Distributed Network Meta-Analysis Estimates Results From Individual-Level Analysis Using Ontario Health Administrative Data On Pediatric Inflammatory Bowel Disease Health Services Use: A Population-Based Cohort Study

Aman Dheri

A thesis submitted in partial fulfillment of the requirements for the

Master of Science degree in Epidemiology

School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

Acknowledgements

I would first like to thank my exceptional supervisor, Dr. Eric Benchimol, who has guided me through this thesis with unwavering support. Dr. Benchimol, I cannot express enough gratitude for your mentorship or all that you have done. You gave me every opportunity to develop my research skills and guided me through all aspects of my degree with my best interests at heart. Your passion for research, personal growth, and ongoing learning and problem-solving inspired me to embrace and push through all the challenges I faced, and I would not have been able to do any of this without you. I truly could not have asked for a better mentor.

I also want thank Dr. Ellen Kuenzig, the post-doctoral fellow in the Benchimol group, who made numerous important contributions to the study design, methodology, and data analysis. She gave so much to this journey in knowledge, advice, and support – both intellectually and as a friend – to make this thesis a success. Ellen, you were a constant lifeline, and I am very grateful to have had your support.

To my thesis advisory committee members, including my supervisor and Drs. Ellen Kuenzig, David Mack, and Sanjay Murthy, I want to thank you for not only your insightful contributions, which improved this project greatly, but also for constantly encouraging me and pushing me become a better researcher. Your support and guidance have helped me grow much over the last couple of years, and I am grateful for the faith you all have put in me. I hope I can take what I have learned from our time together and make each and every one of you proud.

To the entire Benchimol group, friends and colleagues at the Ottawa Hospital Research Institute and ICES, and 2017 uOttawa School of Epidemiology cohort, thank you for your friendship. I am lucky to have been surrounded by such genuinely kind and intelligent people, and I will always cherish our shared memories.

Lastly, but most certainly not least, my dearest family and friends, near and far, this thesis really belongs to you; the people who have stood by my side through this journey. Your unconditional love and support were pivotal for this thesis. To my family – Mom, Dad, Pam, and Raja – in particular, you each made many sacrifices to make this dream a reality for me, and words cannot summarize the gratitude I will forever hold for each of you.

This work was funded by a Foundation Grant from the Canadian Institutes of Health Research (CIHR).

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI.

This study was approved by the Children's Hospital for Eastern Ontario (CHEO) research ethics board. With the guidance of my supervisor, thesis advisory committee, and Dr. Gilaad Kaplan, I carried out the study design, analysis, and reporting. ICES data was extracted and provided to the student by ICES analysts Jessy Donelle and Glenys Smith. Dr. Ellen Kuenzig and ICES analysts Sarah Spruin and William Petrcich also provided data and coding support.

Table of Contents

Glossary

Distributed Network Analysis: The study design used to overcome privacy regulations restricting the sharing of individual-level data across studies or regions. Involves the application of identical study design, methods, and shared code to each region (network) then combined to obtain an overall estimate.

Heterogeneity: Variation between estimates that is not due to chance.

IBD-related: Diagnostic codes for inflammatory bowel disease, or any codes related to the signs, symptoms, or extra-intestinal manifestations of the disease (see Appendix B).

IBD-specific: Diagnostic codes for inflammatory bowel disease (ICD-9: 555.x or 556.x; ICD-10: K50.x or K51.x).

Individual-level analysis: Analysis performed using data collected on each individual unit (in this study, each unit was represented by a patient).

Local Health Integration Network (LHIN): Administrative units involved in the delivery of local health care in regions defined by the Ministry of Health and Long-Term Care (MOHLTC), which were in effect for the duration of the study period.

LHIN-based analysis: In this study, the simulation of a distributed network analysis by conducting analysis using individual-level data in each LHIN to produce a local effect estimate, coupled with the meta-analysis of effect estimates from all LHINs to produce a provincial estimate.

Meta-analysis: A statistical method of combining multiple effect estimates to derive an overall summary effect estimate.

Abbreviations

CanGIEC: Canadian Gastro-Intestinal Epidemiology Consortium

CD: Crohn's disease

CHEO: Children's Hospital of Eastern Ontario

CI: Confidence interval

CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database

CIHR: Canadian Institutes of Health Research

CNODES: Canadian Network for Observational Drug Effect Studies

DSEN: Drug Safety and Effectiveness Network

ED: Emergency department

ERCLAIMs: OHIP's Emergency Claims database

FDA: Food and Drug Administration

FE: Fixed effects

FY: Fiscal year

HR: Hazard ratio

HRDN: Health Research Data Network

IBD: Inflammatory bowel disease

ICD: International Classification of Diseases and Related Health Problems

IPD: Individual patient data

IRR: Incidence rate ratio

LHIN: Local Health Integration Network

MOLTC: Ministry of Health and Long-Term Care

OCCC: Ontario Crohn's and Colitis Cohort

OHIP: Ontario Health Insurance Plan

OMOP: Observational Medical Outcomes Partnership

OR: Odds ratio

RE: Random effects

RPDB: Registered Persons Database

SPOR: Canada's Strategy for Patient-Oriented Research

UC: Ulcerative colitis

List of Tables

List of Figures

Abstract

Over the last couple of decades changes to pediatric inflammatory bowel disease (IBD) care may have altered health services use among these children. I used a retrospective matched cohort design and population-based health administrative data to first quantify trends in IBD health services and surgical outcomes in Ontario IBD children diagnosed between 1994-2012. I then used these results to validate the distributed network analysis method – a method being increasingly used in Canadian multi-province studies where privacy regulations prevent sharing of individual-level data across provincial borders - using Ontario's Local Health Integration Networks. I found (1) decreasing hospitalizations and surgical outcomes but increasing outpatient visit rates, suggesting changing patterns of health care use in Ontario children with IBD, and, (2) distributed network analyses is a satisfactory privacy-preserving alternative to individual-level analysis under the conditions tested in my study, providing a tested analysis method for researchers using multi-jurisdictional data.

Chapter 1. Introduction

1.1 Introduction to Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic, relapsing and remitting immune-mediated disease mainly affecting the gastrointestinal tract. Its symptoms include abdominal pain, diarrhea, nausea, vomiting, anemia, weight loss, fever, and fatigue. The severity of the symptoms can limit participation in day-to-day tasks and, consequently, reduce quality of life. The chronic nature of the disease imposes long-term stress on patients and a significant economic burden on both the public health care system, patients and their caregivers.[1] The estimated direct costs (*e.g.*, health service or pharmaceutical costs) of caring for IBD patients in Canada in 2018 was $1.28 billion, with an additional $1.29 billion in indirect costs (*e.g.*, absence from work or alternative therapies).[2–4] However, both direct and indirect costs are likely underestimated due to few Canadian studies included in the analysis and limitations on the availability of data.[2,3]

IBD consists of two major types: Crohn's disease (CD) and ulcerative colitis (UC). In both CD and UC, the disease course typically follows a pattern of active disease (flares) and remission (no active inflammation). In 2013, 60% of the Manitoban IBD population was estimated to be in remission, with the remainder experiencing mild, moderate, or severe disease activity.[5] Patients with CD can have inflammation throughout the gastrointestinal tract. CD can extend through all layers of the bowel wall, sometimes resulting in fistulae and abscesses. In addition, patients with CD may develop fibrostenotic complications resulting from progressive

scar tissue and hypertrophic smooth muscle at affected areas of the intestinal lumen.[6] In contrast, UC primarily affects the colon and the inflammation does not typically extend below the mucosal surface of the intestine. Severe and serious complications of UC, such as bowel perforation or toxic megacolon, may lead to death.[7] Furthermore, active inflammation of the colon, whether in CD or UC, increases the risk of colorectal cancer. Presently, there is no cure for CD or UC, and treatments minimize inflammation, allowing a patient to enter remission. When patients are non-responsive to medical therapy or develop complications, surgical intervention may be required.[8]

1.2 Epidemiology of Inflammatory Bowel Disease

1.2.1 The Rising Prevalence and Incidence of Inflammatory Bowel Disease in Children Residing in Canada

In 2018, the prevalence of IBD in Canada was estimated to be 0.7%; this corresponds to approximately 270,000 Canadians, including 135,000 CD patients, 120,000 UC patients, and 15,000 patients with IBD type unclassified.[4,9] The prevalence has been rising and is expected to continue to increase to 403,000 Canadians by 2030 (national prevalence of 0.95%).[4,9] In Canadian children the prevalence of IBD is increasing.[10] The prevalence of IBD among Canadian children was 62 per 100,000 population in 2008 and is expected to rise 4.3% per year to reach a national prevalence of 159 per 100,000 in 2030.[10] Canada also has one of the highest incidence of pediatric IBD in the world.[11] While pediatric IBD incidence (<16 years) was stable overall in Canada from 1999-2010, IBD incidence increased by 7.0% per year in children under five years of age.[12] In Ontario, the incidence of IBD has been rising in children under 10 years of

age.[13] Specifically, IBD incidence increased 5.0% per year in Ontario children of six months to four years of age and 7.6% per year in children of five to nine years of age.

