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Population

Adult new metformin users (*N* = 66,084) in Alberta, Canada, with an initial treatment intensification for type 2 diabetes between 2008 and 2019

Objective

To examine the intersection between location of residence along the rural–urban continuum and sulfonylurea use for management of type 2 diabetes

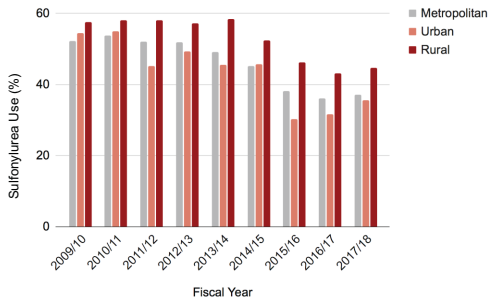
Analysis

Multivariable logistic regression was conducted to compare the odds of sulfonylurea-based initial treatment intensification according to location of residence.

Findings

1. Although sulfonylureas continue to be the most common antihyperglycemic drug class used at first treatment intensification (dispensed to 46% of individuals), use declined over time across the province.

2. Trends by location demonstrated a 4-year delay in the decline of sulfonylurea use in rural, compared with urban and metropolitan locations (see figure).



3. After adjusting for potential confounders, people living in a rural area were significantly more likely to start a sulfonylurea compared with residents of a metropolitan area (adjusted odds ratio 1.34; 95% CI 1.29–1.39).

Implications

The sustained use of sulfonylureas in rural areas, when other options are available, is concerning. This research sheds light on rural health care challenges beyond infrastructure.

Further work to identify whether similar drug therapy trends occur in other chronic disease states and jurisdictions is warranted.

Limitations

Unable to determine whether dispensed drug therapy was clinically appropriate

ARTICLE HIGHLIGHTS

- We conducted this research to elucidate a clearer picture of rural health care and its challenges beyond infrastructure.
- We sought to describe trends of sulfonylurea use for treatment intensification of type 2 diabetes in Alberta, Canada, and examine differences in trends by place of residence.
- We found that, although sulfonylureas are the most common antihyperglycemic drug therapy dispensed at first treatment intensification, use declined over time across the province. We also uncovered a 4-year delay in this decline in rural areas.
- Our findings are troubling and provide a basis to expand understanding of the influence of residence on processes of care.

Rural Residence Is Associated With a Delayed Trend Away From Sulfonylurea Use for Treatment Intensification of Type 2 Diabetes

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OBJECTIVE

To examine the intersection between location of residence along the rural–urban continuum (metropolitan, urban, and rural) and sulfonylurea dispensation records for the management of type 2 diabetes.

RESEARCH DESIGN AND METHODS

This retrospective cohort study used administrative health records of adult new metformin users between April 2008 and March 2019 in Alberta, Canada. Multivariable logistic regression was performed to examine the association between sulfonylurea-based treatment intensification and location of residence.

RESULTS

Treatment was intensified in 66,084 (38%) of 171,759 new metformin users after a mean of 1.5 years. At treatment intensification, mean age was 55 years, 62% of users were male, and 27% were rural residents. The most common antihyperglycemic drug, given to 30,297 people (46%) for treatment intensification, was a sulfonylurea. At the beginning of our observation period, the proportion of people dispensed a sulfonylurea at first treatment intensification was highest in rural (57%), compared with urban (54%) and metropolitan (52%) areas ($P = 0.009$). Although proportions decreased over time across the province, rural residents continued to constitute the highest proportion of sulfonylurea users (45%), compared with urban (35%) and metropolitan (37%) residents ($P < 0.001$), and the trend away from sulfonylurea use was delayed by ∼4 years for rural residents. Adjusting for potential sources of confounding, rural residence was associated with a significantly higher likelihood of using a sulfonylurea compared with metropolitan residence (adjusted odds ratio 1.34; 95% CI 1.29–1.39).

CONCLUSIONS

Variation in sulfonylurea dispensation across the rural–urban continuum provides a basis for continued research in the differences in process of care by location.

All individuals have a right to high-quality health care regardless of where they live. However, literature shows that rural areas often lack hospitals or specialized care, leading to inequities in health care access and, subsequently, poor health outcomes (1–5). Although these are indisputable barriers to health care, these structural

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components are only part of the rural health care picture. Process is described as "interactions that occur between providers and patients, including, but not limited to, what providers do with, to, and for their patients" (6) and is an additional consideration to structural components in Donabedian's framework to examine the quality of health care services (7). Therefore, process of care is broad and encompasses the clinical decision-making of all clinicians involved in a patient's health care journey, the knowledge translation process involved in making a clinical decision and how clinicians are informed of new research and therapies, as well as individual patient behaviors and health care perceptions. Considering this, we measured process through pharmacy dispensation records as a proxy for prescribing practices and clinical decision-making. We examined the intersection between location of residence and patterns of antihyperglycemic drugs dispensed for treatment intensification in people with type 2 diabetes, with a focus on sulfonylurea use.

