

Original Article

## Population-Based Evidence From a Western Canadian Province of the Decreasing Incidence Rates and Trends of Inflammatory Bowel Disease Among Adults

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### Abstract

**Background and Aims:** Canada has one of the highest inflammatory bowel disease (IBD) incidence rates worldwide. Higher IBD incidence rates have been identified among urban regions compared to rural regions. The study objectives were to (i) estimate IBD incidence rates in Saskatchewan from 1999 to 2016 and (ii) test for differences in IBD incidence rates for rural and urban regions of Saskatchewan.

**Methods:** A population-based study was conducted using provincial administrative health databases. Individuals aged 18+ years with newly diagnosed Crohn's disease or ulcerative colitis were identified using a validated case definition. Generalized linear models with a negative binomial distribution were used to estimate incidence rates and incidence rate ratios (IRRs) adjusted for age group, sex and rurality with 95% confidence intervals (CIs).

**Results:** The average annual incidence rate of IBD among adults in Saskatchewan decreased from 75/100,000 (95% CI 67 to 84) in 1999 to 15/100,000 (95% CI 12 to 18) population in 2016. The average annual incidence of IBD declined significantly by 6.9% (95% CI -7.6 to -6.2) per year. Urban residents had a greater overall risk of IBD (IRR = 1.19, 95% CI 1.11 to 1.27) than rural residents. This risk difference was statistically significant for Crohn's disease (IRR = 1.25, 95% CI 1.14 to 1.36), but not for ulcerative colitis (IRR = 1.08, 95% CI 0.97 to 1.19).

**Conclusions:** The incidence of IBD in Saskatchewan dropped significantly from 1999 to 2016 with urban dwellers having a 19% higher risk of IBD onset compared to their rural counterparts. Health care providers and decision-makers should plan IBD-specific health care programs considering these specific IBD rates.

**Keywords:** Crohn's disease; Epidemiology; Incidence; Inflammatory bowel disease; Ulcerative colitis; Urban population

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## INTRODUCTION

Inflammatory bowel disease (IBD), comprising of ulcerative colitis (UC) and Crohn's disease (CD), is a long-term disorder causing inflammation in the gastrointestinal system (1). As a worldwide disease with predominance in developed countries, IBD is estimated to affect as many as 1.5 million individuals in North America and 2.5 to 3 million people in Europe (2,3). The incidence of IBD varies considerably geographically. The highest incidence of IBD has been described in westernized countries (4). However, recent epidemiological studies have also described increasing incidence trends of IBD in areas that previously reported low rates of the disease, including Asia, South America and Middle East (5–10). Thus, countries including, China, India, Turkey and Brazil are reporting increasing incidence rate of IBD as opposed to European and North American countries who have demonstrated variable patterns of decreasing, plateauing and increasing rates of the disease (4–11). As a result, the differences in the incidence rates between developed and developing countries have been reducing (4,12–14).

Canada is among countries with the highest incidence rate of IBD (15). In 2018, it was estimated that 270,000 people were living with IBD in Canada (16). Population-based studies assessing the incidence of IBD in different Canadian provinces have provided varying results in the trends of the disease. Some provinces have described decreasing incidence rates of IBD, while others have reported stable trends over time or increasing incidence rates among specific age groups (15,17,18).

Furthermore, over the past two decades, numerous studies assessing differences between location of residence and IBD in places such as Europe, North and South America have found a higher risk of IBD (both CD and UC) in urban areas compared to rural locations (8,19–21). Most of these studies have pinpointed westernized lifestyle and urbanization as the key reasons behind this risk. Likewise, in Canada, extensive population-based studies regarding IBD epidemiology and location of residence have been assessed. All these studies revealed rurality as a protective factor for IBD (19–21).