1.2.2 The Impact of Inflammatory Bowel Disease in Children

The rising rates of IBD among children is particularly concerning because earlier disease onset poses unique challenges for the child, the family, and society. This includes increased direct costs of care,[14] a greater burden on family,[15] longer duration of care services required, and a longer period of living with a lower quality of life. In addition to IBD affecting the education and physical well-being of children, IBD also affects their mental health.[16,17]

A Manitoba study found that patients diagnosed with childhood-onset IBD had greater odds of obtaining higher education degrees or diplomas, although this was highly dependent on socioeconomic status and diagnosis of mental illness.[18] Another study found children with IBD achieved similar educational results to children without IBD.[19] However, IBD children also face academic struggles. These struggles include absences from school and difficulty in taking examinations.[20] Students with more severe IBD reported greater difficulty completing their schoolwork[21] and may underperform compared to their non-IBD peers.[19] Between IBD subtypes, the academic achievements of children with UC did not match those of their peers with CD.[22]

Children may also exhibit growth delays or impairments as a result of nutritional deficiencies, inflammation, or certain medications.[23] In addition, the risk of colorectal cancer is higher in children with IBD,[24] and, compared to adults, children with IBD have a more pan-enteric disease phenotype.[25] This results in a greater disease burden and increased likelihood of therapy with biologic medications.

Children with IBD are at a higher risk of depression and anxiety, which may be lowered by treating underlying inflammation with anti-tumour necrosis factor (anti-TNF) therapies.[26,27] At a time where self-esteem is particularly vulnerable, adolescents with IBD experience anxiety stemming from their body image and lack of control over their health.[28]

1.2.3 Risk Factors for Inflammatory Bowel Disease

The etiology of IBD remains largely unknown, but is believed to result from the complex interaction between genetic factors, environmental exposures, the gut microbiome, and the dysregulation of the immune system by these factors.[29,30] However, challenges in identifying the interactions arise due to differences in risk factors across subtypes of IBD. For example, smoking is specifically associated with adult-onset ileal CD but quitting smoking increases the odds of UC.[31,32] Additionally, NOD2 is associated with early-onset CD but not UC, and genetic risk scores can differentiate between UC, colonic CD, and ileal CD.[32–34]

IBD has a genetic basis, as determined by multiple genome-wide association studies (GWAS).[35] There is a higher risk and adjusted odds of IBD in first-degree relatives of IBD patients,[36,37] and a review article also found more cases of monozygotic twins concordant for CD than discordant for the disease.[38] In addition, GWAS implicate different genes in the risk of IBD in specific ethnicities.[39] Jewish people are more likely to be diagnosed with IBD; Canadian Jewish people have 4 times greater odds of CD and 7.5 times greater odds of UC than non-Jewish people.[37] While a review study suggested it is possible the lifestyle of Ashkenazi Jews may pose as a risk factor for the development of IBD in this population,[40] genetic mutations specific to Ashkenazi Jews have been associated with CD.[41,42] However, Ashkenazi Jews in

Israel have a lower incidence than Ashkenazi Jews from Western countries,[40,43] which highlights the importance of environmental factors.

The highest IBD incidence rates are found in developed countries in the Western world, and IBD incidence increases as countries become more industrialized.[44–46] UC appears to emerge faster than CD in developing countries, but eventually they reach equal rates.[44] The environmental influence on IBD has also been demonstrated in immigration studies. There was an increased incidence of UC in South Asian people following immigration to the UK.[47] In Canada, immigrants had a lower incidence of IBD than non-immigrants (7.3 versus 23.9 cases per 100,000 person years), but IBD was more common in those immigrating at younger ages compared with those immigrating later in life.[48] Ontario-born children of immigrants from some regions (*e.g.*, South Asia) had similar incidence rates to children of non-immigrants, while children of immigrants from other regions (*e.g.*, East Asia and Pacific, Latin America and Caribbean) had lower incidence rates.[49]

Living in an urban environment during early childhood is associated with a higher incidence of IBD.[29] Rural residence in children under 10 years of age in particular was a protective factor in the development of IBD, which suggests early-life environmental exposures are important in the development of IBD.[29] This is consistent with studies implicating a multitude of early-life factors in IBD development, including antibiotics[50] and air pollution,[51] while regular contact with farm animals protects against IBD development.[52] Furthermore, while socioeconomic status was not higher among IBD patients in Manitoba,[53] IBD was found to be more prevalent in white collar workers in Germany.[54]

Sex differences have also been reported in children with IBD. In Canadian children diagnosed with IBD between 2014-2017, there was a male predominance in CD, but the presence

of UC was similar between the sexes.[55] In Ontario specifically, there was a male predominance in CD for children diagnosed before 15 years of age, and there was a female predominance in UC.[13] Both sex hormones and other factors may impact the development of IBD.[56] For example, sex-based differences in IBD incidence appear to have increased over time[56] and vary across the world. A systematic review of Western population-based cohorts found a lower incidence of CD in females aged 10-14 years compared to males (incidence rate ratio [IRR]: 0.70, 95% confidence interval [CI] 0.53 to 0.93),[56] but in the Asia-Pacific regions, CD incidence was higher in males of both the 10-14 and 15-19 year age groups compared to females.[57] In UC children residing in the Western cohort, female UC patients aged 5 to 9 years had a higher incidence compared to males (IRR: 1.22, 95% CI 1.05 to 1.41).[56] In contrast, the incidence of UC in children residing in the Asia-Pacific region was higher in males of the 15-19 year age group.[57] Furthermore, although males were found to have a higher hazard of growth failure (hazard ratio [HR] of females versus males: 0.28, 95% CI 0.12 to 0.63), female children generally experienced worse disease outcomes than males, suggesting a possibly heightened severity of disease in females compared to males.[58]

Environmental factors and genetics also influence the microbiome,[59,60] which differs in IBD patients compared to healthy populations.[61–63] IBD patients were found to host lower microbial diversity, increased pathobionts, and decreased commensal microbes compared to healthy populations.[63–65] Microbial composition and abundance have also been associated with disease severity,[66] and mucosal inflammation in IBD has been associated with decreases in microbial diversity.[65,67] Microbiome differences distinguish between IBD subtypes. For example, the CD microbiome is less stable overtime compared to the UC microbiome, and CD and UC patients can diverge on individual species abundance and/or diversity.[61,63,68] Age

correlation studies of *Bacteroidetes* also show opposite associations in CD and UC children, which is thought to be attributable to immunological differences between the two groups.[69] Since the human microbiome is influenced by a multitude of factors, including host genetics, lifestyle, diet, and environment, or interactions between these factors, it is often difficult to discern the causes of host dysbiosis. Studying environmental risk factors and the microbiome of children can provide valuable insight into the etiology of IBD since children have not accumulated many life years, and changes to microbiome are likely to result from early life exposures and genetics.