Historically, sulfonylureas have been the most common class of antihyperglycemic drugs used secondarily to metformin despite ongoing controversy surrounding cardiovascular safety (8). However, there is a growing trend away from using sulfonylureas, which is illustrated in the literature and clinical practice guidelines as early as 2018 (9). These studies, observing trends as far back as the early 1990s, describe the overall decline in the use of sulfonylureas and increase in the use of newer drug classes such as dipeptidyl peptidase 4 inhibitors (DPP-4is), glucagon-like peptide 1 receptor agonists (GLP-1ras), and sodium-glucose cotransporter 2 inhibitors (SGLT-2is) once they were marketed in the mid-2000s (10–18). The introduction of these new agents into the market provides alternatives for clinicians to consider when treatment intensification is required. This is especially true if weight gain and hypoglycemia risk are concerns or if additional benefits beyond lowering glucose level is required (19). Taken together, these factors may explain the trend away from using sulfonylureas.

Our study objective was to describe the use of sulfonylureas in Alberta, Canada, and determine whether a similar trend away from its use occurred. Because we were interested in examining the effect of residence along the rural–urban continuum on process of care, we also distinguished trends by place of residence. We hypothesized that rural residents may have a different pattern of sulfonylurea use than urban and metropolitan residents.

RESEARCH DESIGN AND METHODS

Data Source and Study Population

We conducted a retrospective cohort study using administrative data provided by Alberta Health, a branch of the provincial government that oversees administration of health care in Alberta, Canada. Multiple databases of patient health records of eligible Albertans between 1 April 2008 and 31 March 2019 were linked using individual, anonymized identification numbers. All adults at least 18 years of age and eligible for health care benefits in Alberta for a minimum of 12 months prior to cohort entry were included (Supplementary Fig. 1) (16). To mitigate prevalent user bias and ensure that initial antihyperglycemic management followed clinical practice guideline recommendations, a new user design was used (9,19,20). Therefore, an individual entered the cohort as a new metformin user, which was defined as having no history of antihyperglycemic drug use for at least 12 months before cohort entry (15,20,21).

Considering that we were interested in drug therapy use at treatment intensification, individuals with no intensification of drug therapy (i.e., metformin monotherapy throughout the observation period) were excluded, as were individuals who had less than 1 year of follow-up or any gaps greater than 12 months in health benefit eligibility (Supplementary Fig. 1). People were also excluded if they had a diagnosis of gestational diabetes 9 months prior to treatment intensification or anytime during follow-up based on the presence of ICD-10 code O24.xx (Supplementary Fig. 1) (22).

Exposure Variable: Rural–Urban Continuum

To analyze the effect place of residence had on antihyperglycemic drug use over time, we used a postal code translator file provided by Alberta Health (23). We followed the work of others to link the forward sortation area from the postal code to one of seven geographic boundaries along the rural–urban continuum that Alberta Health uses in health-system planning, surveillance, and reporting (2,24,25). Low prescription use was observed in some years and locations, increasing the chance of a type II error. To mitigate this, we followed Alberta Health methods and collapsed the geographic boundaries into three categories: metropolitan (metropolitan and moderate metropolitan influence), urban, and rural (moderate urban influence, rural center area, rural, and rural remote). These categories are defined by population density, distance to and travel patterns of those seeking health and nonhealth services, local industry, resources, and infrastructure, and places of work and commuting behaviors (24).

Outcome Variable: Sulfonylurea-Based Treatment Intensification

Pharmacy dispensation records were reviewed to identify when other antihyperglycemic medications were started by new metformin users. We defined a treatment intensification date as the first dispensation date for an antihyperglycemic medication class other than metformin. One or more antihyperglycemic medication classes could be started on the same treatment intensification date and the first treatment intensification date could occur on the same day metformin was started (Supplementary Fig. 1). Treatment intensification dates were grouped according to Alberta Health fiscal year (April to March) for assessment of trends over time.

The World Health Organization Anatomical Therapeutic Chemical classification code was used to identify which antihyperglycemic medication was dispensed. Medications were categorized as DPP-4i, GLP-1ra, insulin, SGLT-2i, sulfonylureas, and other (namely, repaglinide, acarbose, and thiazolidinediones). Repaglinide, acarbose, and thiazolidinediones were grouped together because of their low use throughout the observation period. Treatment intensification was considered sulfonylurea based if a sulfonylurea medication was started, regardless of initiation of any other antihyperglycemic medication classes on the same day. Treatment intensification that did not include a sulfonylurea medication was considered non-sulfonylurea based.

Covariates

Covariates were selected on the basis of previous studies and available data (14–17,21,26,27). These include fiscal year, age at treatment intensification, biological sex, duration of treated diabetes, number of clinician visits in the past year, hospitalization in the past year, number of

non-antihyperglycemic medications dispensed in the past year, a count of chronic conditions, and diabetes-related complications. The number of clinician visits, non-antihyperglycemic medications, and chronic conditions violated the linearity assumption if they were left as continuous variables (28); therefore, these covariates were categorized using cut points that best fit the data and were clinically meaningful. Baseline chronic conditions and diabetes-related complications were flagged by any relevant ICD-9 or ICD-10 code in the individual's health record (from hospitalization, emergency room, or clinician visits) at any time prior to treatment intensification. This time frame was used because we believe that any historical conditions or complications, whether or not the patient was actively experiencing symptoms or undergoing treatment, may influence a clinician's clinical decision-making (29,30).