Epidemiologic studies on the incidence trends of IBD are essential to provide researchers clues to the etiology of IBD. Information on this topic will provide evidence on how rapidly the disease is decreasing or increasing in a given region. Moreover, understanding the differences between IBD and location of residence is crucial for designing effective strategies needed to reduce, prevent and treat individuals living with the disease. Data on the incidence in Western Canada are lacking since year 2000. Therefore, this study aimed to (i) estimate the incidence rates and trends of IBD in Saskatchewan and (ii) determine if the incidence rates of IBD in urban settings are higher than those in rural areas.

## METHODS

### Study Design, Participants, and Setting

A population-based cohort study was conducted using administrative databases for the province of Saskatchewan. This western Canadian province has approximately 1.2 million people, most residing in one of the two largest cities, Regina or Saskatoon (22,23), and around 35% of the population is dispersed in rural and remote areas (23). Saskatchewan has a universal health care system (24) stewarded by the provincial Ministry of Health which routinely collects data of health care utilization on almost the entire covered population. In this study, we included data from all individuals 18 years and older newly diagnosis of IBD, including CD and UC, between fiscal years April 1st, 1999, to March 31st, 2016. The data source spans from 1990 to 2018. However, the study population was restricted for 1999 and 2016 to allow for backward and forward washout period. We excluded individuals less than 18 years of age due to data unavailability and because there is no validated pediatric IBD case definition for Saskatchewan administrative health data. For several years, no pediatric gastroenterologists were available in Saskatchewan and patients were required to access colonoscopies and pediatric IBD care in neighbouring provinces.

### Data Source

Three de-identified databases were linked and used in this study (i.e., hospital discharge abstracts, Person Health Registration System [PHRS] and physician services claims). The Discharge Abstract Database (DAD) contains information on hospitalizations completed when patients are discharged from an acute-care facility, and includes inpatient hospitalizations, diagnostic procedures (including endoscopies) and day surgeries (22,25). All data were accessed through the Saskatchewan Health Quality Council (HQC). The PHRS captures individual demographic characteristics including the year of birth, sex, date of health care coverage (initiation and termination), the status of health insurance coverage and location of residence (22). The Medical Services Billing database captures information submitted by physicians to claim reimbursement from the provincial government for services delivered to patients (22,25). Salaried physicians are required to submit claims for the care they provided, a process known as 'shadow-billing'. Although shadow-billing could lead to under-reporting (22), the case definition used in this study required multiple inpatient and outpatient health care contacts, so this is unlikely to affect our results.

### Case Definition

Diagnosed incident IBD cases were identified by applying a case definition that was validated in Manitoba (26). This algorithm has been used in other population-based studies in

Saskatchewan (16,19,25) and has been proven to be one of the most accurate case definitions to identify adults with the diagnosis of IBD (27). For this case definition, the International Classification of Disease version 9 (ICD-10) and 10 (ICD-10) codes were used. This case definition requires five or more physician claims or hospitalizations with the diagnosis of IBD, either CD (ICD-9 555.x and ICD-10-CA K50.x) or UC (ICD-9 556.x and ICD-10-CA K51.x), within at least 2 years of continuous health care coverage, or a minimum of three health care contacts with these diagnostic codes if individuals had less than 2 years of continuous health care coverage (25,26). We classified eligible cases as CD or UC based on the most prevalent diagnosis (25). After identifying eligible IBD cases, an 8-year washout period was used to distinguish between the incident and prevalent diagnosed IBD cases; specifically, 8 years of continuous health care coverage without IBD health care contacts (i.e., either hospitalizations or physician billing claims) were required prior to the date of diagnosis (i.e., the first eligible health care contact of the case definition). This 8-year washout period has been previously used in IBD studies based on administrative health data (18,28).

### Definition of Rural/Urban Status

All diagnosed incident IBD cases were assigned to rural or urban residence location at the date of the diagnosis of IBD. There is no standard definition of rurality in Canada. Various definitions have been proposed by Statistics Canada to define rural and urban residence. These definitions include the 'population size, population density, or the economic and social influence of a city on neighbouring regions' (29). A 2017 Canadian study conducted by Benchimol et al. (20) validated the rural/urban definition and outlined the Census Metropolitan Areas (CMA) definition as the best option. In this study, we used an approach adopted by the Saskatchewan HQC. Individuals with a residential postal code within a CMA or Census Agglomeration with a population of 15,000 or more inhabitants were classified as living in an urban residence. This definition has been used in previous population-based studies in the province (25).