The environmental, gut microbial, and genetic factors can each interact with the host immune system. For example, sun exposure triggers the natural synthesis of Vitamin D. Vitamin D plays a role in the immune response, and a deficiency in serum levels of this vitamin was associated with a greater hazard of IBD,[70] suggesting the lack of sun exposure could be a contributing factor to the pathogenesis of IBD by dysregulating the immune response. Immune dysregulation in response to gut microbiota is also believed to contribute to the pathogenesis of IBD by promoting abnormal inflammation.[71] Mutual genetic mutations between IBD and other autoimmune diseases have been identified, which suggests these disorders may have shared pathogenesis via immune dysregulation from a common genetic basis.[72]

1.3 Health Services Utilization in Inflammatory Bowel Disease

1.3.1 Health Services Costs for Inflammatory Bowel Disease

The direct costs of IBD care in Canada are $1.28 billion per year and include the costs of medication, hospitalizations, surgeries, and outpatient visits.[2] Costs of care may not necessarily

reflect trends in health services use. For example, the in-hospital costs for UC have increased by 6% per year despite decreasing colectomy rates in Alberta.[73] IBD patients are more likely to incur health care expenses and to use health services compared to patients without IBD. For example, in Manitoba, children with IBD had a median of 11 physician visits in the 6 months before and after their diagnosis compared to 2 physician visits for children without IBD (rate ratio: 3.48, 95% CI 3.28 to 3.68).[74] This elevated use of outpatient physician services continues beyond five years after diagnosis. The average direct cost of health services per person in Manitoba are higher in IBD patients ($3896) than their non-IBD counterparts ($1826), with higher costs for CD patients than UC patients, and higher costs for females with IBD compared to males.[75] Of the patients who were hospitalized, the average cost in 2005/2006 was relatively similar between children with and without IBD ($13,495 versus $12,607), but a higher percentage of IBD children were hospitalized compared to children without IBD (15% versus 7%).[75] The differences in average direct costs per person between IBD and non-IBD patients was greatest among children ($3842 versus $333), and hospital inpatient costs accounted for 47% of the costs in IBD children but only 27% in children without IBD.[75] Health care planners looking to prepare for the current and future cost-effective delivery of care to IBD children would benefit from understanding the trends in health services use and surgical outcomes in this population.

1.3.2 Predictors of Health Services Use in Patients with Inflammatory Bowel Disease

Multiple factors can influence patterns of health services use in IBD patients. Beyond disease extent and severity, some of the most common factors include age, sex, social and economic circumstances, and rural residence.

The age at which children are diagnosed influences their health services use.[76] Children diagnosed with IBD before 6 years of age had fewer outpatient visits, emergency department (ED) visits, and hospitalizations than those diagnosed with IBD after 10 years of age.[76] Older children had a higher hazard of visiting the ED (HR: 1.06, 95% CI 1.04 to 1.08) and used the ED more often within three years of diagnosis (IRR: 1.10, 95% CI 1.07 to 1.13) for IBD-related reasons compared to children diagnosed at a younger age.[77] Likewise, there is a higher hazard of surgery in children diagnosed at a later age (HR: 1.07, 95% CI 1.04 to 1.10), and this association was present in both CD and UC subgroups.[77] In CD children, the hazard of intestinal resection was lower in children diagnosed with IBD before the age of 6 compared to children diagnosed at 10 years of age or older (HR for males: 0.58, 95% CI 0.34 to 0.99; females: 0.35, 95% CI 0.16 to 0.78).[76] In another study, the odds of surgery within three years of diagnosis was lower in CD children under 10 years of age who were diagnosed in 2001-2004 compared to those diagnosed in 1994-1997 (odds ratio [OR]: 0.67, 95% CI 0.48 to 0.93), but this difference was not observed in children diagnosed at 10 years of age or older (OR: 1.22, 95% CI 0.76 to 1.94).[78] In UC children, the colectomy hazard in children under 6 years of age compared to children 10 years of age or older was lower in males (HR: 0.42, 95% CI 0.21 to 0.85), but not females (HR: 0.88, 95% CI 0.047 to 1.63).[76] These higher surgical outcomes among children diagnosed at an older age has been replicated in some studies[79,80] but not others.[81,82]

Health service utilization and surgery needs differ depending on sex. Adult females had lower rates of ED visits than males (IRR: 0.92, 95% CI 0.90 to 0.93).[83] In contrast, a US study found higher odds of ED visits (OR: 1.1, 95% CI 1.1 to 1.2) and hospitalizations (OR: 1.3, 95% CI 1.3 to 1.4) in females compared to males.[84] Other US studies found females have lower rates of intestinal resection (IRR: 0.80, 95% CI 0.76 to 0.85) and colectomy (IRR: 0.84, 95% CI 0.76

to 0.94) compared with males.[85,86] In international studies, one group found no sex differences in the hazard of intestinal resection,[87] while another found more females underwent intestinal resection within five years after diagnosis compared with males (64% versus 52%, p=0.03).[88] In Canada, females with CD (of any age) had lower odds of surgeries following hospital admission compared to males (OR: 0.76, 95% CI 0.70 to 0.83), though this difference was not seen in UC patients (OR: 0.93, 95% CI 0.82 to 1.05).[89] In contrast, a Quebec study found males had a higher hazard of colectomy (HR: 1.47, 95% CI 1.26 to 1.72).[90] In Manitoba, while UC males of any age had a higher hazard of a colectomy within 90 days from diagnosis compared to females (HR: 2.63, 95% CI 1.58 to 4.36), the hazard for a colectomy greater than 90 days from diagnosis was no different between sexes (HR: 1.22, 95% CI 0.97 to 1.53).[91] In children, the findings have also been conflicting. No differences in surgical rates were seen between sexes in Scottish studies,[92,93] and a US study found no difference in rates of intestinal resection between sexes in CD children.[79] In contrast, another US study found female children with CD had a 54% higher hazard of surgery compared to males (HR: 1.54, 95% CI 1.08 to 2.19).[80] In Canadian children with IBD, females generally used more health services than males. Specifically, female children had more hospitalizations (IRR: 1.23, 95% CI 1.08 to 1.36) and ED visits for IBD-related reasons (IRR: 1.33, 95% CI 1.16 to1.53) within three years of diagnosis compared with male children.[77] However, no sex differences were found in the surgery rates in Ontario children.[77]

Socioeconomic status plays a role in IBD health services use. A multicentre study from Paris found that, while both high and low income groups experience the same disease severity, adults with low income status were more likely to be hospitalized (56% versus 40%, p=0.04) but had lower odds of surgery (OR: 0.42, 95% CI 0.18 to 0.97).[94] In Ontario, children living in lower income neighbourhoods had more outpatient visits (IRR: 1.07, 95% CI 1.001 to 1.14) and

hospitalizations (IRR: 1.21, 95% CI 1.08 to 1.36) for IBD-related reasons within 3 years of diagnosis and a higher hazard of ED visits for IBD-related reasons within 10 years of diagnosis (HR: 1.21, 95% CI 1.09 to 1.35) than those living in higher income neighbourhoods.[77] Children with CD diagnosed between 2000-2004 and living in low income neighbourhoods also had higher odds of undergoing surgery within three years of diagnosis compared to children in high income neighbourhoods (OR: 1.66, 95% CI 1.23 to 2.25).[77]

IBD health services use has been reported to differ across races. US studies have found Caucasian CD patients visited primary care physicians (mean visits per year: 1.31 versus 0.21, $p<0.05$) and gastroenterologists (mean visits per year: 3.2 versus 2.3, $p<0.05$)[95] for care more often than African Americans and had a higher incidence rate of intestinal resection surgery compared to other CD minorities (IRR for African Americans versus Caucasians: 0.68, 95% CI 0.61 to 0.76; Hispanics versus Caucasians: 0.70, 95% CI 0.60 to 0.83; Asians/Pacific Islanders versus Caucasians: 0.31, 95% CI 0.16 to 0.59).[85] UC African American and Hispanic patients had lower incidence rates of colectomies compared to Caucasian and non-Hispanic Caucasian American patients, respectively (IRR for African Americans versus Caucasians: 0.46, 95% CI 0.35 to 0.60; Hispanics versus non-Hispanic Caucasians: 0.74, 95% CI 0.59 to 0.93).[86] A reduced need for surgery in South Asians was also reported in a UK study ($p=0.003$).[96] In contrast, another US study found non-Hispanic African Americans had higher hospitalization and surgery to prevalence ratios (7.3% and 0.9%, respectively) compared to non-Hispanic Caucasian and Hispanics (3.0% and 0.56%, and 2.7% and 0.32%, respectively).[97] Over time, bowel resection rates in Caucasian and Hispanic CD patients decreased by almost half from 1998 to 2003, but not in African Americans,[85] and similar trends were observed in UC patient colectomies.[86]

