutic groups most commonly used to treat diabetes: insulin, metformin, sulfonylurea, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, dipeptidyl peptidase 4 (DPP4) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist, thiazolidinedione (TZD), other ADD, and combination product. Exposure to each drug group was evaluated separately, such that any individual could be exposed to and contribute to multiple drug groups before and during pregnancy.

## Analyses

The characteristics of cohort members were determined using the estimated date of conception (defined previously) as the index date and were tabulated overall and by province. The characteristics included

calendar year of each pregnancy episode; maternal age; comorbid chronic health conditions that can be reliably captured in administrative health care data, such as asthma and pre-existing diabetes; and multiple measures of health care resource intensity, such as number of outpatient physician visits, hospitalizations, and prescription medications dispensed in the preceding 183 days. For each cohort, we documented the presence of ADD claims according to each ADD therapeutic group before pregnancy, at any time during pregnancy and by trimester, overall and stratified by maternal age (10 to 24 years, 25 to 29 years, 30 to 34 years, and 35 to 54 years), and calendar year.

# Findings

**Main Take-Aways**

We identified 249,063 unique live birth or stillbirth pregnancy episodes among 166,529 unique individuals. In total, 3,308 individuals (2.0%) had pre-existing diabetes and 21,031 individuals (12.6%) had GDM without pre-existing diabetes.

Overall, 3.8% of pregnancies were exposed to insulin, 3.1% to metformin, and 0.3% to a sulfonylurea at some point during pregnancy. Insulin use increased as pregnancies progressed, rising from 1.3% in the first trimester to 3.7% in the third trimester. ADD use also increased with maternal age and over the course of the study period.

Among the 4,058 pregnancy episodes in persons with pre-existing diabetes, 86% were exposed to insulin at some point during pregnancy, 50.4% to metformin, and 15.4% to a sulfonylurea. While the use of insulin rose sharply throughout pregnancy, the use of other ADDs remained stable. The number of people taking metformin and sulfonylureas increased with maternal age, but insulin use stayed high (85% to 88%) across all age groups.

Among the 24,448 pregnancy episodes in persons without pre-existing diabetes but with GDM, insulin (23.4%) and metformin (18.9%) were the most common medications used during pregnancy, with little variation across maternal age. The use of both medications increased sharply throughout pregnancy and over the study period.

## Patient Characteristics

After application of the study entry criteria, we identified 249,063 unique live birth or stillbirth pregnancy episodes among 166,529 unique individuals. The corresponding counts were 4,058 (1.6%) and 3,308 (2.0%), respectively, among persons with pre-existing diabetes and 24,448 (9.8%) and 21,031 (12.6%), respectively, among those without pre-existing diabetes but with GDM (Table 1). These counts correspond with 1.50 unique pregnancy episodes per person overall, 1.23 unique pregnancy episodes per person among those with pre-existing diabetes, and 1.16 unique pregnancy episodes per person among those without pre-existing diabetes but with GDM.

Table 2 summarizes the baseline characteristics of the 3 provincial cohorts at the level of pregnancy episode: 163,764 (65.8%) from Manitoba, 60,906 (24.5%) from 2017 onward in Saskatchewan, and 24,393 (9.8%) among those receiving social assistance in Ontario. The mean age of the cohorts was similar, approximately 30 years, although the percentage of episodes among persons aged 10 to 24 years varied, ranging from 13% in Saskatchewan to 27% in Ontario. The baseline maternal comorbidity profile and health service intensity also varied by province, with generally lower disease prevalence and service use in Saskatchewan; and the highest disease prevalence and service use in Ontario. For example, 0.7% and 1.2% of pregnancy episodes were associated with maternal diabetes and asthma, respectively, in Saskatchewan, whereas the corresponding prevalence estimates in Ontario were 6.1% and 6.0%, respectively. Similarly, the average number of outpatient physician visits in the 183 days preceding conception was 2.5 in Saskatchewan versus 6.3 in Ontario, and the average number of baseline prescription claims were 3.1 in Saskatchewan and 27.3 in Ontario.

Table 3 presents the baseline characteristics of the combined multiprovincial cohort, overall and for the subsets of pregnancy episodes in persons with pre-existing diabetes (1.6%) and those without pre-existing diabetes but with GDM (9.8%). Those with pre-existing diabetes and those with GDM were relatively older (mean age 32 years versus 30 years among all cohort members), with a much higher percentage aged 35 years or older (> 30% versus 19% among all cohort members). Among those with pre-existing diabetes (defined as using a non-metformin ADD or metformin with a diabetes diagnosis during the 183 days preceding conception) 76% had a diagnosis code for diabetes. Relative to those with GDM, those with pre-existing diabetes were more likely to have diagnosis codes for obesity (4.4% versus 1.8%), hypertension (7.4% versus 2.9%), and chronic kidney disease (0.7% versus 0.1%), and were more likely to visit a doctor and fill prescriptions (Table 3).