### Statistical Analysis

Generalized linear models with a negative binomial distribution were used, considering a good model fit when observing a Pearson  $\chi^2$  / residual of degree of freedom ratio closer to 1 (30,31). A negative binomial distribution was chosen due to its ability to accommodate over-dispersed count data (30). Incidence was modelled considering as dependent variable the observed number of IBD incidence cases and as independent variables sex, rural/urban place of residence, fiscal year and age group stratum (i.e., 18 to 29 [reference], 30 to 39, 40 to 49, 50 to 59, 60+ years old). The natural logarithm of the Saskatchewan population at risk in each age group stratum stratified by sex

and location of residence (i.e., rural or urban) was used as an offset variable in the models. Information about the population at risk derived from the PHRS database.

The models were used to estimate incidence rates and incidence rate ratios (IRRs) with their corresponding 95% confidence intervals (95% CIs). A linear trend test across the years was estimated. Also, an interaction term between year and location of residence was tested in the model. A nominal  $\alpha = 0.05$  was adopted for all tests of statistical significance. SAS version 9.4 (SAS Institute, Cary, NC, USA) with the GENMOD procedure was used for all analyses. The Saskatchewan Biomedical Research Ethics Board (REB) approved this study as BIO 91.

## Results

In total, 4908 individuals with the diagnosis of IBD were included in the study. In this group, 1447 (29.9%) people were living in rural areas and 3392 (70.1%) in urban locations. Table 1 describes the demographics of the study cohort.

### Incidence of IBD

The observed number of individuals diagnosed with IBD decreased from 608 in 1999 to 141 in 2016; in other words, we recognized a reduction of about 76% in the number of incident cases during the study period. The overall annual average incidence rate of IBD decreased from 75 (95% CI 67 to 84) per 100,000 population in 1999 to 15 (95% CI 12 to 18) per 100,000 in 2016. This decrease was evident for both diagnosed UC and CD cases. The average incidence rate of diagnosed UC decreased from 36 (95% CI 31 to 42) to 6 (95% CI 4 to 8) per 100,000 population, and the incidence rate of diagnosed CD decreased from 37 (95% CI 32 to 42) to 8 (95% CI 6 to 10) per 100,000 people from 1999 to 2016 respectively.

An average annual decline of 6.9% (95% CI -7.6 to -6.2) in the incidence rate of diagnosed IBD was identified from 1999 to 2016 (Figure 1). Similarly, we observed a decrease of 7.7% (95% CI -8.6 to -6.8) and 6.0% (95% CI -6.8 to -5.2) in the incidence rate of diagnosed UC and CD (Figure 2).

By rural/urban location of residence, an average annual decrease of 7.1% (95% CI -7.9 to -6.3) and 6.5% (95% CI -7.7 to -5.3) was observed, respectively, among urban and rural dweller (Figure 3). The interaction between year and location of residence was not statistically significant ( $P = 0.61$ ).

### Incidence Rate Ratios

Urban Saskatchewan residents had a 19% higher risk (IRR = 1.19; 95% CI 1.11 to 1.27) of diagnosed IBD in comparison to those living in rural areas. Similarly, individuals living in urban areas had a 25% higher risk of diagnosed CD (IRR = 1.25; 95% CI 1.14 to 1.36) than those in rural settings; however, this association was not significant among those with diagnosed UC (IRR = 1.08, 95% CI 0.97 to 1.19).