Residence in an urbanized location also affects patterns of health services use in IBD patients. In the US, UC patients admitted to urban hospitals had higher odds of colectomy compared to those who were admitted to rural hospitals (OR: 2.2, 95% CI 1.5 to 3.2).[86] Canadian IBD patients living in a rural area at the time of diagnosis had similar rates of outpatient visits for IBD-related reasons compared to those living in an urban area (IRR: 0.99, 95% CI 0.92 to 1.07), but they had higher hospitalization rates (IRR: 1.27, 95% CI 1.04 to 1.56).[98] This increased rate of hospitalization among rural-dwellers was unique to CD patients.[98] Patients living in rural areas also visited the ED more often for IBD-related reasons (IRR: 1.33, 95% CI 1.25 to 1.40).[98] While individuals with CD living in rural Ontario had higher odds of repeat intestinal resection (OR: 1.55, 95% CI 1.16 to 2.08), this difference was not observed in Alberta and Manitoba.[98] Repeat intestinal resection has also been associated with rural residence at diagnosis in children (HR: 1.58, 95% CI 1.05 to 2.37),[99] but the hazard of first surgery was no different between rural and urban patients for both CD and UC patients (HR for CD: 0.98, 95% CI 0.88 to 1.07; UC: 0.92, 95% CI 0.78 to 1.06).[98]

1.3.3 Temporal Trends of Health Service Use in Inflammatory Bowel Disease

Patients with IBD often visit outpatient clinics and emergency departments and may require hospitalizations. On average, Canadian adults with IBD have approximately 4 IBD-related outpatient visits per year.[100] In the US, a cross-sectional study of adults with IBD found outpatient visits for IBD reasons increased by 70% between 2005-2010, which then stabilized until 2013 before decreasing by 20% until 2016.[101] Canadian children with IBD had 3 to 4 outpatient visits per year[76] and visited physician offices twice as often as their non-IBD peers five years after their diagnosis.[74] In a 2011 study, health services utilization rates in Ontario

children with IBD were noted to be changing.[78] Between 1992 to 2004, Ontario children had declining numbers of primary care visits; areas with low primary care visit rates had higher ED visit rates.[102] However, outpatient visit rates among children with IBD have not changed in Ontario when comparing those diagnosed in 2001-2004 with those diagnosed in 1994-1997 (IRR for CD: 0.96, 95% CI 0.92 to 1.01; UC: 0.99, 95% CI 0.92 to 1.06).[78]

Patients with IBD had higher odds of visiting the ED than those without IBD (OR, 1.66, 95% CI 1.54 to 1.78).[103] Ontario adults with IBD, on average, visit the ED 0.28 to 0.34 times per year for IBD-related reasons.[100] Ontario children with IBD visit the ED on average 0.1 times per year for IBD-specific reasons, and 0.2 to 0.3 times per year for IBD-related reasons.[76] In children residing in the US, ED visit rates increased in both children with IBD (24% increase from 2006 to 2010, $p<0.01$)[104] and children with other diseases (11% increase from 2006 to 2011, $p<0.01$).[105] The number ED visits in the US for adults with IBD has also increased between 2006 and 2016.[101] However, the increases described in the US studies may have been a result of either true increases in ED visits or increasing prevalence of the disease because these studies were cross-sectional in nature and could not follow patients after they left the ED. Time trends of ED visit use in Canadian children with IBD are limited.

Adults with IBD are hospitalized on average 0.15 to 0.19 times per year for IBD-related reasons.[100] In the US, hospitalizations in adults with IBD increased from 79,939 (95% CI 74,093 to 85,785) in 2005 to 95,960 (95% CI 92,230 to 99,690) in 2016 ($p<0.0001$), though this study was cross-sectional in nature and may reflect either true hospitalization rate trends or increasing prevalence of IBD.[101] In Ontario children, approximately 25-35% of children diagnosed with IBD between 1994-2009 were hospitalized within one year of diagnosis.[76] In the US, the hospitalization rates in children with CD and UC increased by 3.8% (95% CI 3.0 to 4.5%) and

4.5% (95% CI 4.3 to 4.7%) per year, respectively, between 1997 and 2009.[106] Ontario children with IBD diagnosed in 2001-2004 were also found to have three times higher adjusted odds of hospitalization compared to children diagnosed with IBD between 1994-1997 (OR for CD: 3.22, 95% CI 2.15 to 4.83; UC: 2.83, 95% CI 1.55 to 5.19).[78] Over this same time frame, the frequency of hospitalization did not change (IRR for CD: 0.97, 95% CI 0.90 to 1.05; UC: 0.95, 95% CI 0.85 to 1.06).[78] Another Canadian study reported a decreased hazard of overnight hospitalization among children diagnosed with IBD between 2002-2010 (post-biologic era) compared with children diagnosed between 1987-2002 (pre-biologic era) (HR: 0.66, 95% CI 0.53 to 0.81).[74] Consistently, studies have reported reduced health services use outcomes in patients with IBD over time in recent years,[90,107,108] and the decreases have been associated with the introduction of biological therapies into clinical practice.[109–112] However, the decrease may be coincidental rather than caused by increasing biologic utilization. An Ontario study of adults with IBD found that, while hospitalization and surgical rates for CD and UC were decreasing over time, the trends did not decrease more rapidly after market approval of infliximab compared to the predicted time trends projected from pre-infliximab years.[113] The authors postulated that the lack of association between infliximab market penetrance and time trends of health services utilization may be due to improper use or underuse of infliximab. Aside from anti-TNF biologics, newer biologic medications have been increasingly used in IBD care and other factors have also changed in pediatric IBD care. For example, studies have also reported increased use of specialist care over the years, which is associated with better outcomes in IBD patients.[13,83,108]

With the multiple expected changes to IBD care it is likely that health services utilization patterns in Canadian IBD children have altered with time. It is probable that emergency department visits and hospitalizations have decreased over the past two decades. Outpatient

clinic visits may not have changed significantly because patients often require ongoing care from their health care provider for monitoring.

1.3.4 Trends in Intestinal Resection and Colectomy among Patients with Inflammatory Bowel Disease

When patients do not respond to medical therapies or develop complications from their disease, surgery may be required. The 1-, 5-, and 10-year risks of intestinal resection in patients with CD were 19.1%, 34.4%, and 49.0%.[8] A systematic review reported a decreasing surgery risk in IBD patients of all ages since the mid-20th century,[8] and is consistent with Canadian studies on IBD surgical time trends.[114,115] Compared to adults and the elderly, children with CD have lower risks of intestinal resection.[8,74,77,116,117] The 1-, 5-, and 10- year risks of intestinal resection in children with CD were 7.9%, 25.5%, and 35.6%, respectively.[8] In Canadian children with CD, the 1-, 5-, and 10-year risks of intestinal resection were 8-9%, 21-23%, and 27-29%, respectively.[74,77,116] An Ontario study reported a decrease in the three-year risk and odds of intestinal resection in children with CD diagnosed in 2001-2004 (after infliximab came to market) compared to those diagnosed in 1994-1997 (13.6% versus 18.8%, respectively, OR: 0.67, 95% CI 0.48 to 0.93).[78] A similar decrease in the risk of intestinal resection was observed in Manitoban children.[74]

The risk of colectomy in children with UC is higher than in adults,[8,74,77,91,116] but temporal trends remain unclear. The 1-, 5-, and 10-year risks of colectomy in UC patients were 4.4%, 10.1%, and 14.6%, respectively, and UC surgeries across all ages have been decreasing over time.[8] Colectomies among Canadian adults with UC have become less common with time.[90,91,107,118] In children, the 1-, 5-, and 10-year risks of colectomy were 6.7%, 17.4%, and

21.6%.[8] The respective 1-, 5-, and 10-year risks of colectomy in Canadian children with UC were 8-9%, 12-16%, and 15-21%.[74,77,116] Decreasing rates of colectomy in children with UC were reported in Manitoba (2002-2010 versus 1987-2001 diagnosis year p=0.05),[74] but not Ontario.[78]

Decreases in surgical rates have been accompanied by increased access to gastroenterologist care and an increased use of newer, more effective medical therapies,[78] making it unlikely to determine a single reason for temporal changes.

1.4 Use of Health Administrative Data in Inflammatory Bowel Disease Health Services Research

Routinely collected health data is defined as data that is regularly collected for its primary purpose, such as administrative purposes for economic and policy planning, but can subsequently be used to fulfill other needs, such as research.[119,120] Health administrative data is one type of routinely-collected health data, comprised of data collected for the purposes of administering the health care system. Examples of health administrative data include physician billing data, hospitalization records, procedure records, and medication prescription data.[119] The files originate from medical records created by health care providers. The information from these records are coded and submitted for their intended purposes, after which they can be used for health care research. Data collected and analyzed from health service providers is therefore considered "secondary" data analysis since research is not the primary role of these data.

Routinely collected health data may lack the level of detail of clinical data or of prospectively collected research data, may be miscoded upon entry into the electronic health

system, or may omit vital information required to reduce bias or adequately evaluate a hypothesis. This data is also typically collected retrospectively, further giving rise to issues such as inconsistent data capture and missing data. Therefore, validation of the data, including algorithms to identify patients with a specific health state and codes identifying outcomes, is an essential step to conducting such research.