Table 4 presents data on the use of ADDs among all live birth or stillbirth pregnancies just before and during pregnancy by trimester. Overall, 3.8% of pregnancies were exposed to insulin, 3.1% to metformin, and 0.3% to a sulfonylurea at some time during pregnancy. Other therapies were less frequently prescribed. Insulin use increased over the course of pregnancies, rising from 1.3% during the first trimester to 3.7% during the third trimester. Metformin use was stable over the course of pregnancies and was prescribed to 2.2% of pregnancy episodes in the 183 days preceding conception. Although used infrequently, dispensing of sulfonylureas and other therapies appeared to decline over the course of pregnancies. ADD use during pregnancy increased with maternal age (Table 5), with 2.3% prescribed insulin among those aged 10 to 24 years versus 6.9% among those aged 35 to 54 years. The trend was similar for all therapies. ADD use during pregnancy also increased over time (Figure 1), with insulin prescriptions rising from 3% of pregnancy episodes in 2012 to more than 5% overall in 2022. The trend was similar for metformin, rising from 1.8% of pregnancy episodes in 2012 to 4.7% in 2022 (Figure 1).

We identified 4,058 pregnancies among persons with pre-existing diabetes, 86% of whom were prescribed insulin at some time during pregnancy, 50.4% were prescribed metformin, and 15.4% were prescribed a sulfonylurea (Table 6). Compared to all live birth or stillbirth pregnancies, pregnancies among persons with pre-existing diabetes were more likely to be among older women. For example, 32.2% of persons with

pre-existing diabetes were aged 35 to 54 years versus just 18.7% in the overall cohort (Table 3). As shown in Table 6, the prevalence of insulin use among persons with pre-existing diabetes rose sharply over the course of pregnancy, increasing from 65.2% in the first trimester to 81.8% in the third. At the same time, the prevalence of prescriptions for metformin and sulfonylureas dropped from 46.2% and 14.5%, respectively, in the first trimester to 26.8% and 3.0%, respectively, in the third. The drugs prescribed to those with pre-existing diabetes also varied by maternal age (Table 5). For example, the percentage of pregnancies exposed to metformin was 64.9% among persons aged 35 to 54 years versus 31.0% among those aged 10 to 24 years. Similarly, the percentage exposed to a sulfonylurea was 19.3% among those older than 35 years compared with 8.6% among those aged 10 to 24 years. In contrast, importantly, the percentage of pregnancies exposed to insulin did not vary by age — they were consistently 85% to 89%. Prevalence of use of the more commonly used ADD were relatively stable over the course of the study period (Figure 2). The exception was the less commonly used ADDs (i.e., SGLT-2 inhibitor, DPP4 inhibitor, GLP-1 receptor agonist, TZD), which collectively increased from 5% in 2012 to 26% in 2022.

Table 7 presents data on ADD use during pregnancy episodes among persons without pre-existing diabetes but with GDM. The most commonly prescribed drugs were insulin (23.4%) and metformin (18.9%), with little variation by maternal age (Table 5). For both drug groups, use increased sharply throughout the course of pregnancy, from 1.8% in the first trimester to 22.7% in the third trimester for insulin, and 7.8% to 14.3% in the first and third trimesters, respectively, for metformin. Prevalence of use of both drug groups also increased over the course of the study period, particularly for metformin, which rose from 12% in 2012 to 27% in 2022 (Figure 3).

## Strengths and Limitations

**Main Take-Aways**

To our knowledge, this is the first multiprovincial, population-based study of ADD use during pregnancy in Canada, and the first Canadian project to use the Sentinel CDM to study drug use during pregnancy.

Strengths of this study include use of data from multiple provinces and inclusion of both publicly and privately insured residents. We were also able to categorize pregnancies according to whether there was pre-existing diabetes or GDM.

However, this study has some limitations. As in any study of administrative data, there is risk for misclassification, including the precise timing of conception, the presence of diabetes and other health concerns, and whether ADD initiated before conception continued during pregnancy.

To our knowledge, this is the first multiprovincial, population-based study of ADD use during pregnancy in Canada, and the first Canadian study to use the Sentinel CDM in the setting of pregnancy. Study strengths include its use of population-based data with broad geographic representation, inclusion of both publicly and privately insured residents, and our ability to use diagnosis codes and prescription drug claims to subclassify

pregnancies according to presence of pre-existing diabetes and GDM. However, as with any study of administrative data, it has important limitations.

First, we assumed that medications that were dispensed were taken, with the period of exposure defined by the "days supplied" with each claim. For example, medications dispensed immediately before conception may have been discontinued once pregnancy was confirmed.

Second, ADD exposures during pregnancy were counted independently for each drug category. We did not determine the prevalence of exposure to multiple medications simultaneously (which, for example, may have been the case for combinations of ADD, such as metformin and insulin), and we did not explore potential reasons for changes in treatment.

Third, our results are limited to pregnancies with a live birth or stillbirth outcome. We did not include pregnancies that ended in a spontaneous abortion or induced abortion, which our prior work suggests could represent up to 40% of pregnancies.[8]

Fourth, the definitions we used for diabetes and GDM have not been formally validated, and some misclassification of diabetes status is possible. However, the prevalence of GDM we observed was similar to that reported in a recent Canadian study of diabetes in pregnancy.[2]

Fifth, over time, a growing percentage of pregnant persons with pre-existing diabetes were prescribed an ADD that is not generally recommended for use during pregnancy, including sulfonylureas and increasingly an SGLT-2 inhibitor, DPP4 inhibitor, or GLP-1 receptor agonist.[3] Figure 2 shows that an increasing percentage of women continued taking these drugs during pregnancy. Because there are limited data on the safety of these therapies during pregnancy, further research is needed to understand the rationale for and safety of their use during pregancy.[9]

Sixth, due to data limitations, the Ontario cohort was limited to persons who were receiving social assistance and covered by the Ontario Drug Benefit (ODB) program. Compared with Ontarians of the same age and sex who are not ODB program beneficiaries, ODB program beneficiaries are more likely to have diabetes and other chronic diseases.[10,11] In our study, Ontarians had more comorbidities and used more medications and health services than persons from Manitoba and Saskatchewan. Although the Manitoba and Saskatchewan cohorts were more broadly representative of the general populations there, results from these provinces may not necessarily generalize to other Canadian provinces or territories or outside Canada.

