Epidemiology and Direct Health Care Cost of Inflammatory Bowel Disease in Saskatchewan: A Population-Based Study

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In the Department of Community Health and Epidemiology
University of Saskatchewan Saskatoon

By

JESSICA A. OSEI

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Jessica Osei

Master of Science in Community and Population Health Sciences
Department of Community Health and Epidemiology University of Saskatchewan Saskatoon

ABSTRACT

Worldwide studies have described an increasing prevalence of inflammatory bowel disease (IBD). Canada is a country with one of the highest IBD prevalence and incidence rates and with an estimated direct health care cost of $1.2 billion in 2018. Also, evidence shows variations in the incidence rate trends over time across Canadian provinces. This study aimed to estimate and test the trends of the incidence, prevalence, and direct health care cost of IBD in Saskatchewan from 1999 to 2016.

Administrative health data from Saskatchewan was used in a population-based cohort study from 1999 to 2016 fiscal years. A previously validated case definition was applied to identify individuals with a diagnosis of IBD. Generalized linear models with negative binomial and gamma distribution were used to model the prevalence/incidence and direct health care cost trends, respectively. Generalized estimating equations were used to account for correlation in the prevalence data. Sex, age group, and rural/urban residence were included as controlling variables. Annual prevalence and incidence rates, average annual changes, and direct health care cost (in 2013 Canadian dollars) were reported with their 95% confidence intervals (95%CI).

In 2016/17, 6,468 IBD cases were observed in our cohort; Crohn's disease: 3,663 (56.6%), ulcerative colitis: 2,805 (43.4%). The prevalence of IBD increased from 341/100,000 (95%CI 340 to 341) in 1999/00 to 664/100,000 (95%CI 663 to 665) population in 2016/17, observing a 3.3% (95%CI 2.4 to 4.3) average annual increase. Also, the estimated health care cost of IBD increased from $1.8 (95%CI 1.6 to 2.0) thousand in 1999/00 to $7.0 (95%CI 6.5 to 7.5) thousand in 2016/17, 9.2% (95% CI 8.6 to 9.9) average annual increase. On the other hand, the incidence rate of IBD declined from 75/100,000 (95%CI 67 to 84) in 1999/00 to 15/100,000 (95%CI 12 to 18) population in 2016/17, corresponding to an average annual decrease of 6.9% (95%CI -7.6 to -6.2).

In conclusion, while a remarkable increase was found in the prevalence and direct health care cost of IBD in Saskatchewan, Canada, a significant decline in the IBD incidence rate of the disease was observed since 1999. Decision-makers and health care providers need to promote policies that face the rising burden of the disease in the province.

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Not forgetting the staff at the Saskatchewan Health Quality Council, Thank you for the help and knowledge imparted in me. This project was supported by the College of Medicine and Devolved Scholarship program (CH&E, University of Saskatchewan), and the Canadian Institutes of Health Research (CIHR) Project Grant.

DEDICATION

This thesis is dedicated to all diagnosed inflammatory bowel disease patients living in Saskatchewan, Canada and across the world. It is my prayer that this work would contribute to policy changes, which can improve their lives.

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LIST OF ABBREVIATIONS

CAD	Canadian dollars
CD	Crohn's Disease
CI	Confidence Interval
CIHI	Canadian Institute of Health Information
CMA	Census Metropolitan Area
CMGs	Case Mix Groups
CPWC	Cost Per Weighted Case
DAD	Discharge Abstracts Database
DIN	Drug identification number
DPG	Day Procedure Group
FY	Fiscal Year
GEE	Generalized Estimating Equations
GLMs	Generalized linear models
HQC	Health Quality Council
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
MoH	Ministry of Health
PSD	Prescription drug plan database
PHRS	Person health registration system
RIWs	Resource Intensity Weights
SHA	Saskatchewan Health Authority
UC	Ulcerative Colitis
USD	United States Dollars

CHAPTER 1: INTRODUCTION

1.1 Background

Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract, consisting of Crohn's disease (CD) and ulcerative colitis (UC) (1). These two conditions are distinguished by their clinical locations. While UC affects only the large intestine (i.e., colon and rectum), CD can cause inflammation in any part of the gastrointestinal system, comprising the mouth to the anus (2). The peak onset of CD manifests in the third decade of life whereas UC has no typical age of onset (age of diagnosis varies) (3). Symptoms of IBD include fatigue, diarrhea, malnutrition, abdominal pain, and weight loss which could affect patient's quality of life (4).

The etiology of CD and UC is unclear (2, 5). However, studies indicate numerous possible causes. The suggested causes include the complex interactions among genetics, the immune system, and environmental factors (2, 5), such as deficiency of Vitamin D, smoking, diet, and migration patterns (5, 6, 7). For instance, studies have discovered that individuals who emigrated from places with a lower incidence rate of IBD to areas of higher rate had an increased probability of developing either UC or CD (8, 9).

1.2 Epidemiology

The rates of IBD differ across geographical locations (10). Studies have shown higher rates of IBD in developed countries, mainly in Europe and Northern America, contrasted to lower rates observed in Asia, Africa, and the Middle East (5, 10, 11). Researchers have estimated that about 0.5% of the general population in developed countries have IBD (12). In the last decades, epidemiological studies have reported increasing trends over time in the prevalence and

incidence of IBD (10, 12). This increase is predominant in areas that previously had low disease rates. As a result, the prevalence and incidence rate differences between developed and developing countries are narrowing (12).

Canada has one of the highest prevalence and incidence rates of IBD (13), with a total annual medical cost of 2.57 billion Canadian dollars (CAD) (2018 estimate) (14, 15). Recently, studies have explored the epidemiology of IBD in different Canadian provinces. Most of these works identified an increasing burden of IBD over time (13, 16-19). For instance, in 1999, Manitoba's prevalence rates for CD and UC reported by Bernstein et al. (19) were, respectively, 198.5 and 169.7 per 100,000 population. These rates increased to 271.4 (CD) and 248. 6 (UC) per 100,000 population in 2006 (17). In the same year, the prevalence of IBD for British Colombia and Alberta ranged between 160.7 and 283 per 100,000 population (17), while Nova Scotia's prevalence was 318.5 for CD and 247.9 for UC per 100,000 population (17). In 2018, 270,000 Canadians were estimated to have IBD (0.7% of the population) and this number is projected to increase to 403,000 by 2030 (18).

In addition, Benchimol and colleagues (20) assessed the relationship between IBD and rural/urban households at the time of diagnosis using different rurality definitions. The authors identified that rural place of residence was a protective factor for IBD in most of the used definitions. This study confirmed what Bernstein et al. (17) previously hypothesized, a lower risk of developing IBD for individuals residing in rural places compared to those in the urban areas in Canada.

1.3 Economic Burden of IBD

In 2018, the estimated annual direct and indirect medical costs of IBD in Canada were,

accordingly, 1.28 billion and 1.29 billion CAD (14, 15). Direct costs of IBD, are driven by hospitalizations, medications, and physician visits which in 2012 were estimated at 395 million, 521 million, and 132 million CAD, respectively (16). While indirect costs of IBD are incurred expenses deriving from reduced productivity related to the disease (15). These costs include absence from work and reduced productivity due to illness, premature retirement, and premature death (15). For example, in 2012, IBD premature death cost in Canada was 9.4 million CAD (15), whereas medical absenteeism was estimated to be as high as 1.57 billion CAD in 2014 (15, 21). Nonetheless, some of these costs have decreased recently with the introduction of more effective treatments (14, 16).

1.4 IBD and Biologics

At present, IBD has no cure (16). Individuals living with IBD need regular medications, while others might require surgical procedures to remove unhealthy sections of the bowel (14). Early detection and new treatments have enhanced the well-being of patients (14). This enhancement is due to the diversity and efficacy in the medications used to treat IBD, especially with the initiation of biologic agents (14, 16). Biologic medications currently approved in Canada for IBD include Infliximab, Adalimumab, Golimumab, Ustekinumab, and Vedolizumab (14). Most of these medications are approved for moderate to severe cases of IBD (22, 23).

Historically, patients with IBD, particularly CD patients, required surgery at some point in their illness (24-26). In recent days, surgery has become less common with the introduction of biological therapies (16). While biologics have contributed to the improvement of the disease, the associated costs of these medications have been challenging for patients and health care systems (14, 16). Biologic medications are expensive, with an annual per-patient cost ranging

between 23,000 and 38,000 CAD (27).

In Canada, inpatient medications are provided with no cost to patients (28). Outpatient medications, on the other hand, maybe funded fully or partially depending on the drug plan benefit available in the province (28). Given that many Canadians pay out-of-pocket for prescribed medications, some patients abstain from taking these medications due to their inability to cover the cost (29, 30).

Each province in Canada is responsible for the administration and management of its drug plan (28). The eligibility and coverage for drug plans vary among provinces (28). Some drug programs require the "fail first therapy", i.e. patients are denied from obtaining a "more effective treatment" until they have demonstrated to their insurer that previous medications were not successful (31). As a result, low-income patients or those with inadequate insurance coverage face some challenges in bearing expenses for IBD medications such as biologics (31). In Saskatchewan, the required conditions before individuals can be eligible for biologic medication coverage include "failure or intolerance to traditional medication" (32). To date, limited research has been conducted to evaluate the health care costs of IBD in the province of Saskatchewan over time.

1.5 Saskatchewan

Saskatchewan is a province in central Canada covering 651,000 square kilometers with a population of approximately 1.2 million (33, 34). Nearly one-third of the total population lives in the provincial capital, Regina, or the largest city of the province, Saskatoon. In 2016, each of these two cities had a population of over 215,000 census metropolitan areas (35). Approximately, 35% of the population in Saskatchewan is dispersed in rural and remote areas (35).

The Saskatchewan health care system consists of different units that function to establish a community of healthy people (36). These units include the Ministry of Health (MoH), Saskatchewan Health Authority (SHA), and eHealth. While the MoH ensures that health care service is provided to residents in the province, the SHA delivers a timely health care service of high quality for the whole province (36). The development and implementation of the electronic health record is the responsibility of the eHealth Saskatchewan (36). These units cooperate to provide high-quality service that meets the needs of the community (36).

Saskatchewan residents are eligible to receive full health coverage except those whose coverage is delivered by federal health insurance (e.g., federal inmate prisoners, Canadian Forces), approximately 1% of the population (33, 34).