Statistical Analysis

Covariates of sulfonylurea and non–sulfonylurea-based treatment intensification were compared using a χ^2 test for categorical variables and a *t* test for continuous variables. Multivariable logistic regression was used to examine the outcome of interest: sulfonylurea-based therapy at first treatment intensification. The explanatory variable was place of residence along the rural–urban continuum. An interaction test was performed between sex and place of residence to identify whether sex modifies the effect of place of residence on sulfonylurea use. The main model included all covariates described in the previous section.

Recognizing the importance of laboratory data in the decision to prescribe antihyperglycemic medications, we conducted a subgroup analysis of individuals for whom this information was available. Individuals in this subgroup had had both kidney function laboratory tests (estimated glomerular filtration rate or creatinine clearance) within 1 year prior to the first treatment intensification, and a glycated hemoglobin (HbA_{1c}) measurement within 90 days of treatment intensification. We considered an individual to have kidney dysfunction if they had an estimated glomerular filtration rate $\leq$60 mL/min/1.73 m^2 or creatinine clearance $\leq$60 mL/min in the year prior to first treatment intensification (16,31). An HbA_{1c} $\geq$8.5% was used to consider individuals had an elevated HbA_{1c} (19).

Stata, version 16.1, was used for all analyses; coding is available upon request. The University of Alberta Research Ethics Board approved the conduct of this study (no. Pro00066037).

RESULTS

Descriptive Statistics

Of 351,070 Albertans identified with at least one antihyperglycemic drug dispensation between 1 April 2008 and 31 March 2019, 171,759 were adult new metformin users (Fig. 1). A total of 66,084 new metformin users (38%) had at least one treatment intensification with at least 1 year of follow-up. At the first treatment intensification, the mean time since metformin initiation was 1.5 years, mean age was 55 years, and 62% of participants were men. A sulfonylurea was used to intensify therapy in 30,297 people (46%)—as a single agent by 28,484 people and in combination with other antihyperglycemic drugs by 1,813 people. The next most common drug classes at first treatment intensification were DPP-4is (*n* = 14,256), insulin (*n* = 6,027), SGLT-2is (*n* = 4,944), and GLP-1ras (*n* = 2,905). The grouping of those using repaglinide, acarbose, and thiazolidinediones comprised 6,873 people.

At baseline, people with a sulfonylurea-based intensification had, on average, fewer clinician visits and hospitalizations in the last year compared with those dispensed a non–sulfonylurea-based treatment ($P < 0.001$) (Table 1). Those with a sulfonylurea-based intensification also took, on average, fewer other medications and had fewer complications and comorbidities, proportional to those not using a sulfonylurea-based therapy. Other baseline characteristics are presented in Table 1.

Primary Outcome

At the beginning of our observation period, the proportion of people dispensed a sulfonylurea at first treatment intensification was highest in rural areas (57%), compared with urban (54%) and metropolitan (52%) areas ($P = 0.009$). Although proportions decreased over time across the province, rural residents continued to compose the highest proportion of sulfonylurea users (45%) compared with those in urban (35%) and metropolitan (37%) areas ($P < 0.001$), and the trend away from sulfonylurea use was delayed by ~4 years for rural residents (Fig. 2). After adjusting for potential confounders, people living in a rural area were significantly more likely to start using a sulfonylurea than residents of a metropolitan area (adjusted odds ratio1.34; 95% CI 1.29–1.39) (Supplementary Fig. 2). Of note, we found no interaction between sex and place of residence.

Subgroup Analysis

Of the 29,987 people with laboratory data available, kidney dysfunction was significantly associated with a lower likelihood of sulfonylurea use and elevated HbA_{1c} was significantly associated with a higher likelihood of sulfonylurea use at first treatment intensification (Supplementary Fig. 3). When these laboratory values were considered in the model, the association between rural residence and sulfonylurea use was consistent with our main results.

CONCLUSIONS

In this study, we describe how sulfonylureas are used for the intensification of type 2 diabetes treatment after initial metformin therapy across the rural–urban continuum. Although use is waning, sulfonylureas remain the most common second-line antihyperglycemic drug class dispensed when treatment intensification is required. Although there is a large body of evidence illustrating trends in antihyperglycemic drug therapy used in type 2 diabetes, most take a system-level approach or use a cross-sectional study design. These studies describe the increase in the use of newer drug classes such as the DPP-4is, SGLT-2is, and GLP-1ras, and the decline in use of sulfonylureas (10–18). However, due to the nature of the study design, these studies lack temporality, or rather, they are unable to describe where in the overall treatment strategy antihyperglycemic drug classes are used (i.e., first-line, second-line, and so on) (10–18,21,32). Consistent with this literature, our data also revealed that, over time, there is a trend away from using sulfonylureas, and by using individual-level, longitudinal data, we were able to classify this sulfonylurea use as the first treatment-intensification instance. It is likely that newer agents with promise of weight loss and cardiovascular risk reduction played a role in this decline.