Seventh, in Saskatchewan, the required drug claim data elements were available only from January 2017 onward. If trends in drug use and maternal characteristics before 2017 were unlike those in Manitoba and Ontario, the introduction of Saskatchewan data in 2017 may have influenced general trends in maternal characteristics and drug use over the course of the study accrual period. For example, prevalence of insulin use increased sharply after 2017 (Figure 1). Consequently, overall trends in drug use should be interpreted cautiously.

Finally, because our main objective was to study drug use and not outcomes, we cannot comment on the safety or effectiveness of the drug exposures we observed. Those questions can only be answered with studies that are specifically designed to answer them.[8,12-14]

## Conclusions and Implications for Policy-Making

**Main Take-Aways**

We successfully demonstrated the feasibility of replicating the FDA Sentinel analysis using Canadian data transformed into the Sentinel CDM.

Our findings confirm that a growing percentage of pregnancies are being exposed to ADDs in Canada, including to newer therapies for which there are limited safety data. This highlights the importance of ongoing surveillance and targeted studies of the real-world use and safety of ADDs during pregnancy.

We set out to evaluate the feasibility of replicating an FDA Sentinel analysis of ADD in pregnancy using Canadian administrative health data transformed into the Sentinel CDM. We demonstrated that it was feasible to replicate the FDA study in a timely manner.

Overall, 3.8% of live birth or stillbirth pregnancies were exposed to insulin, 3.1% to metformin, and 0.3% to a sulfonylurea at some time during pregnancy. The overall treatment rates from 2012 to 2022 were higher than those observed in the FDA Sentinel study, which reported a prevalence of 4.4% for exposure to any ADD from 2001 to 2013.[1] In an Alberta study of patients with GDM, the percentage treated with an ADD during pregnancy was 31.4% in 2014, with 28.3% of patients receiving insulin and 3.2% receiving metformin.[5] By comparison, in 2014, we observed insulin and metformin treatment rates among those with GDM of 20% and 9%, respectively. By the end of the study period in 2022, these rates had climbed to 29% and 27%, respectively. In a recent study of 37,762 women with GDM in the US with private drug insurance covering the period 2015 to 2018, insulin use increased from 26% to 44%, metformin use increased from 17% to 29%, and glyburide use decreased from 58% to 27%.[6] These treatment rates are higher than we observed, but the findings of all 3 studies are consistent with recommendations supporting use of insulin and metformin as first- and second-line therapy in GDM.[3,14]

The rates of diabetes and GDM have increased over the past 2 decades. Our findings confirm that an increasing percentage of pregnancies is being exposed to ADDs in Canada, including to newer therapies for which there are little to no safety data. These results highlight the need for ongoing surveillance and targeted studies of the use and safety of ADDs during pregnancy.

# Authors and Contributors

**CNODES Disclaimer:** The opinions, results, and conclusions contained in this report are those of the authors. No endorsement by Canada's Drug Agency, the provinces, the Manitoba Centre for Health Policy or Manitoba Health, data stewards, participating research centres or the Canadian Institute for Health Information (CIHI) is intended or should be inferred.

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

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

**Oriana Yu** as the content expert, reviewed the scientific protocol and reviewed and approved the report.

**Amani Hamad**, as the Manitoba site investigator, contributed to review of the scientific protocol and review and interpretation of the study results, and reviewed and approved the report.

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

**Donica Janzen**, as the Saskatchewan co-site investigator, reviewed the scientific protocol, contributed to review and interpretation of the study results, and reviewed and approved the report.

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**Xinya Lu**, as the Saskatchewan site analyst, contributed to review of the scientific protocol, conducted analyses at Saskatchewan site and quality checks of results, and review the report.

**Carolina Moriello** as the research assistant, contributed to drafting of the scientific protocol and reviewed and approved the report.

**Robert Platt**, as the methods lead, reviewed and approved the report.

### Contributors

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**Conflicts of Interest**

**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-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 and strategic advisor for a small consulting company developed by former students. No compensation received for this work.

**Donica Janzen** disclosed the following:

Travel Funding or Payment

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

No other conflicts of interest were declared.

### Involvement in CDA-AMC Projects

**J. Michael Paterson**:

- HC0069 Outpatient Paxlovid and Remdesivir Utilization in Canada
- HC0086 Long-Acting Inhalable Drugs for COPD
- HC0099 Drug Utilization in Patients with Major Neurocognitive Disorder
- OS0001 Opioid Use and Diverticulitis
- OS0003 Safety for Tofacitinib
- OS0005 Safety of Ozempic for Type 2 Diabetes
- OS0009 GLP-1 Receptor Agonists and Mental Health Outcomes

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- HC0086 Long-Acting Inhalable Drugs for COPD
- HC0099 Drug Utilization in Patients with Major Neurocognitive Disorder
- OS0001 Opioid Use and Diverticulitis
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- OS0005 Safety of Ozempic for Type 2 Diabetes
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- OS0009 GLP-1 Receptor Agonists and Mental Health Outcomes

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- HC0099 Drug Utilization in Patients with Major Neurocognitive Disorder