1.6 Study rationale and research questions

Saskatchewan had limited information on (a) the prevalence and incidence of IBD, (b) direct health costs of the disease (i.e., IBD-specific hospitalization, medication, and physician costs), and (c) the association between IBD and location of residence (i.e., rural/urban) at the time of diagnosis.

The purpose of this study was to deliver updated information on the epidemiological measures of the disease in Saskatchewan and provide comprehensive up to date data of the direct IBD health care costs in the province over time. The specific research objectives and hypothesis of my thesis were to:

1. Estimate the prevalence and incidence rates of diagnosed cases of IBD in Saskatchewan from 1999 to 2016.

2. Test whether the prevalence and incidence rates of diagnosed cases of IBD were increasing in Saskatchewan from 1999 to 2016.

Hypothesis: The prevalence and incidence rates of diagnosed cases of IBD were increasing from 1999 to 2016 in Saskatchewan.

3. Determine if the incidence rate of diagnosed cases of IBD in Saskatchewan was higher among urban residents compared to the rate of rural residents.

Hypothesis: The incidence rate of diagnosed IBD cases among urban residents was higher than those living in rural Saskatchewan areas after controlling by sex and age.

4. Test whether the IBD-related hospitalization, medication, and physician costs were increasing in Saskatchewan since 1999.

Hypothesis: IBD-related hospitalization costs were decreasing since 1999; while the IBD- related medication costs were increasing, and the IBD-related physician costs were stable over time.

This study is presented in a manuscript-style thesis. Two separate manuscripts were prepared to respond to my research objectives. The first manuscript (Chapter 2), "*Population-based evidence from a western Canadian province of the decreasing incidence rates and trends of inflammatory bowel disease among adults*", answers to the 1st, 2nd and 3rd objectives. The second manuscript (Chapter 3), "*Increasing prevalence and direct health care cost of Inflammatory Bowel Disease among adults: A Population-Based study from a Western Canadian Province*", responded to the 1st, 2nd and 4th research objectives. These manuscripts contribute together to my overall research purpose to deliver updated information on the epidemiological measures of the disease in Saskatchewan and provide comprehensive up to date data of the direct IBD health care costs in the province over time. The last section of this thesis (Chapter 4) summarizes and

discusses the research results and conclusions presented in each of the manuscripts.

This study was approved by the University of Saskatchewan Biomedical Ethics Board as BIO 91, see Appendix A.

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CHAPTER 2: MANUSCRIPT 1

Population-based evidence from a western Canadian province of the decreasing incidence rates and trends of inflammatory bowel disease among adults

2.1 Preface

This chapter presents evidence of the decreasing incidence rates of inflammatory bowel disease (IBD) in Saskatchewan since 1999 and the rural and urban differences in the incidence rates of IBD in the province. This manuscript was led by Jessica A. Osei under the supervision of Dr. Juan Nicolás Peña-Sánchez. This Chapter manuscript was published in the Journal of the Canadian Gastroenterology Association and co-authored with Dr. Juan Nicolás Peña-Sánchez, Dr. Sharyle Fowler, Dr. Nazeem Muhajarine, Dr. Gilaad Kaplan, and Dr. Lisa Lix. The full article citations is:

Osei JA, Peña-Sánchez JN, Fowler SA, Muhajarine N, Kaplan GG, Lix LM. Population-based evidence from a western Canadian province of the decreasing incidence rates and trends of inflammatory bowel disease among adults. Journal of the Canadian Association of Gastroenterology. 2020; gwaa028. https://doi.org/10.1093/jcag/gwaa028

The permission to reproduce this article in my thesis is presented in Appendix B.

2.2 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 the 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 aetiology 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 is lacking since 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.

2.3 Methods

2.3.1. 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 paediatric IBD case definition for Saskatchewan administrative health data. For several years, no paediatric gastroenterologists were available in Saskatchewan and patients were required to access colonoscopies and paediatric IBD care in neighbouring provinces.

2.3.2 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 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 treatment 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.

2.3.3 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 two years of continuous health care coverage, or a minimum of three health care contacts with these diagnostic codes if individuals had less than two 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 eight-year washout period was used to distinguish between the incident and prevalent diagnosed IBD cases; specifically, eight 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 eight-year washout period has been previously used in IBD studies based on administrative health data (18, 28).

2.3.4 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).

2.3.5 Statistical Analysis

Generalized linear models with a negative binomial distribution were used, considering a good model fit when observing a Pearson χ^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. 18-29, 30-39, 40-49, 50-59, 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 (IRR) with their corresponding 95% confidence intervals (95%CI). 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.

2.4 Results

In total, 4,908 individuals with the diagnosis of IBD were included in the study. In this group, 1,447 (29.9%) people were living in rural areas and 3,392 (70.1%) in urban locations. Table 2.1 describes the demographics of the study cohort.

Table 2.1. Descriptive characteristics of the incident cohort of IBD in Saskatchewan between 1999 and 2016 (n=4,908)

Variable	n (%)
Age group, years	
18 to 29	1148 (23.4)
30 to 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)

2.4.1 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 2.1). 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 (Figures 2.2).

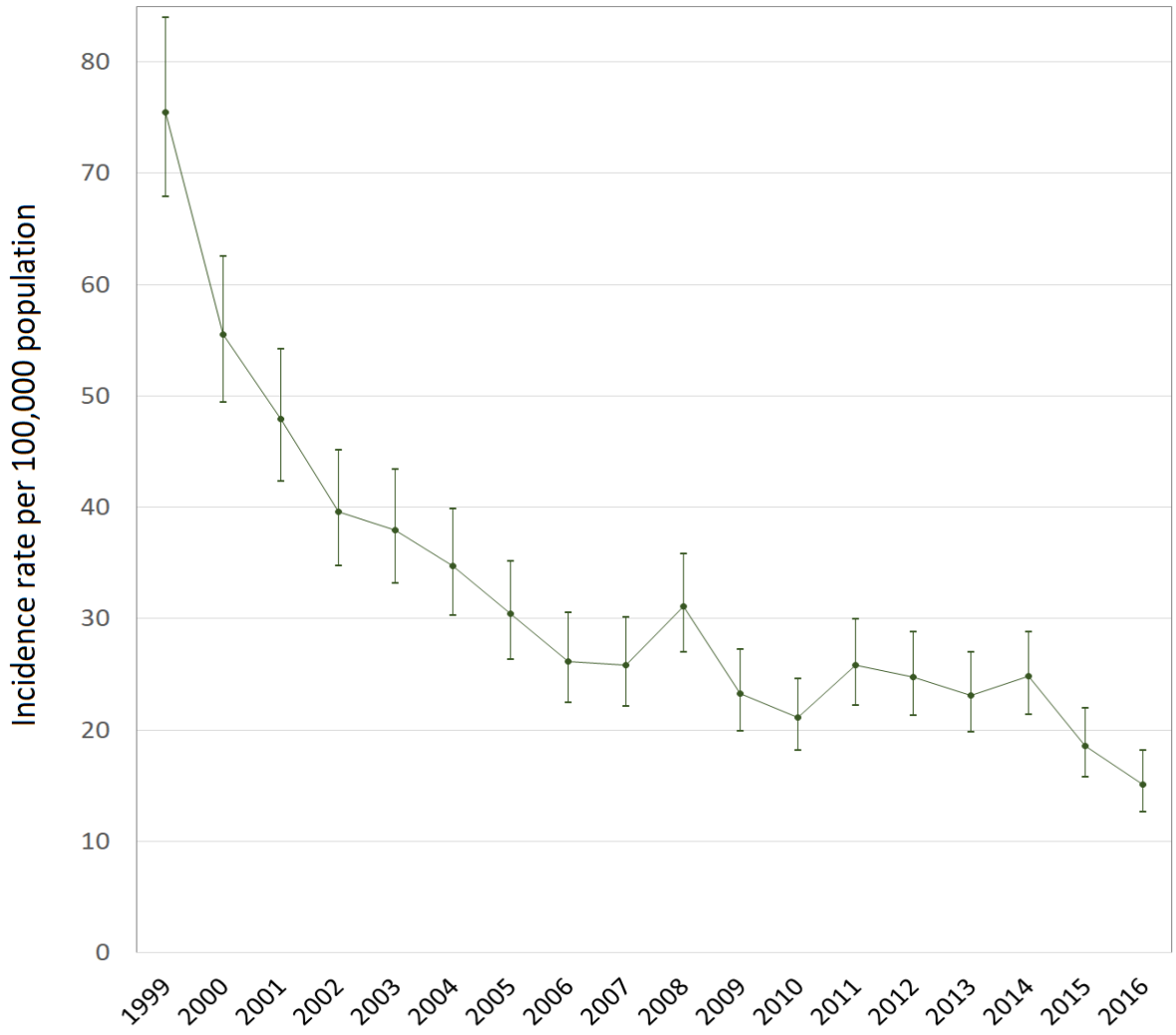

Figure 2.1. Adjusted annual incidence trends of inflammatory bowel disease in Saskatchewan, Canada

Figure 2.2. Adjusted annual incidence trends of ulcerative colitis (UC) and Crohn's disease (CD) in Saskatchewan, Canada

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 2.3. The interaction between year and location of residence was not statistically significant (p=0.61).