However, when place of residence was considered, a 4-year delay in the decline of sulfonylurea use was observed in rural

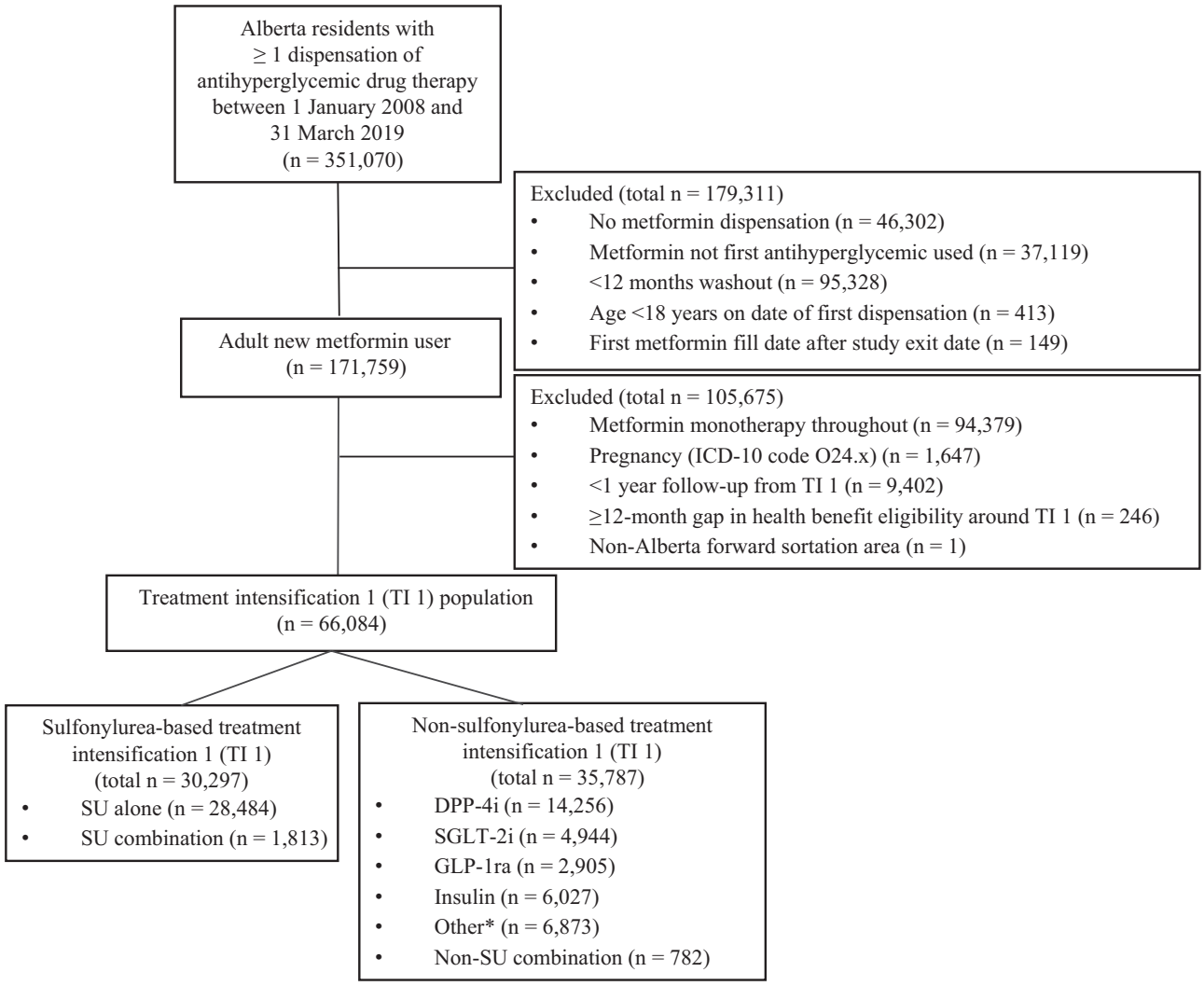

Figure 1—Flow diagram of study population. *repaglinide, acarbose, and thiazolidinediones. SU, sulfonylurea; TI 1, First Treatment Intensification.

areas compared with trends in metropolitan areas at first treatment intensification. To our knowledge, no similar studies have analyzed antihyperglycemic drug use by area of residence; other research has either been conducted on an interprovincial or national scale, used different geographic definitions, or did not consider place of residence as a covariate (10,11,14,16,18). Therefore, our study appears to be the first to describe antihyperglycemic drug dispensation along the rural–urban continuum and, most notably, a sustained use of sulfonylureas in rural areas.

Reasons for the delay in using newer antihyperglycemic agents at first treatment intensification in rural settings merits further investigation from both clinician and patient perspectives. One possible explanation may include barriers to implementing best practices in health care and overall differences in the process of care by rural clinicians. This is well studied in the fields of medicine and nursing, which have identified barriers such as a lack of continuing education initiatives, competing demands, and inconsistent guidelines and protocols between urban and rural health care settings (33–35). Another factor to consider is how clinicians learn about new, emerging therapies and whether rural clinicians have different methods of engagement with new data, compared with their urban and metropolitan colleagues. We were unable to assess whether the dispensed antihyperglycemic therapy was appropriate or best practice; however, this should be considered for future study.