Administrative data also comes with desirable qualities. Compared to primary data collection, this method is both cost and time efficient since it is collected for other primary purposes to begin with. It also allows for population-based studies, rather than a small sample of the population, for a complete analysis, improved statistical power, and greater generalizability of study findings. Population-level data is particularly useful in studying rare diseases or outcomes, especially compared with primary data collection. In addition, administrative data is better able to identify patients with less severe diseases than self-reporting,[121] and reduces biases originating from patients, such as reporting and recall bias. In this project, health administrative data allowed the study of population-based health services use and the capture of patients with a rare, chronic disease, which can range in severity over the disease course.

Canadian provinces have their own health administrative data, and researchers can access these data for scientific studies in most provinces. In Ontario, ICES is a prescribed entity through which researchers can access large amounts of routinely collected health and population data of Ontario residents.[122] Population-based data comes with many advantages for health research but national studies are difficult because of privacy laws preventing researchers in one province from sharing individual-level data with researchers in another provincial jurisdiction.

1.5 Issues in Conducting Epidemiological Research Using Pooled versus Individual-Level Data

1.5.1 Introduction to Distributed Network Analysis

Population-level health administrative data is available for research in most Canadian provinces and presents an opportunity to evaluate the national picture of health and disease and to compare health services utilization and care provision across Canada. However, provincial privacy legislations prevent the sharing of individual-level health administrative data with researchers outside of the province. This poses challenges for researchers interested in conducting nation-wide studies of health-related research.

Distributed network analysis is a method that allows researchers to conduct a multi-regional study without violating patient privacy.[123,124] This approach involves applying the same study methodology and shared programming code to each database in each region, though the code may need to be adapted to the data structure and variable names of each database.

Distributed networks have several positive qualities, making them an attractive alternative to use when individual-level data cannot be shared between regions. By keeping the analyses local, and performed by the people who are most familiar with their data structure, the experts at each site will have a better understanding of the data, biases, and interpretations of the results, and researchers are better able to capture differences in exposures, outcomes, populations across regions in geographically large or diverse studies.[123,125] The distributed network approach also prevents the need for the development and maintenance of a centralized data warehouse system.[123,124] In addition, the sharing of code across regions and standardization of the study design and analysis reduces methodological bias, and population-based observational

epidemiology studies employing the distributed network approach benefit from reduced selection bias.[126] Finally, replication of the research is conducted in each region, which allows researchers to examine the statistical consistency of the analyses between regions.[126]

The distributed network analysis in Canada-wide studies provides provincial estimates of effect size, which are then combined to generate national-level estimates. Canadian initiatives, such as the Canadian Network for Observational Drug Studies (CNODES) and the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC), have used distributed network analysis in multiple provinces and then used meta-analysis to produce an aggregate estimate. Meta-analysis is a convenient method for improving power to detect statistically significant effects.[127,128] This is particularly useful in studies of rare outcomes or illnesses, or where one would expect to find small effect estimates. Meta-analysis can also improve generalizability of study findings since it can incorporate a larger and more diverse sample.[126] Finally, since meta-analysis requires only the effect estimate and its variance, it involves less data sharing and preserves patient privacy better than sharing individual-level data.[129] However, it can be less time-efficient, especially if provincial analyses are inconsistent and need to be changed and re-run, or if additional analyses are required.[130] In addition, meta-analysis of separate multi-variable regression models using Canadian health administrative data has not been demonstrated to produce similar effect estimates as individual-level regression analysis under a variety of conditions such as differing event rates, sample sizes, number of regions, regression model types, and heterogeneity.

1.5.2 Canadian Distributed Network Initiatives for Nation-Wide Research

CNODES, which is part of the Drug Safety and Effectiveness Network (DSEN) initiative led by the collaboration of Health Canada and Canadian Institutes of Health Research (CIHR), has used distributed network analysis in order to obtain answers relating to pharmacoepidemiology in a timely manner while meeting privacy and legal standards.[126] Pharmacoepidemiology studies require large sample sizes in order to observe small effect size estimates or rare events, and population-based data across the country allows for increased power to detect these estimates while giving insight on national trends.[126]

CanGIEC is a group of clinicians, researchers, and methodologists across the country looking to improve IBD care and outcomes through health research. They previously utilized distributed network strategies with meta-analysis to derive national estimates on the epidemiology, risk factors, and health service use in Canadian patients with IBD.[29,98]

Apart from CNODES and CanGIEC, the validation of this method will provide a valuable tool for other nation-wide initiatives, such as the Strategy for Patient Oriented Research (SPOR) Canadian Data Platform and the Health Data Research Network (HDRN), looking to improve pan-Canadian health research.

Studies supporting US distributed network initiatives have explored the validity of distributed network analysis and subsequent methods of combining aggregate data.[129,131–135] Other case studies suggest distributed network analysis reflects results from individual-level analysis,[128,136,137] but the method has not been validated for Canadian population-based initiatives under varying study conditions such as type of regression models, differing levels of heterogeneity, and different event rates, sample sizes, or number of regions.

1.5.3 Heterogeneity in Distributed Network Analysis

National estimates are more generalizable and can detect smaller associations due to increased power. They can provide more information than analyzing a specific geographic area, such as a single province. However, effect estimates can vary across regions, which may highlight inherent differences between provinces not related to study design. Statistical heterogeneity in pooled analyses is the excess variation between the individual study or regional estimates that is not due to chance. Rather, it is due to specific characteristics that distinguish the meta-analyzed data within studies or provinces from each other. High heterogeneity may compromise the merit of a meta-analysis because the individual regions may be so different that they cannot be adequately compared. It is, therefore, important to explore the impact of heterogeneity on the accuracy of the meta-analysis. Applying the same method of analysis (*i.e.*, adapting the same programming code) to each province should reduce heterogeneity due to differences in study design. However, heterogeneity may also be influenced by a multitude of factors, such as underlying differences in the study populations, sample sizes, event rate, geographic variation, demographics, or other characteristics.[138] For example, provinces will likely have differing ethnic make-up and environmental exposures. In addition, the information stored in these databases may be inconsistent across provinces. Each province regulates its own health care resource allocation and services offered. These services may depend on political, economic, and social determinants within each province. As a result, databases that store insured claims can vary greatly depending on the services or medications each province is willing or able to cover, or depending on the underlying coding of data.[139]

Meta-analyses are performed using either fixed or random effects models, each with its own assumptions.[140] Fixed effects meta-analysis models assume regions are estimating one true

effect, and the differences between the individual regional estimates are due to within-region error variance (sampling error). Random effects models assume that if the sample size was infinitely large then the regional effects would create a distribution of true effects around a mean, and the regional estimates represent a random sample from this distribution. The differences between the individual regional estimates in random effects meta-analysis models are, therefore, assumed to be due to both the within-region error variance and between-region variance (τ^2, or heterogeneity). In the presence of heterogeneity, researchers conducting meta-analysis will often rely on random effects models to account for the variation in observed associations. Using identical methodologies, as in distributed network analyses, reduces methodological heterogeneity. In this scenario, fixed effect models may be justified.[139] However, differences still exist between provinces and their populations, which may lead to heterogeneity that is better accommodated by random effects models.[139] Therefore, there is a need to better understand the validity of distributed network meta-analysis using both fixed and random effects models and the impact of between-region heterogeneity on the validity of this approach.

1.6 Study Rationales, Objectives, and Hypotheses

1.6.1 Aim 1

1.6.1.1 Objective

My primary objective for this aim was to evaluate temporal trends in health service use (hospitalizations, ED visits, and outpatient clinic visits) and surgical outcomes in Ontario patients diagnosed with childhood-onset IBD between 1 April 1994 and 31 March 2013.

1.6.1.2 Rationale

Many changes to pediatric IBD care have occurred in Canada over the past two decades. Understanding trends in health services use and surgical outcomes of the pediatric IBD population is important to aid in informed policy-making decisions and future health services planning. Furthermore, population-based health administrative data provides opportunities to capture chronic disease patients with ranging disease severity and rare outcomes, which may be otherwise difficult to identify. Since health administrative data are usually collected for billing and recording purposes, they contain a wealth of health services use data that can be used to assess temporal trends.