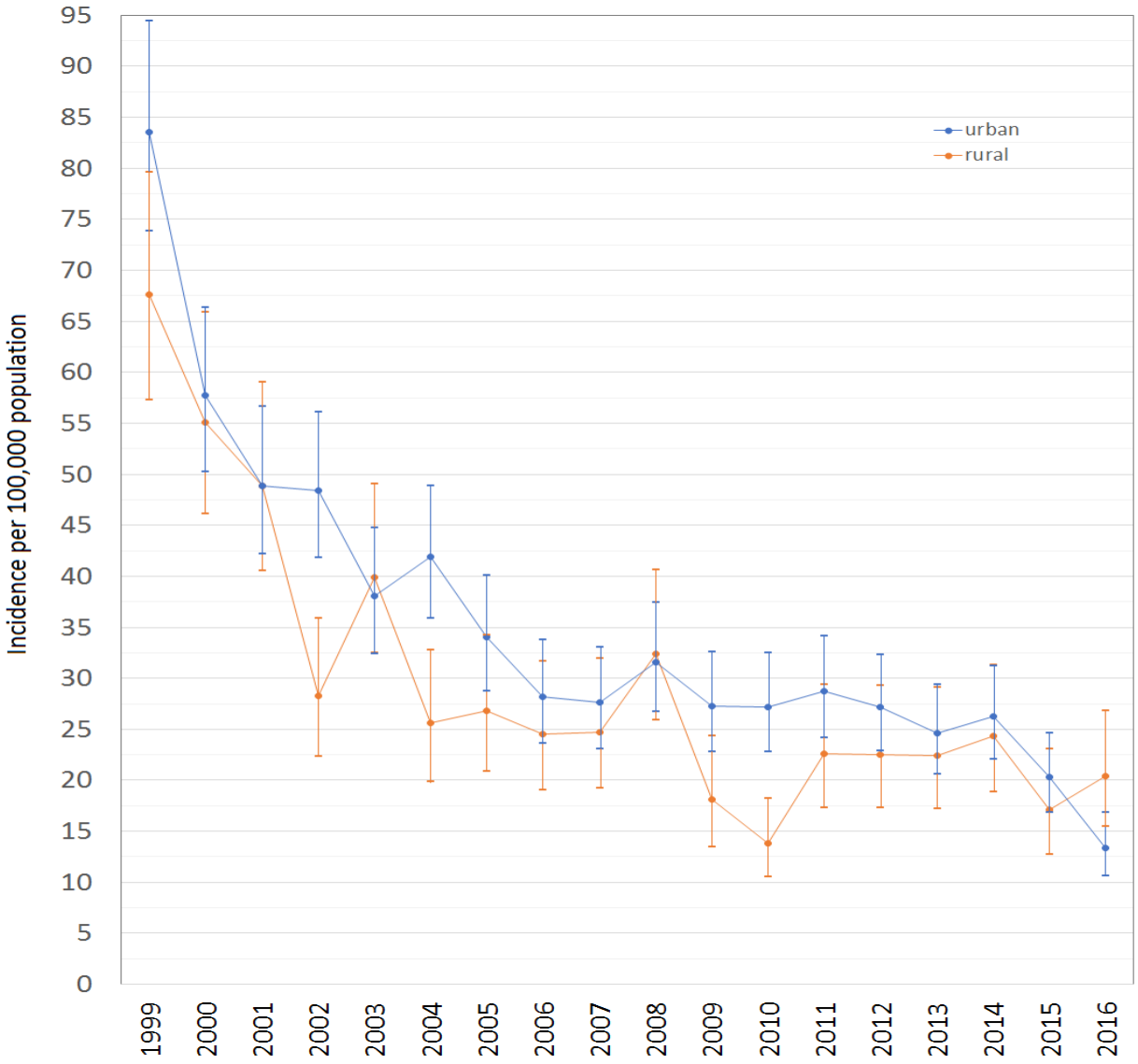

Figure 2.3. Adjusted annual incidence trends of inflammatory bowel disease by urban-rural location in Saskatchewan, Canada

2.4.2 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 0.84-0.96) 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 the18-29 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 2.2.

Table 2.2. Incidence rate ratios (IRR) with corresponding 95% confidence intervals (95%CI) 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	**0.89 (0.84 to 0.96)**	1.02 (0.93 to 1.12)	**0.77 (0.7 to 0.83)**
Age group			
18-29	Ref.	Ref.	Ref.
30-39	1.02 (0.92 to 1.13)	1.07 (0.92 to 1.24)	1.00 (0.88 to 1.13)
40-49	1.08 (0.97 to 1.19)	**1.19 (1.03 to 1.38)**	1.01 (0.90 to 1.15)
50-59	1.02 (0.92 to 1.14)	1.05 (0.90 to 1.22)	0.99 (0.87 to 1.12)
60+	**0.72 (0.65 to 0.80)**	**0.77 (0.66 to 0.89)**	**0.69 (0.61 to 0.78)**
Place of residence			
Rural	Ref.	Ref	Ref.
Urban	**1.19 (1.11 to 1.27)**	1.08 (0.97 to 1.19)	**1.25 (1.14 to 1.36)**

* Statistically significant at alpha = .05 bolded

2.5 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 this 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 to 2015 (33). A recent retrospective population-based cohort study from Ontario observed an increasing incidence trend in the past 11 years for ages 30–60, 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 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 (30-39 and 40-49 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 0.06 to 0.68/100,000 person-years to 5.5/100,000 (41). Conversely, a 2017 systematic review in the United States (US) 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 socioeconomic 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, US, was found to be higher in people located in urban locations than in rural areas (45). In 1991, rates for both CD and UC were higher in northern parts of the US 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, and air pollution (20, 21). In addition, in a 2006 population-based Canadian study, Bernstein and colleagues (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 which 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 is 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.

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CHAPTER 3: MANUSCRIPT 2

Increasing prevalence and direct health care cost of Inflammatory Bowel Disease among adults: A Population-Based study from a Western Canadian Province

3.1 Preface

This chapter presents evidence of the increasing prevalence and direct health care cost of inflammatory bowel disease (IBD) among adults in the province of Saskatchewan from 1999-2016. This work was led by Jessica A. Osei under the supervision of Dr. Juan Nicolás Peña-Sánchez. All authors were equally involved in designing the study, drafting the manuscript, and critically revising the study for important intellectual content. This Chapter manuscript has been submitted for publication in Healthcare Policy journal, and it is cited below as;

Osei JA, Peña-Sánchez JN, Fowler SA, Muhajarine N, Kaplan GG, Lix LM. Increasing prevalence and direct health care cost of Inflammatory Bowel Disease among adults: A Population-Based study from a Western Canadian Province. *Healthcare Policy* (2020) (Under Review).

3.2 Introduction

Inflammatory Bowel Disease (IBD) is a chronic gastrointestinal disorder that comprises of Crohn's disease (CD) and ulcerative colitis (UC) (1). The prevalence of IBD is increasing globally (2). Studies have associated this rise to the western lifestyle, incurability of the disease, and low disease mortality rate (3, 4). The regions with the highest prevalence of IBD include Europe and North America, specifically Canada (2, 3). Today, the number of people living with IBD is estimated between 2.5 and 3 million in Europe, over 1 million in the United States (US), and 270,000 (7 out of 1000) in Canada (2, 3, 5).

In 2013, the annual direct health care cost for managing patients with IBD in Europe was 4.6–5.6 billion Euros (5), while US and Canadian costs were, respectively, 14.6 billion US dollars (USD) in 2014 and 1.2 billion Canadian dollars (CAD) in 2018 (6, 7). The costs associated with IBD are mainly dominated by biologic medications (6, 8), a treatment for IBD made from animal and human live cells (9). Before the introduction of biologic medications, hospitalizations and surgeries were the major cost drivers of IBD (8). Today, biologic medications are the cost drivers of IBD-related direct health care costs (6). For instance, between 2010 and 2015, Canadian spending on immunobiologics increased two-fold at 2.2 billion CAD. This increase accounted for 10.3% of the Canadian pharmaceutical market share (6). IBD is a costly disease (8) with increasing prevalence and medication costs that could pose a substantial economic burden for the health care system.

In the mid-western province of Saskatchewan, detailed evidence on the prevalence and direct health care costs of IBD is limited and needed. Despite a recent Canadian study predicted a rise in the prevalence of IBD in Saskatchewan (3), there are no retrospective evaluations in Saskatchewan of the prevalence trends during the last decades. Also, there is data from

Manitoba, Quebec, and Alberta regarding the health care cost of IBD (6, 10, 11), which may not apply to Saskatchewan given that the pattern and trends might vary across provinces. Local evidence about the actual prevalence and direct health care costs estimates of IBD over time is needed to contribute to health care resources allocation and planning. This study aimed to 1) estimate the prevalence and direct health care costs of IBD among adults, and 2) test if the prevalence and direct health care costs of IBD increased over the past two decades in the Canadian province of Saskatchewan.

3.3 Methods

3.3.1 Setting and data source

A retrospective population-based cohort study was completed utilizing administrative health databases for the mid-Western Canadian province of Saskatchewan, with a population of approximately 1.2 million (12). These data, accessed at the Saskatchewan Health Quality Council (HQC), contain health care information for persons with provincial health care coverage. Excluded are individuals for whom health coverage is provided by the federal government (e.g., members of the Canadian armed forces, inmates in national penitentiaries), who comprise ~1% of the total Saskatchewan population (12)

The administrative data used in this study included the hospital discharge abstract database (DAD), physician services database (PSD), prescription drug plan database (PDP) and person health registration system (PHRS). The DAD has information on inpatient hospitalizations and day surgeries with details of associated diagnoses and procedures, captured each time patients are discharged from acute health care facilities. The PSD records physicians' fee-for-service billing claims submitted to the Ministry of Health for services provided to patients. Physicians

whose payment is not on a fee-for-service basis (e.g. salary) report services through a "shadow billing" claim. The PDP has information about all dispensed outpatient prescription medications; over the counter and inpatient prescription medications are not captured. The PHRS captures individual demographic information, such as age, sex, and location of residence, as well as health care coverage start and end dates. These databases were linked using encrypted identifiers at secured servers at the HQC.

3.3.2 Case definition and study population

A validated algorithm was used to identify cases of IBD (13) between 1999/00 and 2016/17 fiscal years (FY), specifically from April 1st, 1999, and March 31st, 2017. This algorithm considered individuals as IBD cases if they had a) five or more health care contacts with the diagnosis of IBD within two years of continuous health insurance coverage or b) three or more contacts with the diagnosis of IBD with less than two years of health insurance coverage. This case definition was previously validated using self-administered questionnaires and chart reviews and had high sensitivity (74.4-89.2%) and specificity (89.8-93.7%) (13). The International Classification of Disease (ICD) diagnosis codes for CD (ICD-9 555.x and ICD-10-CA K50.xx) and UC (ICD-9 556.x and ICD-10-CA K51.xx) were used to identify IBD cases (13, 14). Eligible cases were classified as CD or UC based on the most frequent diagnosis (14).