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- HC0069 Outpatient Paxlovid and Remdesivir Utilization in Canada
- HC0073 Oral Fluoroquinolones in Canada — Utilization
- HC0086 Long-Acting Inhalable Drugs for COPD
- HC0099 Drug Utilization in Patients with Major Neurocognitive Disorder
- OS0001 Opioid Use and Diverticulitis
- OS0003 Safety for Tofacitinib
- OS0005 Safety of Ozempic for Type 2 Diabetes
- OS0009 GLP-1 Receptor Agonists and Mental Health Outcomes

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- HC0073 Oral Fluoroquinolones in Canada — Utilization
- HC0086 Long-Acting Inhalable Drugs for COPD
- HC0087 Mental Health Disorders with GLP1 Receptor Agonists in Type 2 Diabetes
- HC0099 Drug Utilization in Patients with Major Neurocognitive Disorder
- OS0001 Opioid Use and Diverticulitis
- OS0005 Safety of Ozempic for Type 2 Diabetes
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- HC0086 Long-Acting Inhalable Drugs for COPD
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- OS0001 Opioid Use and Diverticulitis
- OS0005 Safety of Ozempic for Type 2 Diabetes
- OS0009 GLP-1 Receptor Agonists and Mental Health Outcomes

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# Appendix 1: Main Findings

Please note that this appendix has not been copy-edited.

## Table 1: Episode-Level Cohort Attrition, Overall and for Pregnancy Episodes With Pre-Existing Diabetes or Gestational Diabetes

| Entry criteria | Livebirth/Stillbirth | | Pre-existing Diabetes | | Gestational Diabetes | |
|---|---|---|---|---|---|---|
| | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded |
| **Members meeting enrolment and demographic requirements** | | | | | | |
| Enrolled at any point during the query period | 21,175,469 | NA | 21,175,469 | NA | 21,175,469 | NA |
| Had required coverage type (medical and/or drug coverage) | 15,793,566 | 5,381,903 | 15,793,566 | 5,381,903 | 15,793,566 | 5,381,903 |
| Enrolled during specified age range | 9,933,842 | 5,859,724 | 9,933,842 | 5,859,724 | 9,933,842 | 5,859,724 |
| Had requestable medical charts | 9,933,842 | 0 | 9,933,842 | 0 | 9,933,842 | 0 |
| Met demographic requirements (sex) | 5,077,369 | 4,856,473 | 5,077,369 | 4,856,473 | 5,077,369 | 4,856,473 |
| **Members with a valid index event** | | | | | | |
| Had a specified pregnancy outcome during the query period | 285,237 | 4,792,132 | 285,237 | 4,792,132 | 285,237 | 4,792,132 |
| **Pregnancy outcomes with a valid index date** | | | | | | |
| Total number of pregnancy outcomes during the query period | 390,038 | NA | 390,038 | NA | 390,038 | NA |
| Pregnancy outcome within the age range condition assessed at pregnancy outcome date | 381,840 | 8,198 | 381,840 | 8,198 | 381,840 | 8,198 |
| Had sufficient continuous enrolment prior to pregnancy outcome | 249,063 | 132,777 | 249,063 | 132,777 | 249,063 | 132,777 |
| Met inclusion and exclusion criteria:[b] | 249,063 | 0 | 4,058 | 245,005 | 24,448 | 224,615 |
| Evidence of prior non-metformin antidiabetic drug use | NA | NA | NA | NA | NA | 3,247 |
| Evidence of a prior diabetes diagnosis | NA | NA | NA | NA | NA | 4,103 |
| No evidence of prior non-metformin antidiabetic drug use or prior diabetes diagnosis | NA | NA | NA | 245,005 | NA | NA |
| No evidence of gestational diabetes | NA | NA | NA | NA | NA | 220,173 |
| **Pregnancy episodes with required post-index follow-up** | | | | | | |
| Had sufficient post-index continuous enrolment | 249,063 | 0 | 4,058 | 0 | 24,448 | 0 |
| **Final cohort** | | | | | | |
| Number of members | 166,529 | NA | 3,308 | NA | 21,031 | NA |

| Entry criteria | Livebirth/Stillbirth | | Pre-existing Diabetes | | Gestational Diabetes | |
|---|---|---|---|---|---|---|
| | Remaining | Excluded | Remaining | Excluded | Remaining | Excluded |
| Number of pregnancy episodes | 249,063 | NA | 4,058 | NA | 24,448 | NA |

[a]Cohorts are formed by first evaluating enrolment and demographic requirements as well as index events among members, then evaluating index dates, pre-index history, and post-index follow-up among pregnancy episodes. Because of this, the number remaining often increases from the member- to episode-level steps.

[b]Pregnancy episodes can meet multiple inclusion and/or exclusion criteria; therefore, the total number of pregnancy episodes excluded overall may not equal the sum of all pregnancy episodes in each criterion.