1.6.1.3 Hypothesis

Temporal trends in health services utilization and surgical rates have changed in childhood-onset IBD patients diagnosed in Ontario between fiscal years 1994 and 2012. Specifically, hospitalizations and surgeries may have decreased over time, with increased

emphasis on outpatient management. These changes may be related to improvements in the delivery of care to children with IBD, including, but not limited to, new medications and increased access to specialist care for children with IBD.

1.6.2 Aim 2

1.6.2.1 Objective

My objective for this aim was to compare the results of individual-level analyses with results from distributed network meta-analysis methods using the results from Objective 1. A distributed network analysis was conducted for temporal trends on health services use in each of the 14 Local Health Integration Networks (LHINs) (to simulate different jurisdictions), and the results were meta-analyzed and compared to trends reported by the individual-level analyses. In addition, I explored the impact of statistical factors (*e.g.*, heterogeneity, event rate, statistical approach) on the comparability of these methods.

1.6.2.2 Rationale

Ontario accounts for approximately 40% of the Canadian population.[141] The province can be geographically stratified into 14 LHINs, which were the administrative units of funding and planning for the health system in effect until 2019. With a large population and readily definable sub-regions that act as their own administrative units within the province, data from multiple Ontario LHINs can be used to simulate multiple provinces in the distributed network analysis. The validation of a distributed network analysis provides the scientific community with a verified approach to using meta-analytic methods to obtain accurate estimates using aggregate

data when individual-level data cannot be shared across geographic regions. My work also provides insights on conditions where outcomes should or should not be meta-analyzed and if fixed or random effects models should be used.

1.6.2.3 Hypothesis

Meta-analysis of pooled results from multivariable regression models in multiple regions can accurately approximate the results of regression analysis using individual-level data. Therefore, when individual-level data cannot be shared across regions for analysis, meta-analysis of pooled estimates from a distributed network analysis is a satisfactory alternative.

Chapter 2. Changing Trends of Health Services Use and Surgeries in Ontario Children with Inflammatory Bowel Disease: A Population-based Cohort Study

2.1 Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting disease primarily affecting the gastrointestinal tract. The two most common types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). While IBD is usually diagnosed in early adulthood, the incidence of IBD is rising rapidly in children.[76] Current IBD care aims to manage symptoms of the disease because there is no present cure.

IBD costs the Canadian health care system an estimated $1.28 billion annually; this includes the costs of medication, hospitalizations, surgeries, outpatient visits, and emergency department visits.[2] Because mortality from IBD is low, children with IBD live with their disease for a long time and, therefore, will likely require more care over the course of their life, resulting in greater costs to the health care system over their lifespan compared with individuals diagnosed at older ages. In addition, IBD during childhood presents unique challenges including delayed growth, increased school absenteeism, and impaired psychosocial wellbeing.[19,23,26–28,116]

Recent years have seen numerous changes in the care of pediatric IBD patients, including, but not limited to, increased specialist care,[100] the introduction and proliferation of biologic therapies, and improved diagnostic capacities. The impact of these improvements on

health care utilization among children with IBD remain uncertain. A previous study found that the odds of hospitalization has increased in Ontario children with IBD but the frequency of hospitalizations has remained stable.[78] Further, temporal trends in emergency department (ED) visits have not been well documented[76] and the frequency of outpatient visit rates remained stable between 1994 and 2004.[78] A systematic review and meta-analysis reported decreasing surgical outcomes among IBD patients over the past half-century.[8] Decreasing rates of intestinal resection among children with CD in Ontario have been reported, while rates of colectomy in children with UC have been stable in Ontario[78] but decreased in other Canadian provinces.[91,118]

As the prevalence of IBD among Ontario children continues to rise,[13] the care of these children will place an increasingly heavy burden on the Ontario health care system. Updated health services utilization trends are necessary for health care decision makers to understand the current and future health care needs of IBD children and prepare cost-effective measures of meeting these needs. Thus, I aimed to assess the temporal trends of health services utilization and surgeries among Ontario children with IBD.

2.2 Methods

The study was approved by the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board.

2.2.1 Study Design and Setting

I conducted a population-based retrospective matched cohort study using health administrative data hosted at ICES to determine changes in hospitalizations, ED visits, outpatient visits, and the need for surgery over time in children newly diagnosed with IBD between 1 April 1994 and 31 March 2013 in Ontario, Canada.

2.2.2 Data Sources

Health administrative data is routinely collected by the Province of Ontario's Ministry of Health and Long-Term Care (MOHLTC) in the process of administering the universal publicly funded health care system, providing a wealth of information on health services use. ICES is a not-for-profit research institute that holds Ontario health data, and other population data, in compliance with legal and privacy requirements. Data include information on demographics, outpatient visits, hospitalizations, outpatient procedures (*e.g.*, colonoscopy), and ED visits. Patients can be deterministically linked across databases using an encrypted unique identifier, enabling longitudinal tracking of patients over time, and cross-sectional tracking of patients across databases.

Office-based outpatient visit records were acquired from the Ontario Health Insurance Plan (OHIP) physician claims database. OHIP is the publicly funded universal provincial health care plan provided to all legal Ontario residents (>99% of the population). The OHIP database collects fee-for-service and shadow billing records from physicians and nurse practitioners, and, therefore, provides an accurate representation of health services use. Physician billings for medical procedures (*e.g.*, colonoscopy) are also included in the OHIP physician claims database. The ICES Emergency Claims database (ERCLAIM) includes physician billings for patients seen in the ED and is derived from the OHIP physician claims data. For OHIP and ERCLAIM data, one diagnosis is assigned per patient visit, using an abbreviated 3-digit version of the International Classification of Disease, 9th Revision (ICD-9) coding system.

Data on hospitalizations and surgeries were obtained from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), which collects data abstracted from patients' medical charts at discharge by professional, certified medical coders. This database includes up to 25 diagnostic codes and 20 intervention codes related to the hospitalization. Medical diagnoses are coded using the International Classification of Disease, 9th Revision (ICD-9) system prior to 1 April 2002 and the ICD-10 (ICD 10th revision) system thereafter. Data additionally capture whether each diagnosis was the reason for admission (most responsible or contributing), comorbidity, and any additional diagnoses made while in hospital. Interventions are coded using the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) prior to 1 April 2002 and the Canadian Classification of Health Interventions (CCI) thereafter and include any diagnostic or therapeutic interventions that occurred during the hospitalization, such as endoscopic procedures and surgeries.

Sociodemographic data were derived from the Registered Persons Database (RPDB), which includes date of birth, sex, postal code, and eligibility for OHIP (updated bi-monthly).

2.2.3 Study Participants

I identified all children from 6 months to <18 years of age at diagnosis with IBD from Ontario health administrative data. All incident cases of pediatric-onset IBD in Ontario were included from the Ontario Crohn's and Colitis Cohort (OCCC). The OCCC was created from health administrative data using a two-step validated algorithm.[13] Children who underwent endoscopic evaluation (sigmoidoscopy or colonoscopy) were considered to have IBD if they also had four physician contacts or two hospitalizations with an associated diagnostic code for IBD (CD: ICD-9 555.x, ICD-10 K50.x; UC: ICD-9 556.x, ICD-10 K51.x) within three years of the first health care contact. Children who did not undergo endoscopic evaluation were classified as having IBD if they had seven outpatient physician contacts or three hospitalizations with associated IBD diagnosis codes. The date of the first health care contact with an IBD diagnostic code was considered the date of diagnosis.

The algorithm identified IBD in Ontario children with the following diagnostic accuracies: sensitivity 89.6-91.1%, specificity 99.5-100%, positive predictive value (PPV) 59.2-76.0%, and negative predictive value (NPV) 99.9-100%. The validated algorithm further differentiated CD and UC based on the last five of seven outpatient visits with diagnostic accuracies of: sensitivity 95.1%, specificity 86.0%, PPV 92.0%, and NPV 91.2%.[13] When the algorithm could not identify the IBD subtype, the patient was assigned a diagnosis of IBD type unclassifiable (IBD-U). To distinguish incident from prevalent cases, patients required a three-year lookback period in which they had no contacts with IBD diagnostic codes.[13]

Children with IBD were matched to five children without IBD based on age, sex, rural/urban household, and mean neighbourhood income quintile at the time of IBD diagnosis. Children without IBD were eligible for OHIP for at least as long as their matched IBD patient. A total of 6.9% of children with IBD did not have five matched children without IBD, and 23 (0.4%) children with IBD were unmatched to any children without IBD. Children with IBD who had no matches to children without IBD were excluded only from the analyses of all-cause health services use outcomes (see section 2.2.5, below). Characteristics of the children with IBD that could not be matched are described in Appendix A.