Additionally, males had a lower risk of diagnosed IBD (IRR = 0.89, 95% CI 0.84 to 0.96) than females. This difference was observed in the diagnosed CD group (IRR = 0.77, 95% CI 0.71 to 0.83), but not statistically significant in the diagnosed

UC group (IRR = 1.02, 95% CI 0.93 to 1.12). Similarly, a lower risk of diagnosed IBD was observed among those aged 60+ (IRR = 0.72, 95% CI 0.65 to 0.80) in comparison to those in the 18–29 age group; this finding was also significant by type of disease (UC IRR = 0.77 [95% CI 0.66 to 0.89] and CD IRR = 0.69 [95% CI 0.61 to 0.78]; [Table 2](#)).

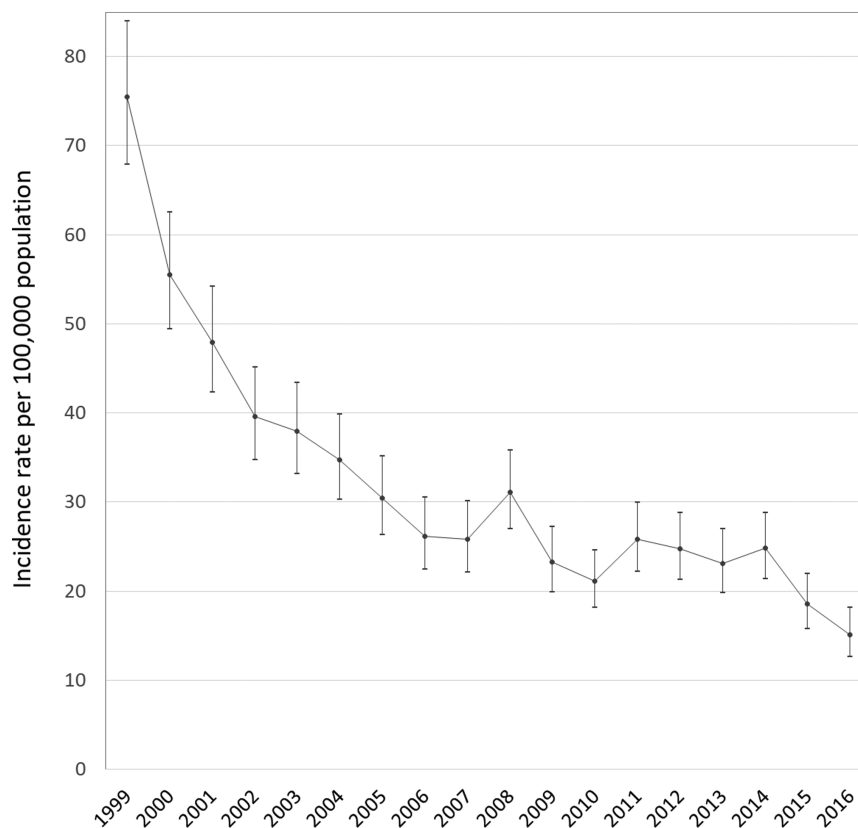
**Table 1.** Descriptive characteristics of the incident cohort of inflammatory bowel disease in Saskatchewan between 1999 and 2016 ( $n = 4908$ )

Variable	$n$ (%)
Age group, years	
18–29	1148 (23.4)
30–39	934 (19.0)
40–49	1052 (21.4)
50–59	838 (17.1)
60+	936 (19.1)
Disease type	
Crohn's disease	2612 (53.2)
Ulcerative colitis	2296 (46.8)
Sex	
Male	2285 (46.6)
Female	2623 (53.4)
Residence location	
Urban	3392 (70.1)
Rural	1447 (29.9)

## Discussion

We conducted a population-based cohort study using administrative health databases to estimate the incidence of diagnosed IBD in the province of Saskatchewan. In Canada, the highest and lowest incidence rates of IBD were previously reported, respectively in Nova Scotia (45.7/100,000 population) and British Columbia (18.7/100,000 population) ([17,19](#)). Our study contributes to these data with a significantly decreasing rate of IBD incidence cases in the province of Saskatchewan.