Prevalent cases were defined as individuals age 18 years and older who met the case definition between 1999/00 and 2016/17 FY. The PHRS was used to determine the population at risk, defined as all individuals 18 years and older with provincial health insurance coverage at any point. The prevalence of IBD, CD, and UC were estimated annually and stratified by sex and age groups. Individuals less than 18 years old were excluded from this study due to the limitations of applying a paediatric IBD case definition, given that patients in Saskatchewan

were required to access paediatric gastroenterology care in neighbouring provinces for several years during the last decade.

3.3.3 Direct health care cost of IBD

Our study adopted a costing approach used in recent Canadian studies (15, 16). We used two approaches to generate a total cost for each prevalent case: macro costs, assigned to inpatient/ day surgery hospital costs, and micro costs, assigned to physician services and prescription medications.

In Canada, individual hospital cost data are not available. Hence, hospitalization costs are obtained using the Canadian Institute for Health Information´s (CIHI) cost per weight cases (CPWC) and resource intensity weight (RIWs) (15, 17). RIWs are case weights for case-mix groups (CMGs), used to measure the intensity of resource use (relative cost) associated with different diagnostic and surgical procedures, and demographic characteristics of an individual (15). CMGs classifies patients expected to use similar hospital resources into clinically meaningful groups (15). The RIWs are also assigned to Day Procedure Groups (DPG), a classification system created for ambulatory day care surgical procedures (without staying overnight) (15). DPG clustering is done based on patient resource utilization and clinical episode similarities. The average cost for a patient's hospitalization is then obtained by multiplying the provincial CPWC by the sum of the RIWs and DPG (15).

Costs of prescription medication claims were estimated by summing the total expenses for dispensed outpatient IBD medications during the study period. IBD medications were defined as medication claims for UC or CD (i.e. immune modulator, biologics, and 5-aminosalicylic acid therapies), which were captured using drug identification numbers (DINs). We constructed a list of DINs for immune modulators (i.e. azathioprine, mercaptopurine, methotrexate,

mycophenolate, and cyclosporine), biologics (i.e. infliximab, adalimumab, golimumab, and vedolizumab) and 5-aminosalicylic acid (i.e. mesalamine, olsalazine sodium, and sulfasalazine).

To obtain IBD physician costs, we summed the costs of outpatient services provided by physicians in the province to diagnosed IBD patients during the study period. These costs were defined as those with the diagnosis of IBD (i.e. CD: ICD-9 555.x and UC: ICD-9 556.x). Hospital, prescription medication, and physician costs were adjusted to 2013/2014 CAD, using the Saskatchewan consumer price index (18).

3.3.4 Statistical analysis

The prevalence and cost data were analyzed using generalized linear models with generalized estimating equations (GEEs), used to address for correlation in the data. The negative binomial distribution (selected based on the model fit assessment) (19) was used to model the prevalence of IBD, CD, and UC. To assess the model fit, the ratio of the deviance to the degrees of freedom was used. We considered a model to have a good fit to the data when this ratio was closer to 1 (19). Covariates for the models of IBD prevalence were sex, FY, and age-group categorized as 18-29 (reference group), 30-39, 40-49, 50-59, and 60+ years old. The model offset was the natural logarithm of the Saskatchewan population at risk.

Using non-zero cost data, the gamma distribution was selected to model total annual direct health care costs of IBD, as well as the annual hospital, physician, and prescription medication claim costs. Model covariates included age-group, sex, fiscal year, diagnosis type (UC or CD), and comorbidity burden (determined using the Charlson comorbidity index) (20). We calculated the comorbidity index based on the diagnoses from hospital and physician claims one year before the index date, defined as the date of the earliest hospital or physician UC or CD diagnoses.

Separate models were fit for IBD hospitalization, medication, physician, and total cost

(defined as the sum of the three components). An exchangeable correlation structure of the GEEs (which assumes observations over time have the same correlation) accounted for dependence among the prevalence and cost observations over time. Changes in prevalence and direct health care cost over time were tested with a linear trend by including FY as a continuous predictor in the models. Estimated prevalence and cost along with their 95% confidence intervals (95%CI) were reported.

The significance level was $\alpha = 0.05$. Statistical analyses were completed using the GENMOD procedure of the Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA). Our study received ethical approval from the University of Saskatchewan Biomedical Research Ethics Board (REB, BIO 91).

3.4 Results

3.4.1 Prevalence of IBD

The number of diagnosed IBD cases in Saskatchewan increased from 2,834 in 1999/00 to 6,468 in 2016/17 FY. The characteristics of the IBD cases in the first and last years of our study period are presented in Table 3.1.

Table 3.1. Descriptive characteristics for individuals meeting the IBD case definition in Saskatchewan, Canada, in 1999/00 and 2016/17 fiscal years

Variable	**1999/00 (n=2,834)**	**2016/17 (n=6,468)**
Age-group, years		
18 to 29	521(18.4)	556(8.6)
30 to 39	689(24.3)	988(15.3)
40-49	785(27.7)	1076(16.6)
50-59	401(14.1)	1607(24.9)
60+	438(15.5)	2241(34.6)
Disease type		
Crohn's disease	1734(61.2)	3663(56.6)
Ulcerative colitis	1100(38.8)	2805(43.4)
Sex		
Female	1493(52.7)	3402(52.6)
Male	1341(47.3)	3066(47.4)

Based on our model results, the prevalence of IBD increased from 341/100,000 (95%CI 340 to 341) in 1999/00 to 664/100,000 (95%CI 663 to 665) in 2016/17, estimating a 3.33% (95%CI 2.37 to 4.30) annual average increase during the study period, Figure 3.1.

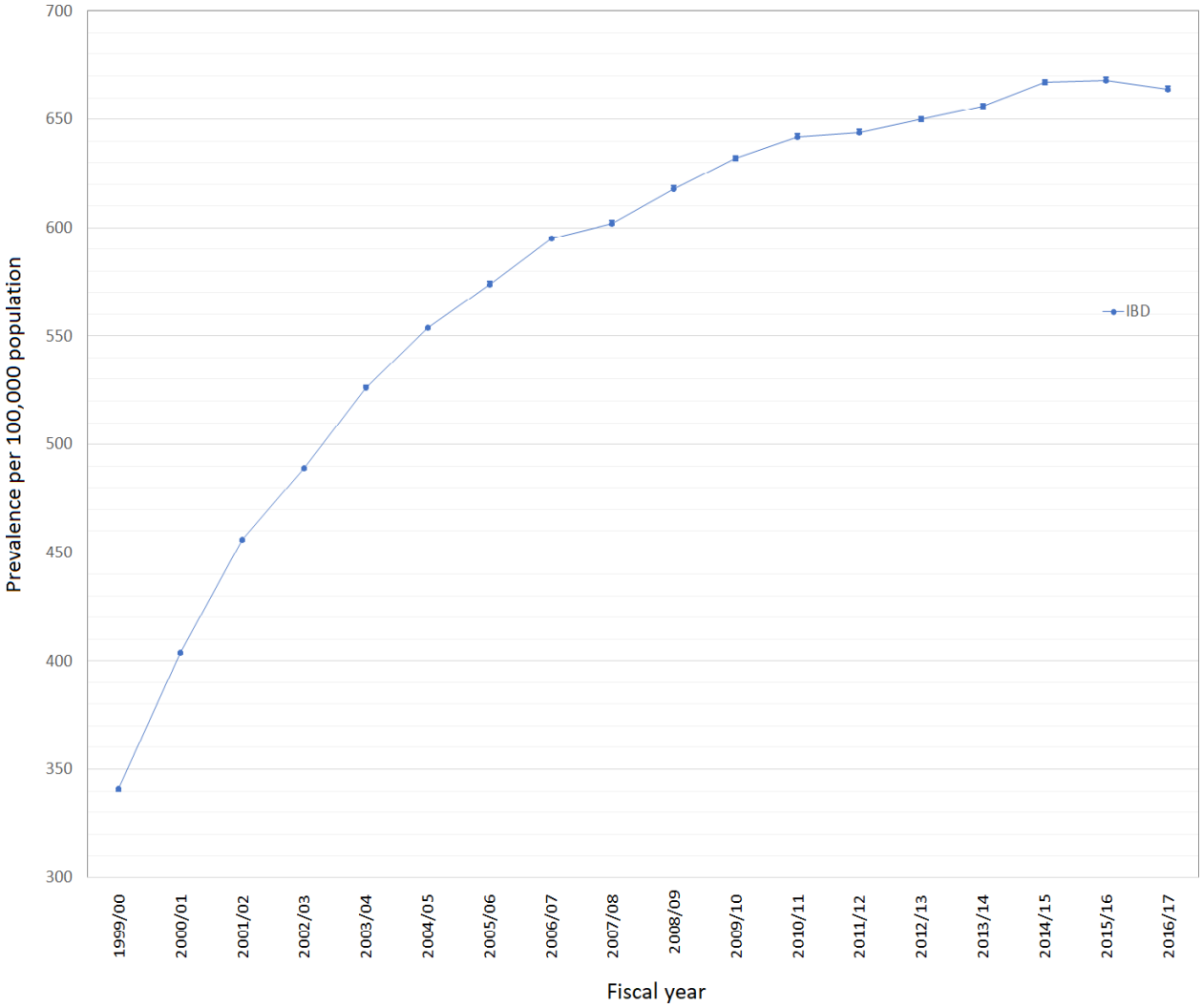

Figure 3.1. Model-based prevalence estimates of inflammatory bowel disease (IBD) in Saskatchewan, Canada

The prevalence of UC increased from 135/100,000 (95%CI 134 to 135) in 1999/00 to 289/100,000 (95%CI 288 to 290) in 2016/17. For CD, the prevalence increased from 201/100,000 (95%CI 201 to 202) in 1999/00 to 375/100,000 (95%CI 375 to 376) in 2016/17. Also, we identified statistically significant increasing linear trends in the prevalence of both UC [3.91% (95%CI 2.78 to 5.05)] and CD [3.09% (95%CI 2.24 to 3.94)] since 1999/00, Figure 3.2.