Children with and without IBD were excluded from the sample if they were missing information on date of birth, sex, and postal codes. Residents of the South East LHIN were excluded due to inconsistencies in OHIP shadow-billings. Children were followed from their date of diagnosis to either (a) death, (b) end of follow up (31 March 2016), (c) migration out of Ontario, or (d) end of OHIP eligibility.

2.2.4 Exposure

The exposure was the fiscal year (FY, April 1 to March 31) of IBD diagnosis (FY 1994-2012, 1 April 1994 to 31 March 2013). The non-IBD controls (children without IBD) were assigned an index date corresponding to the date their matched IBD patient was diagnosed with IBD. FY of diagnosis, or index, was modelled as a linear continuous variable, except when the data suggested an inflection point. In these cases, a spline was used (see Section 2.2.6.4, below).

2.2.5 Outcomes

I described IBD-specific, IBD-related, and all-cause health services use including outpatient clinic visits, ED visits, and hospitalizations. IBD-specific visits were those with an associated diagnosis code of IBD (ICD-9: 555, 556; ICD-10: K50, K51). IBD-related visits included visits with IBD-specific diagnoses, in addition to those with diagnoses of signs, symptoms, and extra-intestinal manifestations of IBD (Appendix B).[76,78,98] In the analyses evaluating hospitalization admissions for IBD-specific or IBD-related diagnoses, the hospitalization encounter was only included if the IBD-specific or IBD-related diagnosis code was the most responsible for the hospitalization or the first, second, or third transfer between hospitalizations or services within the same hospital, or if it was a contributing diagnosis, such as if the diagnosis was a pre-admit or post-admit comorbidity.

I determined the number of each type of encounters per person per year for each health services outcome and the time to the first hospitalization or ED visit. Analyses restricted to patients with IBD evaluated trends in IBD-specific and IBD-related health care encounters. Analyses comparing children with and without IBD included health care encounters for any reason (all-cause). Only health services and surgeries occurring on or after the diagnosis date were included.

I included only hospitalizations with a length of stay ≥48 hours because hospitalizations for <48 hours may have represented a hospitalization for the sole purpose of facilitating bowel preparation for colonoscopy or to facilitate rapid access to biologic medication in these children, and not hospitalization for disease activity and management. In addition, I counted only one hospitalization per episode of care, and therefore a transfer between hospitals was considered a single hospitalization.

For multiple ED visit claims on a given day only one ED visit was considered per day. For outpatient visits, only office-based visits were included. Outpatient visits with an associated infusion, telephone, or tele-medicine code were excluded (Appendix C) to ensure only true outpatient encounters were counted and that trends were not influenced by encounters solely for the purposes of administering an infusion or due to the increased availability of tele-medicine. If a patient had multiple outpatient visit claims in one day, only one outpatient claim was counted for that day.

I also determined whether the patient underwent surgery and the time to first intestinal resection (in CD patients)[114] or colectomy (in UC patients)[142] using previously validated codes to identify surgeries (Appendix D).

2.2.6 Statistical Analysis

2.2.6.1 Regression Models

I reported the characteristics of children included in the study as means with standard deviations (SD), medians with interquartile range (IQR), or proportions, where appropriate. I determined the associations between year of diagnosis and health services use using multivariate maximum-likelihood regression models for count, dichotomous, and time-to-event data. The statistical models used to assess temporal trends in health services use and surgeries are summarized in Table 2.1 and 2.2. I used these models to: (a) determine trends over time of health services use for IBD-specific and IBD-related reasons in children with IBD overall (including IBD-U patients) and stratified by disease type (CD and UC) (excluding IBD-U patients), and (b) compare the trends in all-cause health services use in IBD children to matched children without IBD, who served as the reference population.

Since most Poisson regression models were overdispersed (Pearson χ^2 statistic>1.5),[143] negative binomial regression models were used to account for the overdispersion. In cases where the negative binomial regression models did not converge, Poisson regression was used. Children were followed for 1, 3, and 5 years from the diagnosis or index date in these models, and follow up time was accounted for by setting the offset equal to the natural log of the follow up. I used logistic regression models to assess collinearity among predictors at a maximum variance inflation factor of 2.5.[144,145] Children were followed for 1, 3, and 5 years from the diagnosis or index date in logistic regression models, and patients with incomplete follow up in these models were excluded from these analyses. The Cox proportional hazard assumption was assessed by visual inspection of plots and hypothesis testing using time-varying covariates (Appendices E & F); ties were handled using the exact method because I expected a relatively large number of ties. Patients were followed for 5 years and were censored for either incomplete follow up or end of study period in Cox proportional hazards regression models.

For all models, effect estimates (incidence rate ratios, odds ratios, and hazard ratios) were considered statistically significant if their 95% confidence intervals did not cross the null value of one. The annual change in the outcomes for every one-year increase in diagnosis date was reported as the average annual percentage change (APC), which was calculated by subtracting one from the exponentiated beta-coefficient ($e^{\beta} - 1$).

2.2.6.2 Handling of Missing Data

The regression models excluded patients with missing information on the covariates (children with IBD, n=12; children without IBD, n=26). Children with IBD who could not be

matched to ≥1 non-IBD control (n=23) were excluded from the analyses comparing time trends between patients with and without IBD.

2.2.6.3 Confounding and Effect Measure Modification

Independent variables with potential confounding effects on the association between the exposure and outcome were chosen *a priori* due to their known associations with IBD[12,13,29,54] or health services use.[76,77,98] These variables were: age (dichotomized into 10 years of age or over versus under 10 years of age),[146] sex (male versus female), rural/urban residence (urban versus rural, as defined according to the census definition), and mean neighbourhood income quintile (a five level categorical variable that is a validated approximation of household income)[147] at the date of IBD diagnosis or index date. In the analyses evaluating IBD-specific and IBD-related events in IBD patients (as well as CD and UC subgroups), these confounding variables were included as covariates in each regression model. In the analyses comparing trends in overall health services use between children with and without IBD, the confounding variables were not included since the two populations had been matched on those variables. However, a variable indicating whether the patient had an IBD diagnosis (present versus absent) was included as an additional independent predictor in the analyses of all-cause health services use in children with and without IBD. To determine if the trends between children with and without IBD were different from each other, an interaction term (tested at α=5%) between the year of diagnosis and IBD diagnosis was included.

Effect measure modification between predictors and covariates was assessed at a 5% significance level. Inconsistent statistically significant effect measure modification terms within and across outcomes and models were determined to be a result of random chance due to the

large number of analyses conducted. Effect measure modification terms that were consistently statistically significant within or across outcomes and models were investigated by plotting average annual event rates against time and were determined to have been driven by small cells. As a result, no additional effect measure modification terms were included in the models.

2.2.6.4 Identification and Inclusion of Inflection Points in Exposure Variable

I assessed temporal trend linearity using two methods. The first was a hypothesis test (Kolmogorov-type supremum test of the cumulative martingale residuals at α=5%) in Cox proportional hazards regression models. I also generated plots (Appendix G) to visually assess if the association between fiscal year and the outcomes was linear (*i.e.,* increased or decreased consistently over time). When plots appeared to deviate from linearity, I identified any statistically significant inflection points (α=5%) using Joinpoint Regression Program, Version 4.6.0.0 – April 2018; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute. Preliminary plots of outpatient visit counts per person per year were the only plots suggesting that changes over time were non-linear (*i.e.,* that there were inflection points). These inflection points mostly occurred around 2005 in children with IBD and 1997 in children without IBD. While the knot in year 1997 in children without IBD may have been associated with a change in Ontario's governmental policy, the year 2005 was a notable time in the changes to care in pediatric IBD patients because it was when the first biologic therapies began being used in children.[148] When I allowed for two knots in the rate of IBD-specific outpatient visits occurring within one year of diagnosis in IBD patients, a second knot appeared at 1997, which suggests the 1997 knot was less prominent than the 2005 knot in IBD

patients. I therefore restricted Poisson/negative binomial regression models of changes in the rate of outpatient visits to splines with a knot at 2005.

All statistical analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, North Carolina, USA).

Table 2.1 The multivariable regression models used to assess time trends in health services and surgical outcomes among children with inflammatory bowel disease in Ontario.