Similar decreasing IBD incidence rates have also been reported in some Canadian provinces. For instance, researchers in Québec observed between 2001 and 2008 a decrease in the rates of both CD (from 18.1 to 16.8/100,000 person-years) and UC (from 12.5 to 9.8/100,000 person-years) ([32](#)). A decrease in the incidence of IBD was also reported in Manitoba between 1990 and 2013 ([15](#)), while data from Alberta showed a stable trend in IBD rates between 2010 and 2015 ([33](#)). A recent retrospective population-based cohort study from Ontario observed



**Figure 1.** Adjusted annual incidence trends of inflammatory bowel disease in Saskatchewan, Canada.

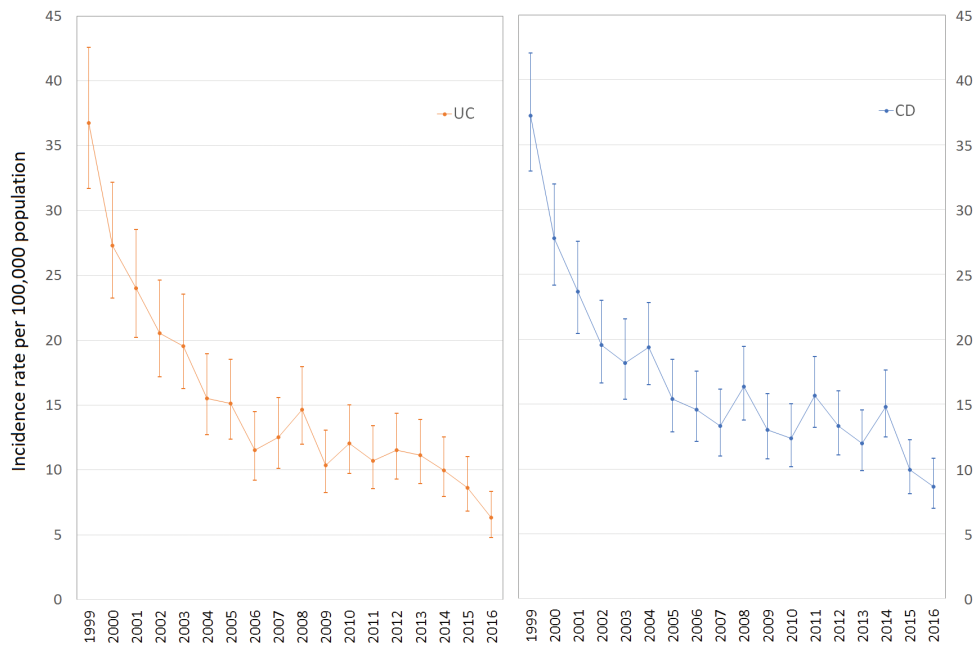


Figure 2. Adjusted annual incidence trends of ulcerative colitis (UC) and Crohn's disease (CD) in Saskatchewan, Canada.



Figure 3. Adjusted annual incidence trends of inflammatory bowel disease by urban-rural location in Saskatchewan, Canada.

an increasing incidence trend in the past 9 years for ages 30 to 60, and a stable trend in other age groups (18). Clearly, these studies indicate variations in IBD rates across Canada which

may be attributed to regional differences in the incidence of the disease and potentially to the discrepancies in the algorithms used to capture the cases of UC and CD. A population-based



**Table 2.** Incidence rate ratios with corresponding 95% confidence intervals (95% CIs) for inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) for demographic characteristics