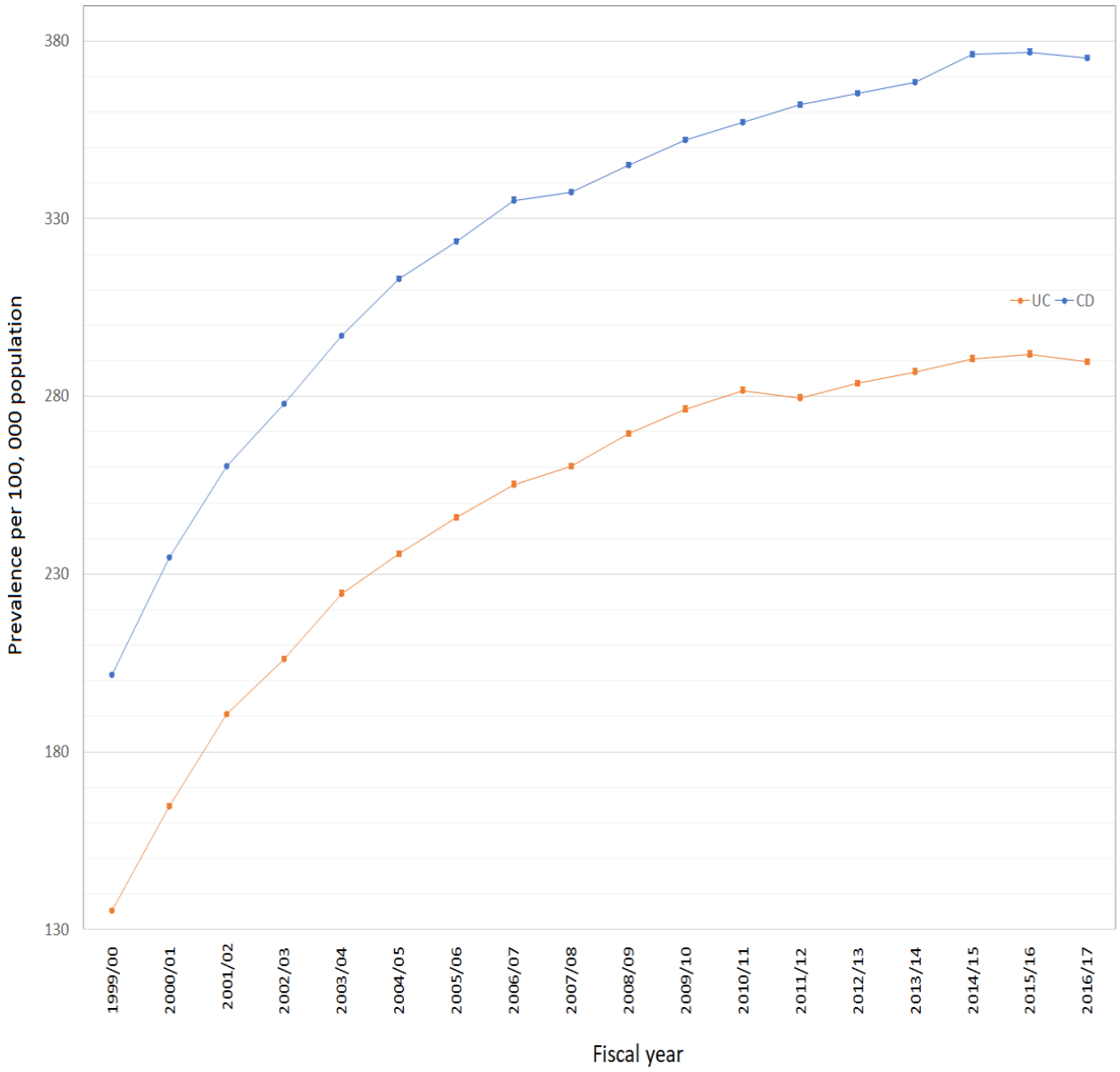

Figure 3.2. Model-based prevalence estimates of ulcerative colitis (UC), and Crohn's disease (CD) in Saskatchewan, Canada

3.4.2 Direct health care costs of IBD

The total estimated direct health care cost of IBD was $7.8 million in 1999/00, observing that prescription medication costs ($3.9 million) and hospital costs ($3.3. million) were the main cost drivers at the beginning of the study period. At the end of the study period, the estimated

total direct health care cost of IBD was $50.9 million. Prescription medication costs accounted for $45.3 million, while hospital and physician costs accounted for $4.2 and $1.4 million, respectively. In fact, hospital and physician costs were 10.8% of the entire estimated direct health care cost of IBD in 2016/17, see Figure 3.3.

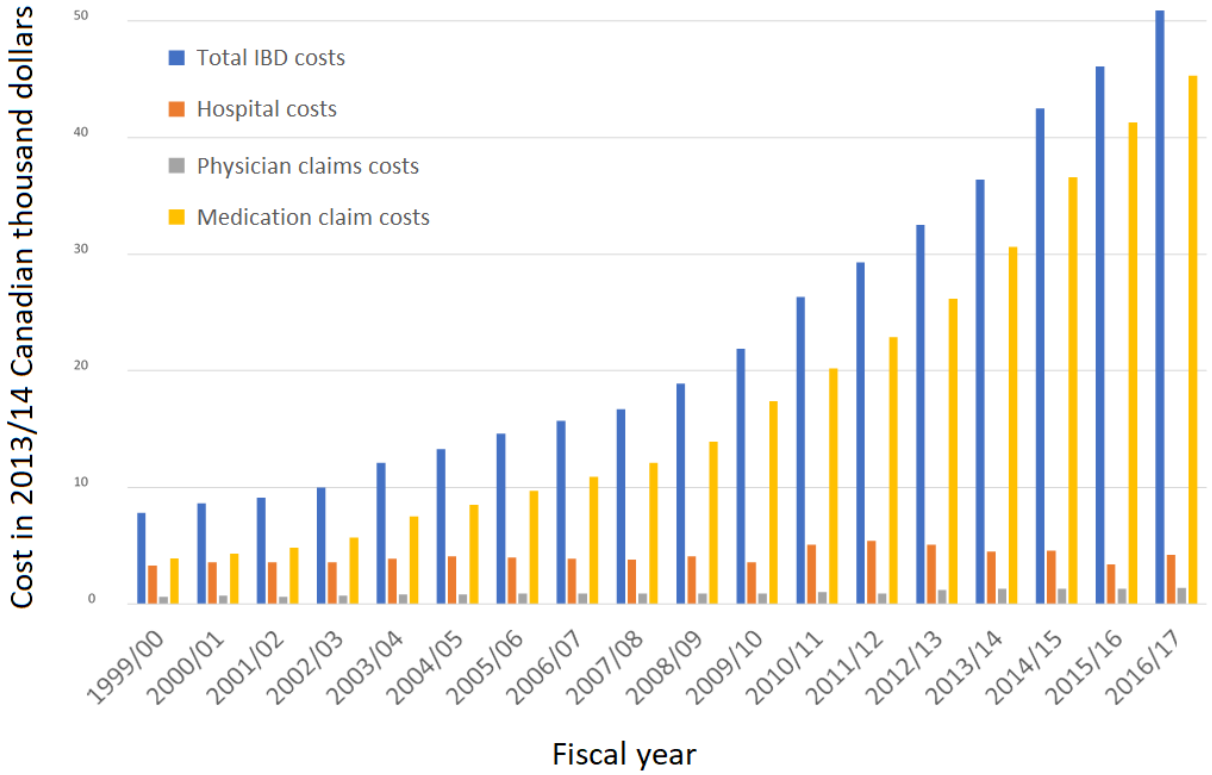

Figure 3.3. Estimated direct health care costs of inflammatory bowel disease (IBD) in Saskatchewan, Canada, from 1999/00 to 2016/17. Costs are presented in 2013/14 Canadian thousand dollars

According to the model-based estimates, the average annual direct health care costs of IBD per patient increased from $1.8 (95%CI 1.6 to 2.0) thousand in 1999/00 to $7.0 (95%CI 6.5 to 7.5) thousand in 2016/17 Figure 4. The average annual increase in direct health care costs of IBD per patient was estimated at 9.2% (95%CI 8.6 to 9.9).

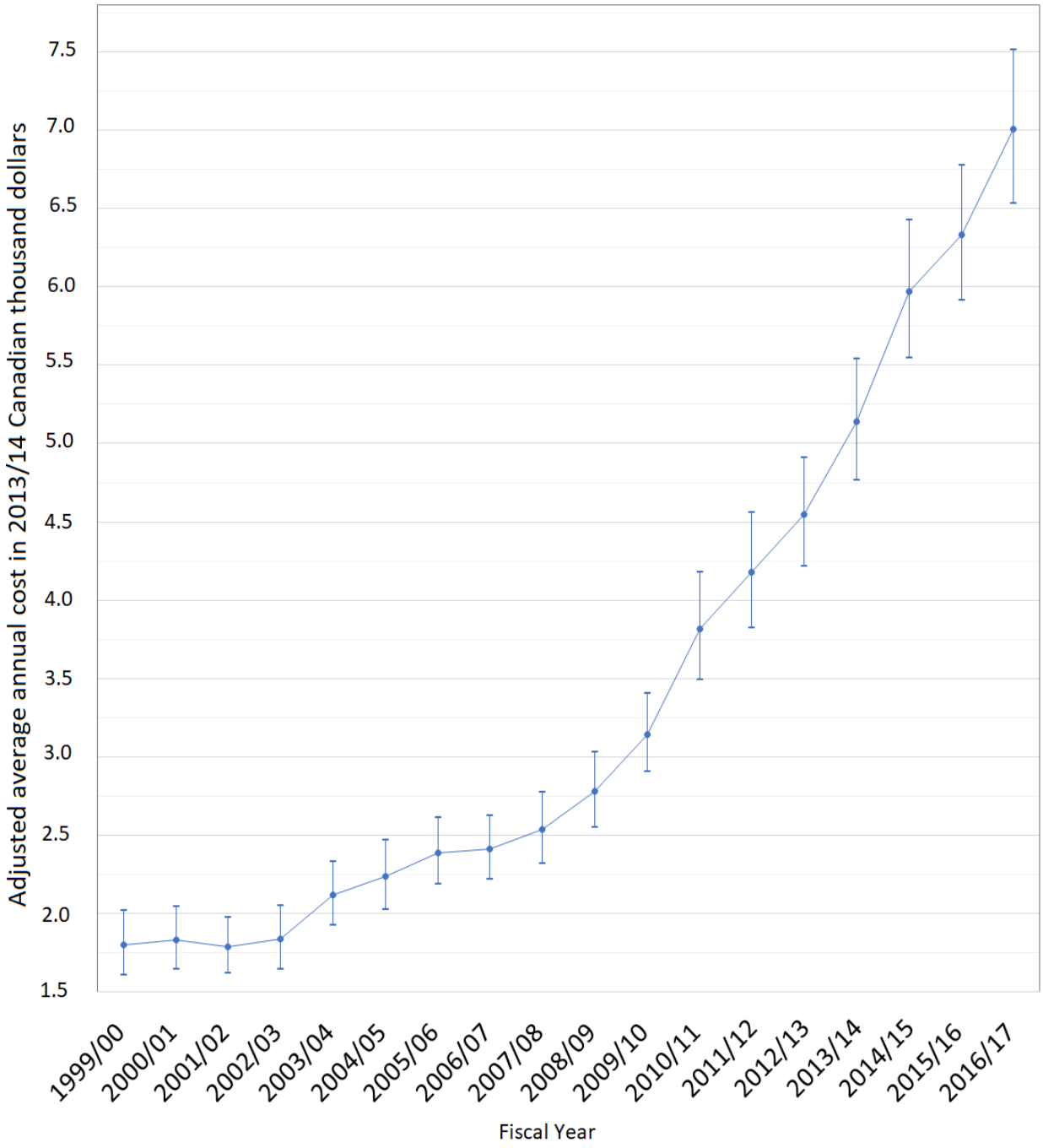

Figure 3.4. Model-based estimates of total average annual direct health care costs of IBD per patient, with their 95%CIs, in Saskatchewan