A patient perspective that possibly could explain our observations was the demographics of a rural population, specifically whether there are more people using publicly funded drug insurance programs in this area. Publicly funded drug insurance in Alberta typically requires a trial of metformin and a sulfonylurea before other agents are covered (36). In Alberta, the most common publicly funded health insurance programs include Assured Income for the Severely Handicapped, Income Support (for low-income individuals), and Coverage for Seniors (Alberta residents aged 65 years and older) (37–39). Although we were unable to characterize whether an individual in our data set used a publicly funded health insurance program, or had drug insurance of any kind, it is unlikely that health care insurance use or socioeconomic status of rural individuals were substantial drivers of sustained sulfonylurea use in rural areas. This is because the largest proportion of individuals accessing publicly funded health insurance programs are located in Edmonton and Calgary, the largest metropolitan cities in our study (37–39).

Table 1—Participant demographics by sulfonylurea use at first treatment intensification

	Sulfonylurea-based treatment (*n* = 30,297)	Non–sulfonylurea-based treatment (*n* = 35,787)	Standardized difference
Area of residence, *n* (%)			0.11
Metropolitan	18,464 (60.9)	23,182 (64.8)	
Urban	2,799 (9.2)	4,001 (11.2)	
Rural	9,034 (29.8)	8,604 (24.0)	
Fiscal year*, *n* (%)†			0.26
2009/2010	2,512 (53.7)	2,166 (46.3)	
2010/2011	2,974 (55.1)	2,425 (44.9)	
2011/2012	3,046 (52.9)	2,715 (47.1)	
2012/2013	3,210 (53.0)	2,851 (47.0)	
2013/2014	3,404 (51.4)	3,224 (48.6)	
2014/2015	3,620 (47.1)	4,064 (52.9)	
2015/2016	3,628 (39.4)	5,570 (60.6)	
2016/2017	3,761 (37.5)	6,281 (62.5)	
2017/2018	4,142 (39.0)	6,491 (61.0)	
Age, mean (SD), years	56.5 (12.8)	54.3 (12.5)	0.17
Male sex, *n* (%)	18,880 (62.3)	21,885 (61.2)	0.02
Time since metformin initiation, mean (SD), years	1.4 (1.9)	1.6 (2.0)	0.11
No. of clinician visits, *n* (%)			0.06
0–6	7,397 (24.4)	7,865 (22.0)	
7–12	7,984 (26.4)	9,351 (26.1)	
13–24	8,044 (26.6)	9,892 (27.6)	
≥25	6,872 (22.7)	8,679 (24.3)	
Hospitalization in the past year, *n* (%)	4,004 (13.2)	5,605 (15.7)	0.07
No. of other prescriptions, *n* (%)			0.06
0–2	9,696 (32.0)	10,006 (28.0)	
3–5	7,796 (25.7)	9,805 (27.4)	
6–8	5,498 (18.1)	7,002 (19.6)	
≥9	7,307 (24.1)	8,974 (25.1)	
Diabetes complications, *n* (%)			
Retinopathy	6,389 (21.1)	7,722 (21.6)	0.01
Nephropathy	1,373 (4.5)	1,933 (5.4)	0.04
Neuropathy	3,031 (10.0)	4,187 (11.7)	0.06
Ischemic heart disease	6,350 (21.0)	7,440 (20.8)	<0.01
Prior stroke	1,167 (3.9)	1,465 (4.1)	0.01
Peripheral vascular disease	1,401 (4.6)	1,752 (4.9)	0.01
Hyperlipidemia	12,656 (41.8)	15,894 (44.4)	0.05
Diabetic foot infection	2,419 (8.0)	3,029 (8.5)	0.02
Prior amputation	158 (0.5)	240 (0.7)	0.02
Dental complications	3,148 (10.4)	3,680 (10.3)	<0.01
Hypoglycemia	554 (1.8)	833 (2.3)	0.04
No. of other chronic conditions,‡ *n* (%)			0.07
0–1	4,900 (16.2)	5,121 (14.3)	
2	8,314 (27.4)	9,300 (26.0)	
3–4	10,981 (36.2)	13,618 (38.1)	
≥5	6,102 (20.1)	7,748 (21.7)	

*Alberta Health's fiscal year runs April to March. †Percentage by fiscal year. ‡As listed in Elixhauser et al. (43).

A patient's perception of their health and health care needs is another factor we considered for the delay in the decline of sulfonylurea use in rural areas. Canadians living in rural communities are less likely to report having unmet health care needs (3). This suggests that rural Canadians have a different expectation of the health care system or higher threshold at which they perceive the need to seek specialized medical care (3). Although we were unable to assess patient perception and behaviors, this must be considered for future study.