## Table 2: Characteristics of Live Birth and Stillbirth Pregnancy Episodes by Study Province, 2012 to 2022

| Characteristic | Manitoba | Saskatchewan | Ontario |
|---|---|---|---|
| Unique persons, n | 100,008 | 46,139 | 20,382 |
| Unique episodes, n | 163,764 | 60,906 | 24,393 |
| **Calendar year, n (%)** | | | |
| 2012 | 14,684 (9.0) | NA | 1,835 (7.5) |
| 2013 | 14,984 (9.1) | NA | 1,904 (7.8) |
| 2014 | 14,997 (9.2) | NA | 2,069 (8.5) |
| 2015 | 15,133 (9.2) | NA | 2,109 (8.6) |
| 2016 | 15,090 (9.2) | NA | 2,176 (8.9) |
| 2017 | 15,305 (9.3) | 10,726 (17.6) | 2,118 (8.7) |
| 2018 | 15,313 (9.4) | 10,647 (17.5) | 2,323 (9.5) |
| 2019 | 14,990 (9.2) | 10,169 (16.7) | 2,779 (11.4) |
| 2020 | 14,741 (9.0) | 9,762 (16.0) | 2,497 (10.2) |
| 2021 | 14,824 (9.1) | 10,343 (17.0) | 2,352 (9.6) |
| 2022 | 13,703 (8.4) | 9,259 (15.2) | 2,231 (9.1) |
| **Age (years), n (%)** | | | |
| Mean (SD) | 29.6 (5.7) | 30.7 (5.0) | 29.7 (6.1) |
| 10 to 24 | 36,009 (22.0) | 7,748 (12.7) | 6,569 (26.9) |
| 25 to 29 | 47,183 (28.8) | 18,672 (30.7) | 6,437 (26.4) |
| 30 to 34 | 51,228 (31.3) | 22,377 (36.7) | 6,214 (25.5) |
| 35 to 54 | 29,344 (17.9) | 12,109 (19.9) | 5,173 (21.2) |
| **Health characteristics, n (%)** | | | |
| Cardiovascular disease | 259 (0.2) | 245 (0.4) | 467 (1.9) |
| Diabetes | 2,173 (1.3) | 437 (0.7) | 1,493 (6.1) |
| Obesity | 1,656 (1.0) | 156 (0.3) | 514 (2.1) |
| Hypertension | 2,208 (1.3) | 565 (0.9) | 680 (2.8) |
| Chronic kidney disease | 47 (0.0) | 20 (0.0) | 82 (0.3) |

| Characteristic | Manitoba | Saskatchewan | Ontario |
|---|---|---|---|
| Asthma | 3,282 (2.0) | 714 (1.2) | 1,458 (6.0) |
| Chronic obstructive pulmonary disease | 196 (0.1) | 25 (0.0) | 141 (0.6) |
| Rheumatic disease | 869 (0.5) | 332 (0.5) | 408 (1.7) |
| **Health service utilization intensity metrics, mean (SD)** | | | |
| Ambulatory encounters | 2.7 (3.2) | 2.5 (2.9) | 6.3 (6.2) |
| Inpatient hospital encounters | 0.1 (0.3) | 0.1 (0.2) | 0.1 (0.4) |
| Filled prescriptions | 3.8 (19.2) | 3.1 (4.9) | 27.3 (59.2) |
| Unique drug classes dispensed | 1.8 (2.5) | 1.7 (2.1) | 5.0 (3.3) |

## Table 3: Characteristics of the Multiprovincial Cohort, Overall and for Pregnancy Episodes With Pre-Existing Diabetes or Gestational Diabetes, 2012 to 2022

| Characteristic | Livebirth/Stillbirth | Pre-existing Diabetes | Gestational Diabetes |
|---|---|---|---|
| Unique persons, n (%) | 166,529 (100) | 3,308 (2.0) | 21,031 (12.6) |
| Unique episodes, n (%) | 249,063 (100) | 4,058 (1.6) | 24,448 (9.8) |
| **Calendar year, n (%)** | | | |
| 2012 | 16,519 (6.6) | 268 (6.6) | 1,038 (4.2) |
| 2013 | 16,888 (6.8) | 296 (7.3) | 1,285 (5.3) |
| 2014 | 17,066 (6.9) | 278 (6.9) | 1,386 (5.7) |
| 2015 | 17,242 (6.9) | 272 (6.7) | 1,389 (5.7) |
| 2016 | 17,266 (6.9) | 302 (7.4) | 1,605 (6.6) |
| 2017 | 28,149 (11.3) | 390 (9.6) | 2,576 (10.5) |
| 2018 | 28,283 (11.4) | 414 (10.2) | 2,785 (11.4) |
| 2019 | 27,938 (11.2) | 450 (11.1) | 3,154 (12.9) |
| 2020 | 27,000 (10.8) | 446 (11.0) | 3,126 (12.8) |
| 2021 | 27,519 (11.0) | 447 (11.0) | 3,135 (12.8) |
| 2022 | 25,193 (10.1) | 495 (12.2) | 2,969 (12.1) |
| **Age (years), n (%)** | | | |
| Mean (SD) | 30 (5.6) | 32 (6.0) | 32 (5.6) |
| 10 to 24 | 50,326 (20.2) | 607 (15.0) | 2,867 (11.7) |
| 25 to 29 | 72,292 (29.0) | 937 (23.1) | 5,382 (22.0) |
| 30 to 34 | 79,819 (32.0) | 1,207 (29.7) | 8,542 (34.9) |
| 35 to 54 | 46,626 (18.7) | 1,307 (32.2) | 7,657 (31.3) |
| **Health characteristics, n (%)** | | | |
| Cardiovascular disease | 971 (0.4) | 71 (1.7) | 100 (0.4) |