As presented in Table 3.2, the prescription medication claim costs per patient dramatically increased from $0.6 (95%CI 0.6 to 0.7) thousand in 1999/00 to $6.0 (95%CI 5.6 to 6.6) thousand in 2016/17, with an estimated average annual increase of 15.6% (95%CI 14.8 to 16.5). In contrast, hospital costs per patient fluctuated from $4.5 (95%CI 3.8 to 5.3) thousand in 1999/00 to $4.6 (95%CI 3.7 to $5.8) thousand in 2016/17, with a no statistically significant change overtime (0.1, 95%CI -0.7 to 0.9). Furthermore, a small average annual percentage increase was observed in physician costs within the study period (0.6, 95%CI 0.3 to 0.9).

Table 3.2. Model-based hospital, physician, and prescription medication claim costs of inflammatory bowel disease (IBD) per in Saskatchewan, Canada, from 1999/00 to 2016/17. Estimated costs of IBD presented in 2013/14 Canadian thousand dollars with their 95% confidence intervals.

Fiscal year	Hospital costs	Physician claims costs	Medication claim costs
1999/00	4.5 (3.8 to 5.3)	0.3 (0.3 to 0.3)	0.6 (0.6 to 0.7)
2000/01	4.9 (4.3 to 5.7)	0.3 (0.3 to 0.3)	0.6 (0.6 to 0.7)
2001/02	4.7 (4.1 to 5.3)	0.3 (0.3 to 0.3)	0.6 (0.6 to 0.7)
2002/03	4.5 (3.8 to 5.3)	0.3 (0.3 to 0.3)	0.7 (0.7 to 0.8)
2003/04	4.5 (4.0 to 5.0)	0.3 (0.3 to 0.3)	1.0 (0.9 to 1.1)
2004/05	4.7 (4.1 to 5.4)	0.3 (0.3 to 0.3)	1.1 (1.0 to 1.2)
2005/06	4.4 (3.9 to 5.0)	0.3 (0.3 to 0.3)	1.2 (1.1 to 1.4)
2006/07	4.7 (4.1 to 5.3)	0.3 (0.3 to 0.3)	1.3 (1.2 to 1.5)
2007/08	4.7 (4.0 to 5.5)	0.3 (0.3 to 0.3)	1.5 (1.3 to 1.7)
2008/09	4.8 (4.1 to 5.6)	0.3 (0.3 to 0.3)	1.7 (1.5 to 1.9)
2009/10	3.9 (3.4 to 4.6)	0.3 (0.3 to 0.3)	2.2 (2.0 to 2.4)
2010/11	5.0 (4.1 to 6.3)	0.3 (0.3 to 0.3)	2.6 (2.3 to 2.8)
2011/12	5.8 (4.6 to 7.2)	0.3 (0.3 to 0.3)	2.9 (2.6 to 3.2)
2012/13	5.0 (4.3 to 5.8)	0.3 (0.3 to 0.3)	3.4 (3.1 to 3.7)
2013/14	4.7 (4.0 to 5.6)	0.3 (0.3 to 0.3)	4.0 (3.6 to 4.3)
2014/15	5.0 (4.2 to 6.0)	0.3 (0.3 to 0.3)	4.8 (4.4 to 5.3)
2015/16	3.7 (3.3 to 4.1)	0.3 (0.3 to 0.3)	5.5 (5.0 to 6.0)
2016/17	4.6 (3.7 to 5.8)	0.3 (0.3 to 0.3)	6.0 (5.6 to 6.6)
Trend estimates*	0.1% (-0.7 to 0.9)	0.6% (0.3 to 0.9)	15.6% (14.8 to 16.5)

* Annual average percentage change with corresponding 95%CI

3.5 Discussion

This retrospective population-based study contributes to the literature with evidence that the estimated prevalence of IBD among adults has been increasing in Saskatchewan, on average at a rate of 3% per annum since 1999. Our results support the findings of a previous study that forecasted a rise in the prevalence rates of IBD in Canada (3). Between 2008 and 2018, Coward et al. (2019) reported an increase in the estimated prevalence rates of IBD from 510 to 725/100,000 population. By 2030, this number is expected to rise to 981/100,000 population, equivalent to an average annual percentage change of 2.9% (3). Also, the estimated prevalence rate of IBD for Saskatchewan by Coward et al. was 636/100,000 in 2018; although, our study identified a slightly higher prevalence of IBD in Saskatchewan, specifically 664/100,000 in 2016/17 (3). The results of our research and previous studies support worldwide studies describing and predicting increasing prevalence rates of IBD (1, 2).

A study in the United States estimated that the prevalence of IBD will increase from 660/100,000 in 2015 to 790/100,000 in 2025 (21). Jones et al. (2019) (22) also forecasted an increase in the number of individuals with IBD in Lothian, Scotland (from 1 in 125 for 2018 to 1 in 98 for 2028). Also, Mafalda and colleagues (4) reported that the prevalence of IBD will be 4 to 6 times higher in Portugal by 2030. Compounding prevalence, where the prevalence grows much more rapidly than the incidence, appears to be inevitable phenomena in the future burden of IBD (2, 3). The increasing prevalence of IBD has a significant financial implication that requires attention from both health care professionals and decision-makers.

Our results confirm that IBD is a costly disease and that direct health care costs are rising. As we identified, the total direct health care cost of IBD in Saskatchewan increased dramatically

from 7.8 million CAD in 1999/00 to 50.9 million CAD in 2016/17, an increase of more than six-fold. Per patient, the average annual direct health care costs of IBD increased from 1.8 to 7.0 thousand CAD within this study period. A similar pattern of increasing health care cost of IBD has also been reported. For instance, a 2020 study published by researchers from South Korea observed a dramatic increase in IBD-related health care costs from 23.2 million USD in 2010 to 49.7 million USD in 2014 (23).

At the end of our study period, most of the IBD costs (almost 90%) were attributed to prescription medication claims. In contrast, other studies estimating the direct health care cost of IBD observed a lower proportion of medications (6, 24). In the Netherlands medications for treating CD and UC accounted for 31% to 64% of total health care costs (24). Higher IBD medication costs in Saskatchewan and Canada, in general, could be related to the lack of a strong position for provinces to negotiate (e.g., for the amount paid for biologics) with pharmaceutical companies (25). Among developed countries, Canada is the only one whose provinces deliver universal health systems without universal drug coverage (26).

Different countries, including New Zealand, Norway, Sweden, Australia, and the United Kingdom, deliver universal health care along with drug coverage managed at the national level (27). For example, aside from publicly funded health services for residents in Great Britain, drug plans are also offered by the National Health Service (28).

Similarly, Australians benefit from a publicly funded health care system along with private health insurance. Medications are delivered through the Pharmaceutical Benefits Scheme to all Australian citizens and residents (28). Currently, Canada has an expensive multi-payer drug system which is handled by numerous public and private schemes (26-28). As a result, Canada spends more on medications.

In 2017, a cost assessment study among 10 developed countries observed lower drug expenditures for countries with single-payer systems compared to those with multiple payers including Canada (27). Indeed, in 2013, the annual per capita pharmaceutical spending in Canada was 713 USD, the fourth-highest worldwide behind the United States (1026 USD), Japan (752 USD), and Greece (721 USD) (29). European countries including Germany (678 USD), France (596 USD), Italy (572 USD), Sweden (459 USD) and Denmark (240 USD) spent less on pharmaceuticals compared to Canada (29). Researchers estimate that the introduction of a single-payer drug plan in Canada could yield savings between 4 to 11 billion CAD annually (25, 26). These numbers illustrate the need for cost-effective strategies that can ease the financial burden of IBD at the provincial and national levels. With universal pharmacare in Canada, access to medications and health care outcomes could be potentially improved while reducing health care costs.

We recognize some limitations of our study. First, misclassification bias in accurately identifying IBD cases is always a concern. This limitation was reduced by applying a validated case definition requiring multiple health care contacts with the diagnosis of IBD. Second, the inclusion of FY as a linear predictor in our model showed a significant annual increase in the prevalence and cost estimates over time. However, the above prevalence and cost figures depict curvilinear features. Therefore, to continue studying the increasing prevalence and cost of IBD, future studies could apply our model-based approach considering non-linear trends. Finally, studies on the indirect health care cost of IBD are needed.

Despite these limitations, our study has several strengths. This study is the first to link multiple administrative health databases to study the prevalence and direct health care costs of IBD in the province of Saskatchewan. Further strengths of this study include its large sample

size, population-based nature, and extensive study period of 18 years, which enabled us to test trends over time.