As with other observational studies that use administrative health data, we cannot rule out the possibility of residual confounding from factors that are unmeasured in our data. For example, clinician practice location and specialty were unmeasured in our data set and have been requested for use in subsequent studies. Another limitation is that changes in drug-therapy dosage were not assessed, nor were trends of other antihyperglycemic drug classes. As newer agents become available and more widely used, research is warranted in this area. Potential for miscoding of diagnostic codes and, subsequently, misclassification of individuals, is a well-known limitation of all studies using administrative data (40). However, administrative health records used in this study

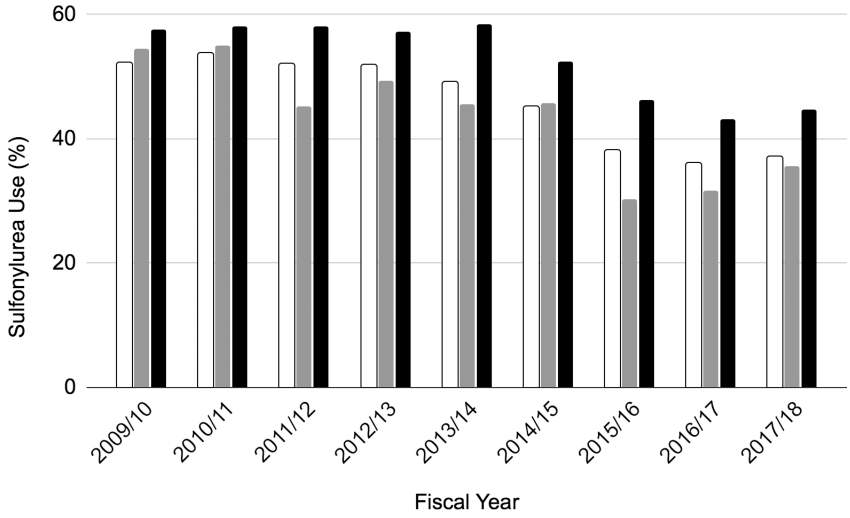

Figure 2—Percentage of people adding sulfonylurea-based therapy at first treatment intensification by fiscal year and residence. White bars, metropolitan areas; grey bars, urban areas; black bars, rural areas.

have internal validation and data cleaning processes to improve the accuracy and completeness of each record (41,42). In addition, when defining covariates, we used sources where available, with acceptable levels of positive predictive values (26,27).