| Characteristic | Livebirth/Stillbirth | Pre-existing Diabetes | Gestational Diabetes |
|---|---|---|---|
| Diabetes | 4,103 (1.6) | 3,101 (76.4) | 0 (0.0) |
| Obesity | 2,326 (0.9) | 180 (4.4) | 437 (1.8) |
| Hypertension | 3,453 (1.4) | 299 (7.4) | 713 (2.9) |
| Chronic kidney disease | 149 (0.1) | 29 (0.7) | 18 (0.1) |
| Asthma | 5,454 (2.2) | 110 (2.7) | 586 (2.4) |
| Chronic obstructive pulmonary disease | 362 (0.1) | 7 (0.2) | 59 (0.2) |
| Rheumatic disease | 1,609 (0.6) | 35 (0.9) | 184 (0.8) |
| **Health service utilization intensity metrics, mean (SD)** | | | |
| Ambulatory encounters | 3 (3.6) | 6 (5.2) | 3 (3.7) |
| Inpatient hospital encounters | 0.1 (0.3) | 0.2 (0.6) | 0.1 (0.3) |
| Filled prescriptions | 6 (24.3) | 17 (27.5) | 6 (29.0) |
| Generics dispensed | 2 (2.5) | 6 (4.1) | 2 (2.8) |
| Unique drug classes dispensed | 2 (2.4) | 6 (3.9) | 2 (2.6) |

## Table 4: Antidiabetic Drug Use, by Trimester, Among All Live Birth and Stillbirth Pregnancies, 2012 to 2022

| Measure | Pre-pregnancy | Any trimester | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|---|
| Total unique pregnancies, n | 249,063 | 249,063 | 249,063 | 249,063 | 249,063 |
| **Drug group, n (%)** | | | | | |
| Insulin | 2,388 (1.0) | 9,515 (3.8) | 3,180 (1.3) | 5,141 (2.1) | 9,135 (3.7) |
| Metformin | 5,446 (2.2) | 7,813 (3.1) | 4,876 (2.0) | 3,704 (1.5) | 4,665 (1.9) |
| Sulfonylurea | 772 (0.3) | 741 (0.3) | 626 (0.3) | 343 (0.1) | 207 (0.1) |
| SGLT-2 | 242 (0.1) | 226 (0.1) | 225 (0.1) | 95 (0.0) | 31 (0.0) |
| DPP4 | 189 (0.1) | 156 (0.1) | 156 (0.1) | 69 (0.0) | 19 (0.0) |
| GLP-1 | 157 (0.1) | 122 (0.0) | 122 (0.0) | 39 (0.0) | 20 (0.0) |
| TZD | 22 (0.0) | 13 (0.0) | Suppressed | Suppressed | Suppressed |
| Other | 14 (0.0) | 12 (0.0) | 9 (0.0) | 7 (0.0) | 6 (0.0) |
| Combination product | 201 (0.1) | 183 (0.1) | 182 (0.1) | 97 (0.0) | 24 (0.0) |

DPP4 = Dipeptidyl peptidase-4 inhibitor; GLP1 = Glucagon-Like Peptide-1; SGLT-2 = Sodium-glucose cotransporter-2; TZD = Thiazolidinediones

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions

## Table 5: Antidiabetic Drug Use, by Maternal Age, in Live Birth and Stillbirth Pregnancies, Among Persons With Pre-Existing Diabetes and Among Persons With Gestational Diabetes, 2012 to 2022

| Cohort and drug group | Maternal age | | | |
|---|---|---|---|---|
| | 10 to 24 | 25 to 29 | 30 to 34 | 35 to 54 |
| **Livebirth/stillbirth pregnancies, n (%)** | | | | |
| Total unique pregnancies, n | 50,326 | 72,292 | 79.819 | 46,626 |
| Insulin | 1,169 (2.3) | 2,048 (2.8) | 3,088 (3.9) | 3,210 (6.9) |
| Metformin | 695 (1.4) | 1,765 (2.4) | 2,761 (3.5) | 2,592 (5.6) |
| Sulfonylurea | 68 (0.1) | 152 (0.2) | 238 (0.3) | 283 (0.6) |
| Other | 46 (0.1) | 90 (0.1) | 155 (0.2) | 236 (0.5) |
| Combination product | 19 (0.0) | 28 (0.0) | 35 (0.0) | 101 (0.2) |
| **Among persons with pre-existing diabetes, n (%)** | | | | |
| Total unique pregnancies, n | 607 | 937 | 1,207 | 1,307 |
| Insulin | 537 (88.5) | 820 (87.5) | 1,022 (84.7) | 1,110 (84.9) |
| Metformin | 188 (31.0) | 406 (43.3) | 605 (50.1) | 848 (64.9) |
| Sulfonylurea | 52 (8.6) | 122 (13.0) | 199 (16.5) | 252 (19.3) |
| Other | 44 (7.2) | 84 (9.0) | 145 (12.0) | 234 (17.9) |
| Combination product | 19 (3.1) | 27 (2.9) | 35 (2.9) | 100 (7.7) |
| **Among persons without pre-existing diabetes and with gestational diabetes, n (%)** | | | | |
| Total unique pregnancies, n | 2,867 | 5,382 | 8,542 | 7,657 |
| Insulin | 604 (21.1) | 1,157 (21.5) | 1,992 (23.3) | 1,966 (25.7) |
| Metformin | 414 (14.4) | 971 (18.0) | 1,729 (20.2) | 1,495 (19.5) |
| Sulfonylurea | 15 (0.5) | 29 (0.5) | 32 (0.4) | 28 (0.4) |
| Other | 6 (0.2) | 9 (0.2) | 9 (0.1) | 0 (0.0) |
| Combination product | 0 (0.0) | Suppressed | 0 (0.0) | Suppressed |