3.6 Conclusions

This population-based study provides detailed evidence on the burden of IBD in the Canadian province of Saskatchewan. We determined that the prevalence and direct health care costs, among adults respectively, doubled and increased more than six-fold over two decades. Thus, in 2016/17 the prevalence and total direct health care cost of IBD, respectively, reached 664/100,000 population and
50.9 million CAD. Additionally, we identified that the average IBD direct health care cost was 7.0 thousand CAD per patient at the end of the study period. While the increasing IBD costs are associated with the rising prevalence of the disease, prescription medication costs are playing a quite significant role in the financial burden of IBD. The increasing prevalence and health care cost trends of IBD over time need to be recognized by health care decision and policymakers. This and future evidence could promote the development of cost-effective health care policies at provincial and national levels that respond to the needs of patients living with IBD and reduce per capita costs of health care. For example, a universal pharmacare plan or reforms seeking to adopt a multi-province public pharmacare could support negotiation arrangements through bulk medications purchasing and produce savings to the Canadian health care system.

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CHAPTER 4: DISCUSSION

4.1 Summary of research

The preceding two chapters presented the epidemiology and direct health care costs of inflammatory bowel disease (IBD) among adults in Saskatchewan between 1999 and 2016 fiscal years (FY). In these studies, diagnosed cases of IBD were identified by applying a validated algorithm (1) using Saskatchewan's health administrative databases. Using a unique encrypted identifier, four databases were linked to produce individual and aggregated level data for analysis. Generalized linear models with negative binomial and gamma distribution were used for data modelling. A generalized estimation equation was used in the prevalence and cost models to account for data correlation.

The first manuscript (Chapter 2) presented IBD incidence rates and corresponding trends over time in Saskatchewan, as well as the differences in the incidence rates of IBD between the rural and urban place of residence at the time of diagnosis. In this study, the incidence rate of IBD in Saskatchewan decreased from 75 per 100,000 inhabitants in 1999/00 to 15 per 100,000 population in the 2016/17 FY. The estimated average annual decrease in the incidence of IBD was -6.9% (95%CI -7.6 to -6.2). Also, I reported that urban Saskatchewan residents were 1.19 (95%CI 1.11 to 1.27) times more likely to be diagnosed with IBD compared to those living in rural Saskatchewan.

The second manuscript (Chapter 3) presented the prevalence and direct health care costs of IBD in the province of Saskatchewan, as well as their trends over time from 1999/00 to 2016/17 FY. In this study, an increasing prevalence of IBD was observed in Saskatchewan. In 1999/00, 3 out of 1000 adults in Saskatchewan were diagnosed with IBD. This number increased to 7 out of 1000, equating to an average annual increase of 3.3% (95%CI 2.4 to 4.3). Likewise,

the direct health care costs of IBD also increased. Since 1999, the per-patient annual direct health care costs of IBD increased from $1.8 (95%CI 1.6 to 2.0) to $7.0 (95%CI 6.5 to 7.5) thousand by 2016, with an average annual increase of 9.2% (95% CI 8.6 to 9.9).

4.2 Comparison with other epidemiological studies

4.2.1 Manuscript 1: Population-based evidence from a western Canadian province of the decreasing incidence rates and trends of inflammatory bowel disease among adults

As suggested by different studies worldwide, the incidence rates of IBD vary geographically (2-4). Epidemiological studies assessing IBD incidence rates in the last century have observed an increasing trend (2), even as more recent works are reporting contrasting findings. Studies from South America, the Middle East, and Asia have observed emerging incidence rates of IBD (2-4). On the other hand, studies from Europe and North America have seen recent decreasing or stable time-trends in the disease (4). A similar divergent pattern has been identified in Canada. The provinces of Nova Scotia, Quebec, and Manitoba have reported decreasing incidence rates of IBD, while Ontario and Alberta have observed increasing or stable trends among certain age categories (5-9). In Saskatchewan, our results show that the incidence rates of IBD have decreased by nearly 7% since 1999.

It is important to highlight that, the cohort used for this study excluded the Saskatchewan paediatric population. Even though the diagnosis of IBD can occur at any age, more rapid increasing incidence rates have been observed in children (10-12). Both Canadian and global studies have observed an increasing incidence rate of IBD among paediatric patients (11, 12). In a recently published systematic review, Sýkora et al. (12) clustered studies based on different geographical locations to assess temporal trends in the paediatric incidence of IBD. Newly

industrialized areas in Asia, the Latin America, and Africa reported increasing incidence trends of IBD with rates ranging between 0.0 and 11.4/100,000 person-years (12). Other examples of increasing onset of paediatric IBD are studies recently carried out in Europe. For instance, Ashton and colleagues observed a 36% increase in a paediatric cohort for Wessex, England, from 2013 to 2017 (13). Virta et al. (14) also reported a rise in the incidence rates of IBD among children in Finland with an average annual increase of 4.1% (95% CI 3.6 to 4.5) from 1987–1990 to 2011–2014.

My study excluded paediatric population because currently there is no validated IBD paediatric case definition for Saskatchewan. Specifically, an adjusted paediatric IBD algothim will be needed because patients in Saskatachean required to access colonoscopies and paediatric IBD care in neighbouring provinces for several years. This exclusion could be one of the reasons, among others, for the observed decrease in UC and CD incidence rates in Saskatachewan. A study in a neighbouring province of Alberta observed a similar decreasing pattern in the incidence rates when excluding individuals less than 18 years old. In their study, stable incidence rates of IBD were observed over time when considering all age groups; however, decreasing incidence rates of IBD among adults were identified in the stratified data analysis (6). Future studies in Saskatchewan and other Canadian provinces could examine the temporal trends of IBD incidence rates among adults and paediatric population separately to better understand if this pattern exists in other provinces.

A westernized lifestyle, including increased urbanization, environmental pollution, changes in lifestyle and diet is a proposed risk factor for IBD (15, 16). This hypothesis has been studied by different epidemiological studies (16, 17). Based on accumulating data, living in an urban environment increases the risk of being diagnosed with IBD (16-18). A recent study from

East Asia reported that IBD rates were higher among urban communities than in rural ones (16). Researchers from Turkey also observed lower prevalence rates of UC in rural (2.2/100,000) than in urban areas (5.9/100,000) (18). Likewise, a multi-provincial study from Canada that tested different definitions of rurality described a higher incidence rate of IBD among urban Canadians when compared to their rural counterparts (19). Furthermore, a Swedish study reported a higher incidence of UC and CD in urban regions (16). These studies and my study results demonstrate that residing in urban environments could increase the risk IBD.

Moreover, regions reporting emerging incidence rates of IBD include those adopting industrialized and westernized lifestyle (3). While the association between IBD and location of residence has been studied extensively (16, 17), the specific environmental IBD risks factor remains unclear and should be the focus of future works. By far, some of the discussed hypotheses comprise differences in diet, exposure to sunlight, air pollution, smoking, and climate or variations in temperature (16). Understanding the relationship between these factors and IBD as well as how they vary in rural/urban locations could provide researchers clues to why urban areas have higher IBD rates than rural ones.

4.2.2 Manuscript 2: Increasing Prevalence and Direct Health Care Cost of Inflammatory Bowel Disease among adults: A Population-Based study from a Western Canadian Province

In my second manuscript, I reported an increased prevalence of IBD from 341 to 664/100, 000 over the study period. The observed increase in the prevalence of IBD was higher than the forecasted numbers for Saskatchewan in a study by Coward S and collaborators (15). In 2018, Saskatchewan's IBD prevalence rate was predicted at 636/100,000 (15) while my 2016 estimate was 664/100,000. Comparing the observed with the forecasted prevalence demonstrates

the rapid growth of IBD in the province.

IBD is a global disease with prevalence rising across different regions, including areas with historically low rates as well as those formally recognized as epicentres of the disease (20). To date, Norway and Germany respectively have the highest reported rate of UC (505/100,000) and CD (322/100,000) in Europe (4). Canada has the highest prevalence cases for CD (319/100,000), whereas the USA reports the highest rate for UC (286/100,000) in North America (4).

Although there is evidence of decreasing or stabilizing incidence rates of IBD in Western countries, the prevalence of the disease continues to increase (4, 21). Today, the prevalence of IBD exceeds 3 million cases for the USA and Europe with studies predicting a rise in disease rates over the following decades (3, 15). For instance, between 2025 and 2030, the prevalence of IBD is expected to stand somewhere between 790 and 981/100,000 population in Canada and the USA (3, 15). In Europe, researchers estimate that about 1.02% of the population in Scotland will have IBD by 2028 (22). Other regions have lower predictions, like Portugal where the prevalence has been estimated between 0.32% and 0.49% for 2030 (23).

The increasing prevalence rate of IBD has been attributed to the chronic nature of the disease, its early diagnosis among young individuals whose life expectancy is minimally affected, and the lack of a cure for the disease (15, 22). Subsequently, the number of newly diagnosed individuals with IBD adds up to the already existing prevalence cases, a concept noted as compounding prevalence, could pose significant financial stress on health care systems (3, 15).

As reported by recent studies, the cost associated with IBD is on the rise (24) and this is what I observed in my results. In my study period, the total direct health care cost of IBD in

Saskatchewan significantly increased from 7.8 million Canadian dollars (CAD) in 1999 to 50.9 million CAD in 2016. Per patient model-based average direct health care cost also increased from 1.8 (95%CI 1.6 to 2.0) thousand to 7.0 (95%CI 6.5 to 7.5) thousand CAD during the same period. This estimate is significantly higher than the Canadian average direct health care cost estimated in 2018 (~ 4.7 thousand CAD per person) (25). My results were also higher than observed IBD estimates in Manitoba, 3.9 thousand CAD in 2012, although lower than those of Quebec for managing UC at 8.9 thousand CAD (25).

Further, my results seem to be lower or similar than the estimates from other developed countries. In a 2010 study of Gleason et al. (25, 26) conducted in the United States, per patient average direct health care costs of IBD were estimated at 22.1 thousand United State Dollars (USD). Likewise, a study from Australia reported an estimate of 10.5 thousand Australian dollars (AUD) for CD and 6.3 thousand AUD for UC (25, 27). In this study, 35.5% of IBD direct health care costs were related to medications (32% for CD and 39% for UC) (27). Their percentage was lower than what was observed in my research; ~ 90% for prescription medication cost.