The research described is exploratory, and we believe it has begun to shed light on rural health care challenges beyond infrastructure. Although we do not know whether patient health outcomes have been jeopardized, our observation of the sustained use of sulfonylureas at first treatment intensification when other options are available is concerning. We have described several possible explanations for these observations, which we plan to elucidate as we expand our understanding of the intersection between process of care and residence through subsequent studies. Additional work to identify whether similar drug therapy trends are occurring in other chronic disease states and jurisdictions is warranted to develop interventional studies aimed at improving processes of care in rural areas.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.K.N., L.C.B., D.T.E., and S.H.S. were responsible for the concept and design of the study. S.H.S. and D.T.E. were responsible for data acquisition. D.K.N. performed the analysis, and all authors interpreted the results. D.K.N. prepared an initial draft of the manuscript. All authors helped revise the manuscript as needed and have read and approved the final manuscript. S.H.S. and D.T.E. are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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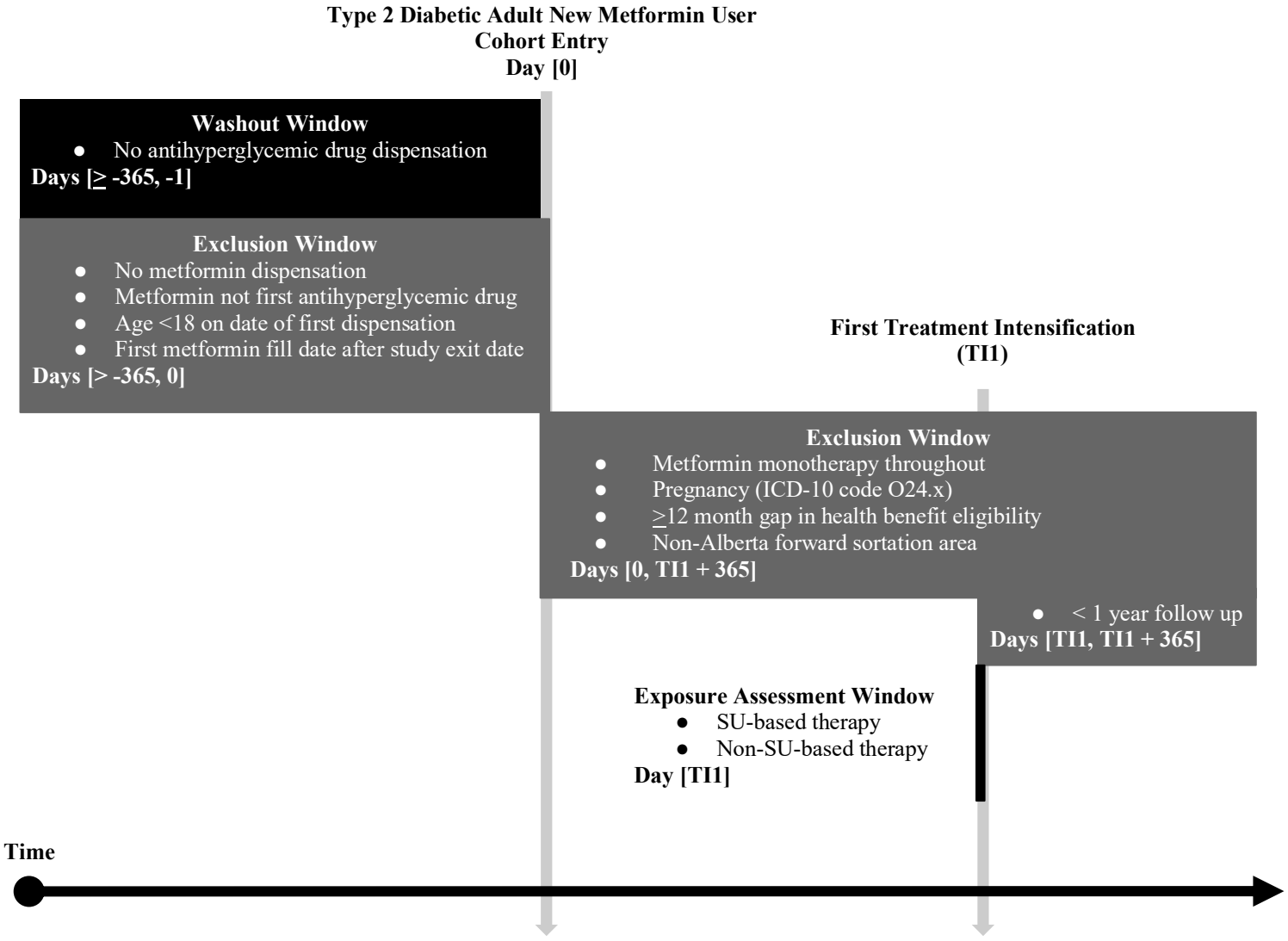
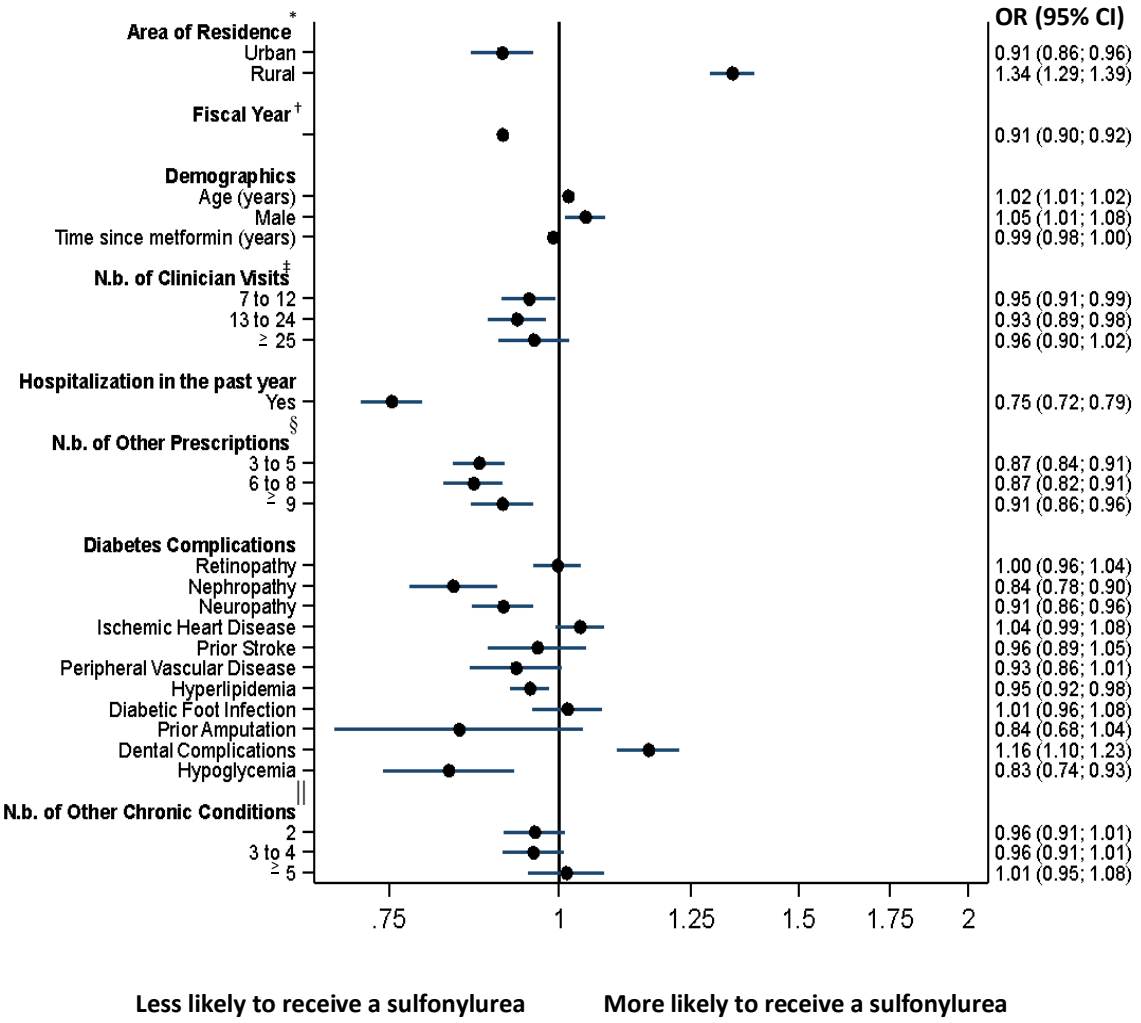
Supplementary Figure S1. Timeline of methodological events