DPP4 = Dipeptidyl peptidase-4 inhibitor; GLP1 = Glucagon-Like Peptide-1; SGLT-2 = Sodium-glucose cotransporter-2; TZD = Thiazolidinediones

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions

## Table 6: Antidiabetic Drug Use, by Trimester, in Live Birth and Stillbirth Pregnancies Among Persons With Pre-Existing Diabetes, 2012 to 2022

| Measure | Pre-pregnancy | Any trimester | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|---|
| Total unique pregnancies, n | 4,058 | 4,058 | 4,058 | 4,058 | 4,058 |
| **Drug Group, n (%)** | | | | | |
| Insulin | 2,370 (58.4) | 3,489 (86.0) | 2,647 (65.2) | 3,169 (78.1) | 3,319 (81.8) |
| Metformin | 2,127 (52.4) | 2,047 (50.4) | 1,875 (46.2) | 1,445 (35.6) | 1,089 (26.8) |

| Measure | Pre-pregnancy | Any trimester | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|---|
| Sulfonylurea | 766 (18.9) | 625 (15.4) | 590 (14.5) | 306 (7.5) | 122 (3.0) |
| SGLT-2 | 240 (5.9) | 218 (5.4) | 218 (5.4) | 92 (2.3) | 30 (0.7) |
| DPP4 | 188 (4.6) | 153 (3.8) | 153 (3.8) | 67 (1.7) | 19 (0.5) |
| GLP-1 | 157 (3.9) | 114 (2.8) | 114 (2.8) | 38 (0.9) | 20 (0.5) |
| TZD | 22 (0.5) | 13 (0.3) | 13 (0.3) | 9 (0.2) | Suppressed |
| Other | 14 (0.3) | 9 (0.2) | 9 (0.2) | Suppressed | Suppressed |
| Combination product | 201 (5.0) | 181 (4.5) | 180 (4.4) | 96 (2.4) | 24 (0.6) |

DPP4 = Dipeptidyl peptidase-4 inhibitor; GLP1 = Glucagon-Like Peptide-1; SGLT-2 = Sodium-glucose cotransporter-2; TZD = Thiazolidinediones

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

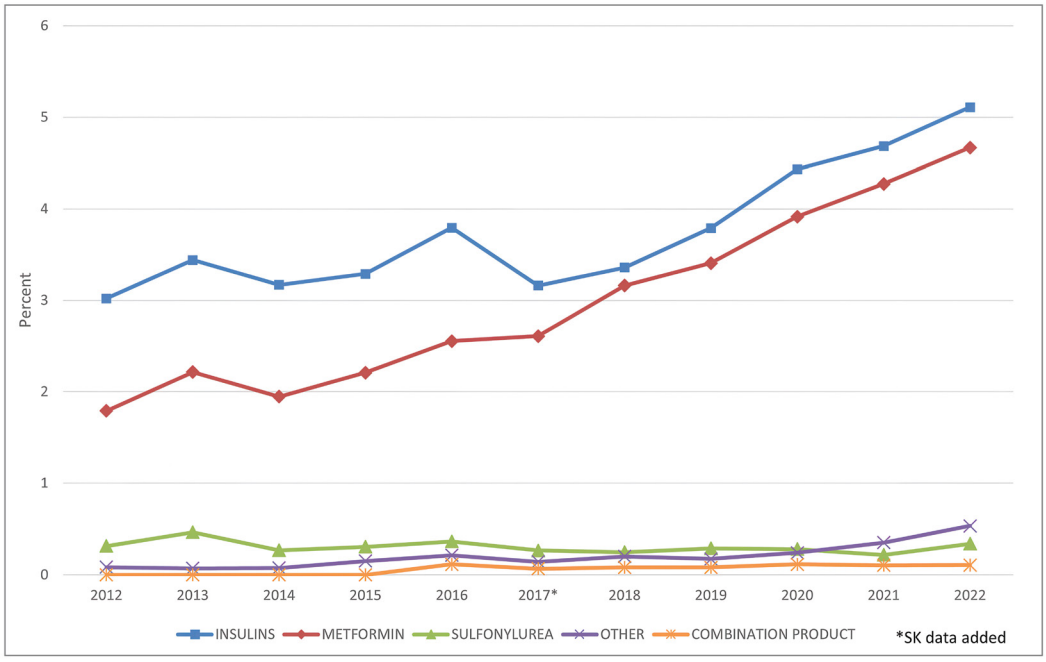
## Table 7: Antidiabetic Drug Use, by Trimester, in Live Birth and Stillbirth Pregnancies Among Persons Without Pre-Existing Diabetes and With Gestational Diabetes, 2012 to 2022

| Measure | Pre-pregnancy | Any trimester | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|---|
| Total unique pregnancies, n | 24,448 | 24,448 | 24,448 | 24,448 | 24,448 |
| **Drug Group, n (%)** | | | | | |
| Insulin | 10 (0.0) | 5,719 (23.4) | 448 (1.8) | 1,766 (7.2) | 5,547 (22.7) |
| Metformin | 1,826 (7.5) | 4,609 (18.9) | 1,911 (7.8) | 2,074 (8.5) | 3,485 (14.3) |
| Sulfonylurea | Suppressed | 104 (0.4) | 25 (0.1) | 30 (0.1) | 81 (0.3) |
| SGLT-2 | Suppressed | 7 (0.0) | 6 (0.0) | Suppressed | Suppressed |
| DPP4 | Suppressed | Suppressed | Suppressed | Suppressed | 0 (0.0) |
| GLP-1 | 0 (0.0) | Suppressed | Suppressed | Suppressed | 0 (0.0) |
| TZD | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other | 0 (0.0) | Suppressed | 0 (0.0) | Suppressed | Suppressed |
| Combination product | 0 (0.0) | Suppressed | Suppressed | Suppressed | 0 (0.0) |