Also, Dutch authors van der Valk et al (25, 28) described the health care costs of CD and UC at 1.600 and 590 euros for patients in the Netherland. Authors from this study associated most of these costs to prescription medications (CD, 64%; UC, 31%), identified as the main cost drivers of IBD direct health care (25-28). The use of biologic medications is improving the management of patients living with IBD but their use is significantly increasing the health care cost of the disease (25). The increasing prevalence of IBD and rising direct health care costs are challenging facts for health care systems.

4.3 Contribution to current literature

This study is the first one to thoroughly assess the epidemiology and direct health care costs of IBD in Saskatchewan. The results presented in my two manuscripts contribute significantly to the field of IBD research. For instance, in a 2018 Impact of Inflammatory Bowel Disease in Canada study, Saskatchewan was among the provinces whose changes in incidence over time were still unknown (5). My study is filling this gap, specifically regarding the Saskatchewan adult population.

Findings from this study are also providing evidence about the evolution of the burden of IBD. From my study results, the prevalence and direct health costs of IBD in Saskatchewan are increasing. Even though my population of interest was limited to one Canadian province, the applied method could be replicated in other jurisdictions in Canada. Thus, the model-based approach used in this study (which considered several variables) can be adopted by researchers in other regions to update the epidemiology of IBD and other chronic diseases and provide solid evidence to health care providers and decision-makers.

Finally, population-based cohort studies using administrative health databases have made landmark contributions in assessing disease surveillance (29, 30). Administrative health databases are effective data sources used to monitor the patterns of health services utilization and surveillance of individuals living with chronic diseases (29). These studies are large and representative of a well-defined population and have extensive follow-up periods which makes it feasible to evaluate trends (29, 30). Researchers could make use of these databases to address numerous research questions or hypotheses focusing on disease outcomes and health services utilization of population health.

4.4 Knowledge Translation

The manuscripts in this thesis have been submitted for publication in peer-reviewed journals. Manuscript 1 has been published in the *Journal of the Canadian Association of Gastroenterology*. Manuscript 2 is currently under review in the *Healthcare Policy* journal. Furthermore, I presented this work at both national and international conferences:

1. The 2018 Saskatchewan Epidemiology Association, Saskatoon, Saskatchewan October 3rd, 2018: poster presentation of my research proposal. My presentation was awarded as the 2nd best poster.
2. The 2019 Saskatchewan Epidemiology Association, Regina, Saskatchewan October 8th, 2019: poster presenting preliminary results.
3. The Canadian Digestive Diseases Week, Montreal, Quebec February 28th, 2020: poster presentation. Abstract published in *Journal of the Canadian Association of Gastroenterology*; available at https://doi.org/10.1093/jcag/gwz047.059
4. 15th Congress of European Crohn's and Colitis Organisation in Vienna, Austria February 14th, 2020: poster presentation. Abstract published in the *Journal of Crohn's and Colitis*; available at https://doi.org/10.1093/ecco-jcc/jjz203.899
5. An abstract of my study was also accepted for an oral presentation at the 2020 Canadian Association of Health Services and Policy Research Annual Conference in May but the Conference was cancelled due to the COVID-19 pandemic; see 2020 CAHSPR book of abstracts, page 163.

4.5 Future directions

My study provided a detailed update about the epidemiology and direct health care cost of IBD in the province of Saskatchewan among adults. However, there is a need for a paediatric cohort in Saskatchewan. Future studies should expand the IBD cohort in Saskatchewan to include the paediatric patients living with the disease. Also, there is a nationwide need for more population-based retrospective studies that adopt a standardized IBD paediatric and adult case definitions to establish the epidemiology of the disease across Canada.

I observed that urban Saskatchewan residents have a higher risk of being diagnosed with IBD (especially CD) than those living in rural areas. These findings are in line with published works looking at the location of residence and IBD (16, 17). Nonetheless, to date, the specific geographical differences of IBD, and the risk factors that may explain these differences are unknown. The focus of forthcoming works should look to establish the cause of the increased risk of IBD (specifically CD) in urban Saskatchewan areas. For example, future work could adopt studies in both rural and urban Saskatchewan regions where patients would be stratified into cases and controls to examine the proposed risk factors of IBD and its outcome on their health retrospectively or prospectively.

One component of my study focused on the direct health care cost of IBD in the adult Saskatchewan population; however, indirect health care costs of IBD could not be considered. Consequently, indirect health care cost needs to be studied in subsequent studies including productivity loss, premature retirement, long-term disability, and absenteeism costs. Information on both direct and indirect health care costs should be available for health care providers and decision-makers to improve health care for patients living with IBD in the province.

I incorporated an 8 years wash-out period to distinguish incidence from prevalence cases

in Saskatchewan. By doing so, all individuals with <8 years of health care coverage were excluded from the incidence study. Different studies estimating the incidence of IBD across Canada have employed different washout periods since there is no specific disease-free period recommended for IBD studies. For instance, the Ontario and Alberta IBD Cohort adopted 8-year washout period for their studies (29, 30). Whereas in Nova Scotia, a 5-year washout period was applied (7). Conversely, Quebec's IBD Cohort applied a 2-year washout period which is not validated (31). Researchers have recommended a specific washout period of 8 years in other chronic diseases such as Multiple sclerosis (32). The Canadian Gastro-Intestinal Epidemiology Consortium could explore different wash-out periods to identify IBD incidence cases across Canada and recommend a standard approach for upcoming national studies including incident cases of IBD.

4.6 Limitations and Strengths of the study

The limitations of this study include all limitations related to the use of health administrative data. By nature, IBD is a long-lasting disease with relapse and remission of symptoms; therefore, misclassification bias may have occurred. For this reason, I included a washout period to differentiate incidence from prevalent cases. However, a few prevalent cases could be misclassified in the earlier years of my study period as I included a washout period of 8 years to minimize this error. Another limitation is that the used IBD algorithm was not validated considering potential rural/urban differences. Further, results from the prevalence and cost model with the fiscal year as a linear predictor exhibited that the burden of IBD is increasing rapidly. However, observation from graphs displayed some curvilinear features; hence, future studies could consider time as non-linear factors to address changes in the patterns of the prevalence and

costs of IBD.

Despite these limitations, administrative health data has several strengths which include the potential to attain large sample sizes with extensive follow-up periods. The study spans an 18-year period which made testing for linear trends feasible. Moreover, the adopted statistical method applied for this study made it possible to control for numerous variables including place of residence and comorbidity burden, both described as important risk factors for developing IBD and health expenditure (19, 33).

4.7 Conclusions

Overall, this thesis offers quantitative evidence of a decreasing incidence and rising prevalence of IBD in the Saskatchewan adult population. Along with the rising disease prevalence, per patient average cost of IBD nearly quadrupled at the end of the study period. The increasing prevalence and costs in Saskatchewan will likely challenge the health care system and current health care models for patients living with the disease in the province. To overcome these challenges, further research and new policies, adequate planning, and cost-effective strategies are needed.

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Appendix A

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio ID
Tracey Sherin	Health Quality Council	91

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Health Quality Council
SK

FUNDER(S)
College of Medicine

TITLE
Epidemiology and direct medical cost of Inflammatory Bowel Disease in Saskatchewan: A Population-Based Study

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
26-Jun-2018	27-Jun-2018	Biomedical Application Secondary Use of Health Data	26-Jun-2019

Delegated Review ☒ Full Board Meeting ☐

IRB 1 Registration #00001471 ☐ IRB 2 Registration #00008358 ☐ Not Applicable ☒

CERTIFICATION
The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. If a protocol has been reviewed at a full board meeting, a subsequent study of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://research.usask.ca/for-researchers/ethics/index.php.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2 2014).

Digitally Approved by Ildiko Badea
Vice-Chair, Biomedical Research Ethics Board
University of Saskatchewan

Please send all correspondence to:

Research Services and Ethics Office
University of Saskatchewan
Room 223 Thorvaldson Building
110 Science Place
Saskatoon, SK Canada S7N 5C9

Appendix B

From: Marshall, John <marshllj@mcmaster.ca>
Sent: Wednesday, July 29, 2020 4:13 PM
To: Osei, Jessica; Journal of Crohn's and Colitis
Cc: PAUL SINCLAIR; Pena-Sanchez, Juan-Nicolas; Jessica Osei-Amankwah
Subject: RE: Permission to reproduce article (JCAG-2020-0010.R1) in Master's thesis

Dear Jessica
Thank you for your inquiry. This is no problem, as our content is published as Open Access.
Regards
John Marshall

John K. Marshall MD MSc FRCPC CAGF AGAF
Professor of Medicine
Director, Division of Gastroenterology
McMaster University
1280 Main Street West (Room 2F59)
Hamilton Ontario L8S 4K1
Telephone +1 905 521 2100 ext. 76782
Fax +1 905 523 6048
Email marshllj@mcmaster.ca

From: Osei, Jessica [jeo046@mail.usask.ca]
Sent: Wednesday, July 29, 2020 11:23
To: Marshall, John; Journal of Crohn's and Colitis
Cc: PAUL SINCLAIR; Pena-Sanchez, Juan-Nicolas; Jessica Osei-Amankwah
Subject: Permission to reproduce article (JCAG-2020-0010.R1) in Master's thesis

Dear Dr. John Marshall, Editor in Chief JCAG:

I am a University of Saskatchewan graduate student completing my Master's thesis entitled *"Epidemiology and Direct Health Care Cost of Inflammatory Bowel Disease in Saskatchewan: A Population-Based Study"*.

I am writing to kindly ask permission to reprint in my thesis a copy of an article recently accepted for publication in the Journal of the Canadian Association of Gastroenterology (JCAG). Please see the full citation of the article below.

> Osei JA, Peña-Sánchez JN, Fowler SA, Muhajarine N, Kaplan GG, Lix LM. T. P Population-based evidence from a western Canadian province of the decreasing incidence rates and trends of inflammatory bowel disease among adults. *Journal of the Canadian Association of Gastroenterology*. 2020; in press. https://doi.org/10.1093/jcag/gwaa028

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Please confirm by email if these arrangements meet with your approval.

I look forward to hearing from you.

Sincerely,

Jessica Amankwah Osei

Jessica Amankwah Osei, BA, MHEM, MSc(c)
Department of Community Health & Epidemiology
College of Medicine, University Saskatchewan, Saskatoon, Saskatchewan, Canada.
Ph.: 639-998 8656; email: jeo046@mail.usask.ca