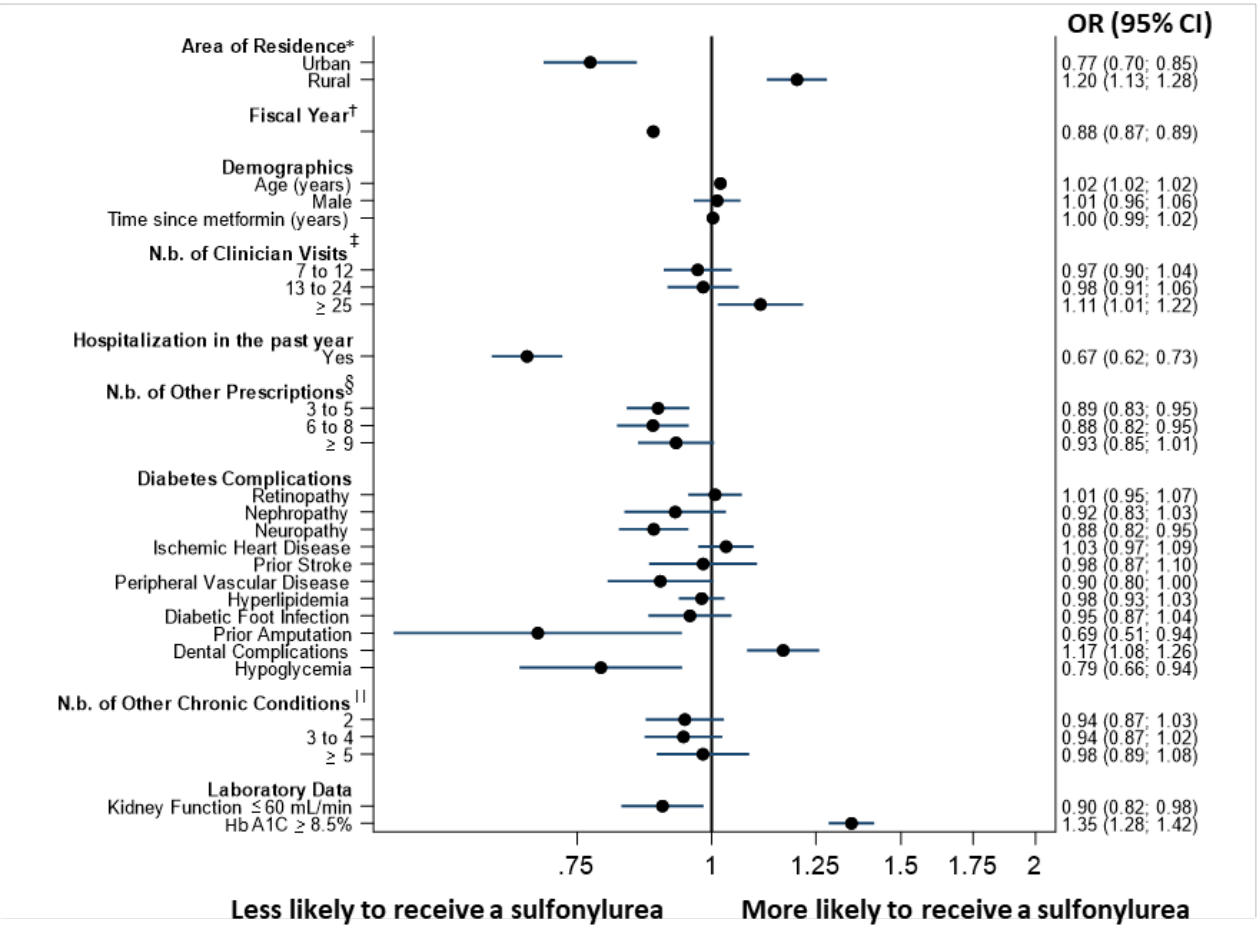
Note. Adapted from Schneeweiss S, Rassen JA, Brown JS, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med 2019;170:398-406.

Supplementary Figure S2. Odds of sulfonylurea-based therapy at first treatment intensification



Note. * reference Metropolitan, † Alberta Health fiscal year is April to March, N.b. number, ‡ reference 0 to 6, § reference 0 to 2, || as listed in Elixhauser and reference 0-1

Supplementary Figure S3. Odds of sulfonylurea-based therapy at first treatment intensification laboratory subgroup



Note. * reference Metro, † Alberta Health fiscal year April to March, N.b. number, ‡ reference 0 to 6, § reference 0 to 2, || as listed in Elixhauser and reference 0 to 1