	IBD	UC	CD
Sex			
Female	Ref.	Ref.	Ref.
Male	<b>0.89 (0.84–0.96)</b>	1.02 (0.93–1.12)	<b>0.77 (0.71–0.83)</b>
Age group			
18–29	Ref.	Ref.	Ref.
30–39	1.02 (0.92–1.13)	1.07 (0.92–1.24)	1.00 (0.88–1.13)
40–49	1.08 (0.97–1.19)	<b>1.19 (1.03–1.38)</b>	1.01 (0.90–1.15)
50–59	1.02 (0.92–1.14)	1.05 (0.90–1.22)	0.99 (0.87–1.12)
60+	<b>0.72 (0.65–0.80)</b>	<b>0.77 (0.66–0.89)</b>	<b>0.69 (0.61–0.78)</b>
Place of residence			
Rural	Ref.	Ref.	Ref.
Urban	<b>1.19 (1.11–1.27)</b>	1.08 (0.97–1.19)	<b>1.25 (1.14–1.36)</b>

Statistically significant values at alpha = 0.05 are bolded.

national study estimating IBD rates using homogenous case definition and methodology, like the model-base estimation used in this provincial study, could provide a clearer picture of the actual trends of the disease across provinces and in Canada as a whole.

Nevertheless, we observed a noticeable decline in the incidence of IBD among adults in Saskatchewan, a pattern previously described in Nova Scotia (17), Quebec (32) and Manitoba (15). The complementing trend of increasing incidence rates of IBD among children has been identified in Canada (18,34,35) and other countries (36,37). This could be one reason behind the observed decline, relative to that of the children, in the incidence rates of CD and UC among adults in Saskatchewan and other Canadian provinces. In other words, the declining incidence trends of IBD among adults might reflect that the disease is starting to be diagnosed in the early stages of life. As presented by Coward et al. (33), the incidence rates of IBD appear to be stable over time in Alberta when considering all age groups (33); although, decreasing incidence rates of UC and CD could be observed in the adult population when stratifying the trends by age groups (33). Thus, the decision to include or exclude individuals under 18 years in epidemiologic studies about IBD could have an impact on the observed trends. Furthermore, in our study, the declining trend in the incidence rates of IBD was consistently observed across age groups; although, two age groups (30 to 39 and 40 to 49 years) had steeper decreasing trends than those observed in the younger and older age groups. Future provincial and national studies could explore incidence rate trends by age groups, including individuals under 18 years and considering birth cohort study designs.

Turning to global epidemiological studies, a 2015 review on the incidence of IBD in Europe reported a rise in the disease. Specifically, an increase in the incidence rate of UC was

observed from 6.0 to 9.8/100,000 person-years from 1962 to 2010, while CD increased from 1.0 to 6.3/100,000 person-years for the same period (38,39). Data from South America have shown a similar pattern. In 2004, Appleyard et al. (40) reported a rise in IBD incidence rates for Puerto Rico from 3.07 to 7.74/100,000 population from 1996 to 2000. In Brazil, researchers also observed a hike in CD rates over a period of 27 years from 0.08 to 0.68/100,000 person-years to 5.5/100,000 (41). Conversely, a 2017 systematic review in the United States by Ng et al. (2) reported the lowest incidence estimates for CD in California (6.3/100,000 person-years) and for UC in Olmsted County (8.8/100,000 person-years). Not surprisingly, these studies also revealed that the incidence rate of IBD varies across the globe. Some researchers have attributed these variations to environmental risk factors and rapid socio-economic development in certain locations (42–44).

Overall, our population-based study showed a higher risk of developing IBD for people living in urban places in Saskatchewan compared to their rural counterparts. Specifically, urban dwellers have a 25% higher risk of CD onset compared to their rural counterparts. Population-based studies conducted in other Canadian provinces have shown similar patterns. Manitoba, for example, reported a 23% lower risk for rural residents, while Alberta showed a 13% higher rate for CD and a 44% higher rate for UC in urban populations (19,20). A 2017 study conducted by Benchimol et al. (20) in four Canadian provinces reported a 10% lower risk of IBD for people living in rural areas in comparison to those in urban areas.

Our results support evidence from studies conducted around the world assessing urban–rural differences in the incidence rates of IBD. Between 1935 and 1975, the incidence rate of CD in Minnesota, United States, was found to be higher in people located in urban locations than in rural areas (45).