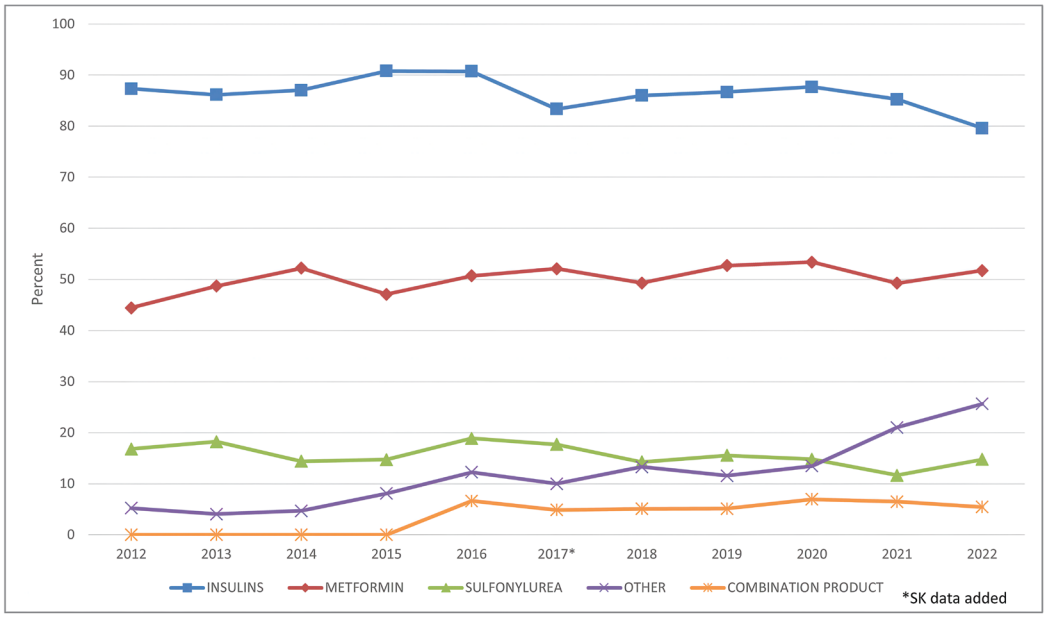
DPP4 = Dipeptidyl peptidase-4 inhibitor; GLP1 = Glucagon-Like Peptide-1; SGLT-2 = Sodium-glucose cotransporter-2; TZD = Thiazolidinediones

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

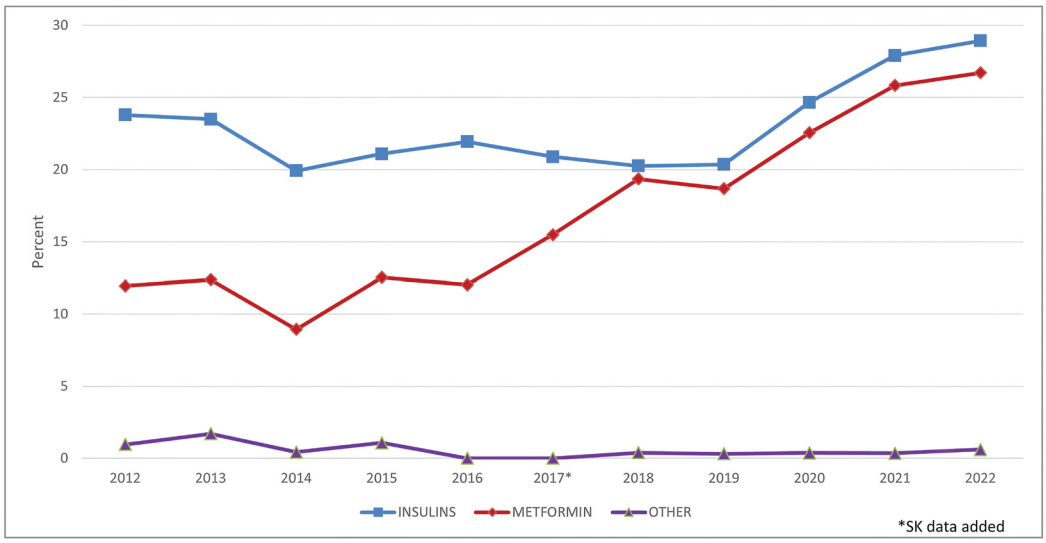
## Figure 1: Percentage of Live Birth and Stillbirth Pregnancy Episodes Dispensed an Antidiabetic Medication at Any Time During Pregnancy by Drug Group and Year, 2012 to 2022




## Figure 2: Percentage of Live Birth and Stillbirth Pregnancy Episodes Among Persons With Pre-Existing Diabetes Dispensed an Antidiabetic Medication at Any Time During Pregnancy by Drug Group and Year, 2012 to 2022



## Figure 3: Percentage of Live Birth and Stillbirth Pregnancy Episodes Among Persons With Gestational Diabetes Dispensed an Antidiabetic Medication at Any Time During Pregnancy By Drug Group and Year, 2012 to 2022



For more information on CoLab and its work, visit [colab.cda-amc.ca](colab.cda-amc.ca).

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