Between 1986 and 1987, rates for both CD and UC were higher in northern parts of the United States than in southern ones, as well as in urban than in rural areas (46). Moreover, European studies reported a similar pattern. For instance, in Poland, a higher incidence rate of IBD was found among urban people compared to their rural counterparts (47). Spanish data from 1981 to 1988 also revealed a higher CD rate in the cities, namely 1.87/100,000 compared with a rate of 0.86/100,000 for rural residents (48). Victoria et al. (8) also observed the same pattern in the Midwest of São Paulo State, Brazil. A recent systematic review that included more than 40 countries reported higher IRRs of IBD for urban locations (21). Suggested explanations of this difference include diet variations, vitamin D exposure, air pollution and physical inactivity (20,21). In addition, in a 2006 population-based Canadian study, Bernstein et al. (19) underlined access to care as a potential by-product of this rural-urban differences. Further research in this field should aim to explain the increased risk of CD in urban Saskatchewan areas.

The strengths of the study include the sample size ( $n = 4,908$  diagnosed IBD incidence cases), with 18-year study period. These study characteristics made it possible to assess the trends in the incidence of the disease over time. Also, our model-based approach enabled us to control our estimates and analyses by rural/urban differences. However, we acknowledge the limitations of using administrative health databases, including the presence of potential misclassification bias in assessing disease surveillance for individuals with chronic diseases (49). To address this, patients with diagnosed IBD were identified utilizing a validated algorithm that captured patients only if they had physician claims or hospitalizations related to ICD-9 or ICD-10 diagnosed codes of IBD. This reduced the effect of misclassifying non-diagnosed IBD patients as diagnosed. Second, since IBD is a disease with relapse and remission of symptoms, there could be difficulties in differentiating incident from prevalent cases. Prevalent cases are more likely to be misclassified in earlier years where washout periods are shorter, which could result in a declining trend in incidence over time (50). To reduce this effect, a washout period of 8 years was incorporated in the study to avoid the overestimation of incidence cases.

Health administrative databases contain rich sources of information that are suitable for population-based epidemiological studies (51,52). Given that the quality of the Saskatchewan health administrative data has evolved in the last few decades with data holdings for 2001 onwards ascertained to have better quality compared to previous years, as a sensitivity analysis, we conducted our statistical analyses with data from 2001 to 2016 fiscal years only. The results of this analysis did not differ significantly from our initially estimated incidence rates, trend tests, and IRR.

In conclusion, our study provides up-to-date epidemiological data on the incidence as well as rural/urban differences of IBD on the province of Saskatchewan. The evidence from this

population-based study confirmed that the incidence rates of both CD and UC among adults are declining in the province. Urban Saskatchewan dwellers were described to be at higher risk of IBD than rural residents. A comprehensive understanding of the burden of IBD on the province of Saskatchewan, in terms of its prevalence and cost, could help with resource allocation and planning, and should be the focus of future studies. We emphasize that health care providers and decision-makers plan IBD-specific health care programs taking into account the presented evidence.

#### What is already known on this topic?

- Previous epidemiological studies in developed countries have reported decreasing, plateauing or increasing incidence rates of IBD.
- Urban dwellers are more likely to develop IBD compared to rural residents.

#### What this study adds?

- Urban dwellers in Saskatchewan, Canada, have a 25% higher risk of developing CD than rural dwellers.
- In 2016, the incidence rate of IBD in Saskatchewan appears to be one of the lowest reported across Canadian provinces.

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*Conflicts of Interest:* The authors disclose no conflicts of interest.

*Author Contributions:* JAO initiated and designed the study, performed data analysis, drafted the manuscript and critically revised the study for important intellectual content. JNP-S, SF and LML designed the study, drafted the manuscript and critically revised the study for important intellectual content. NM and GGK drafted the manuscript and critically revised the study for important intellectual content. All authors

contributed to data interpretation and approval of the final manuscript.

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