Type of Data	Regression Model*	Follow up from diagnosis date (y)	Effect estimate	Population	Exposure	Outcome
Count (Number of events per person per year)	Negative binomial	1, 3, 5	IRR	IBD, CD, UC	Year of diagnosis (linear)	IBD-specific hospitalizations, IBD-related hospitalizations
						IBD-specific ED visits, IBD-related ED visits
					Year of diagnosis (knot at 2005)	IBD-specific outpatient visits, IBD-related outpatient visits
Binary (Event did or did not occur)	Logistic	1, 3, 5	OR	CD	Year of diagnosis (linear)	Intestinal resection
				UC	Year of diagnosis (linear)	Colectomy
Time to first event	Cox proportional hazard	5	HR	IBD, CD, UC	Year of diagnosis (linear)	IBD-specific hospitalizations, IBD-related hospitalizations

Type of Data	Regression Model*	Follow up from diagnosis date (y)	Effect estimate	Population	Exposure	Outcome
						IBD-specific ED visits, IBD–related ED visits
				CD	Year of diagnosis (linear)	Intestinal resection
				UC	Year of diagnosis (linear)	Colectomy

*All models adjusted for age (10y or older versus <10y), sex (female versus male), rural/urban residency, and mean neighbourhood income quintile.

Abbreviations: CD, Crohn's disease; ED, emergency department visits; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; OR, odds ratio; UC, ulcerative colitis; y, years

Table 2.2 The multivariable regression models used to assess and compare time trends in health services outcomes among children with and without inflammatory bowel disease in Ontario.

Type of Data	Regression Model*	Follow up from diagnosis date (y)	Effect estimate	Population	Exposure	Outcome
Count (Number of events per person per year)	Negative binomial	1, 3, 5	IRR	With and without IBD	Year of diagnosis or index date (linear)	All-cause hospitalizations†
						All-cause ED visits
					Year of diagnosis or index date (knot at 2005)	All-cause outpatient visits
Time to first event	Cox proportional hazards	5	HR	With and without IBD	Year of diagnosis or index date (linear)	All-cause hospitalizations
						All-cause ED visits

*All models adjusted for IBD diagnosis (Y/N) and included an interaction term between year of diagnosis and IBD diagnosis to compare trends in children with and without IBD.

†Poisson regression was run for all-cause hospitalizations within 1 year of diagnosis.

Abbreviations: CD, Crohn's disease; ED, emergency department; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; UC, ulcerative colitis; y, years

2.3 Results

2.3.1 Descriptive Statistics

I included 5,518 children with IBD matched to 26,677 children without IBD (Table 2.3). Of included IBD patients, 3,122 (56.6%) were male and they had a mean (SD) age of 13.1 (3.6) years at diagnosis. The median length (IQR) of follow up was 10.1 (5.0) years for children with IBD and 10.4 (5.0) years for children without IBD. Of the children diagnosed with IBD, 58.2% had CD and 35.3% had UC. The algorithm could not identify the IBD type in the remaining 6.5% of IBD children and assigned to these children an "IBD type unclassifiable" diagnosis.

Table 2.3 Characteristics of children with and without IBD included in the study.

Characteristics		IBD (n=5,518)	Non-IBD (n=26,677[a])
Sex	Females	2,396 (43.4%)	11,573 (43.4%)
	Males	3122 (56.6%)	15,104 (56.6%)
Age at IBD diagnosis or index date[b] (years)	Mean (SD)	13.1 (3.6)	13.1 (3.6)
	Median (IQR)	14.0 (5.0)	14.0 (5.0)
Diagnosis	CD	3212 (58.2%)	N/A
	UC	1945 (35.3%)	N/A
	IBD-U	361 (6.5%)	N/A
Rural residence at diagnosis	Urban	4929 (89.3%)	24,630 (92.3%)
	Rural	583 (10.6%)	2,041 (7.7%)
	Missing	6 (0.1%)	6 (0.02%)
Neighbourhood income quintile at diagnosis	First (Lowest)	714 (12.9%)	3,412 (12.8%)
	Second	928 (16.8%)	4,467 (16.7%)
	Third	1092 (19.8%)	5,256 (19.7%)
	Fourth	1285 (23.3%)	6,275 (23.5%)
	Fifth (Highest)	1487 (27.0%)	7,258 (27.2%)
	Unknown	12 (0.2%)	9 (0.03%)
Length of follow up (years)	Mean (SD)	11.0 (5.4)	11.3 (5.4)
	Median (IQR)	10.1 (8.9)	10.4 (9.1)
	Minimum	0.4	2.1
	Maximum	22.0	22.0

[a]6.9% of children with IBD did not have five controls

[b]Date of diagnosis in IBD patients, and the same date in matched non-IBD patients.

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, IBD type unclassifiable; IQR, interquartile range; N/A, not applicable; SD, standard deviation; UC, ulcerative colitis

2.3.2 Time Trends in Health Services Utilization

2.3.2.1 Hospitalizations

The rate of IBD-specific hospitalizations within one, three, and five years of diagnosis declined over time by -1.9% (95% CI -2.7 to -1.0%), -2.4% (95% CI -3.3 to -1.9%), and -2.5% (95% CI -3.2 to -1.8%) per year, respectively (Table 2.4). IBD-related hospitalization rates similarly declined in IBD patients. In subgroup analyses, similar decreases were observed in children with CD but less consistently in children with UC. In children with UC, IBD-specific and IBD-related hospitalization rates decreased within three years of diagnosis (IBD-specific: -1.5%, 95% CI -2.9 to -0.0001%; IBD-related: -1.8%, 95% CI -3.2 to -0.3%) and IBD-related rates decreased within five years of diagnosis (-1.4%, 95% CI -2.8 to -0.0004%). The rate of hospitalizations among children with UC within one year of diagnosis for combined IBD-specific and IBD-related reasons, and within five years of diagnosis for IBD-specific reasons did not decrease significantly.

Rates of all-cause hospitalizations within one, three, and five years of diagnosis decreased by -1.8% (95% CI -2.4 to -1.2%), -2.6% (95% CI -3.3 to -1.8%), and -2.7% (95% CI -3.3 to -1.8%) per year in children with IBD and by -2.8% (95% CI -4.6 to -0.9%), -3.4% (95% CI -4.4 to -2.3%), and -4.3% (95% CI -5.1 to -3.5%) per year, respectively, in children without IBD (Table 2.5). Compared to children with IBD, children without IBD experienced a larger magnitude of decrease in rates of hospitalizations within five years from the index date, but not within one or three years of the index date (one-year interaction term p=0.35; three-year interaction term p=0.23; five-year interaction term p=0.003).

The hazard of first IBD-specific hospitalization decreased by -1.8% (95% CI -2.4 to -1.0%) per year in IBD patients; a comparable decline was seen in the hazard of first IBD-related

hospitalization (Table 2.6). A similar trend was observed in subgroup analyses in CD patients. However, in UC patients, the decrease in hazard was less pronounced. It was statistically significant for IBD-specific hospitalizations (-1.3%, 95% CI -2.5 to -0.1%) but not IBD-related hospitalizations (-1.2%, 95% CI -2.4 to 0.0%). The hazard of any type of hospitalization decreased faster in children without IBD (-4.0%, 95% CI -4.8 to -3.1%) compared with IBD patients (-1.6%, 95% CI -2.3 to -1.0%; interaction term $p<0.0001$) (Table 2.7).

2.3.2.2 Emergency Department Visits

IBD-specific ED visit rates did not change over time. However, IBD-related ED visit rates within one, three, and five years of diagnosis increased by +1.8% (95% CI +0.8 to +2.8%), +1.4% (95% CI +0.6 to +2.2%), and +1.5% (95% CI +0.7 to +2.3%) per year, respectively (Table 2.4). This trend was seen in CD patients, while only rates of IBD-related ED visits within five years of diagnosis increased (+2.0%, 95% CI +0.7 to +3.3%) in UC patients.

Rates of ED visits for any reason increased slightly among IBD patients for visits within three (+0.8%, 95% CI +0.1 to +1.6%) and five years of diagnosis (+1.0%, 95% CI +0.3 to +1.6%); the rate of ED visits within one year of diagnosis remained stable (+0.8%, 95% CI -+0.03 to +1.7) (Table 2.5). In children without IBD, the rate of any type of ED visit within one year of diagnosis slightly decreased (-0.7%, 95% CI -1.2 to -0.2%), but the rates within three and five years of diagnosis remained unchanged (three-year: -0.3%, 95% CI -0.7 to 0.0%; five-year: -0.2%, 95% CI -0.5 to +0.1%).

The hazard of the first IBD-specific ED visit was stable over time (-0.2%, 95% CI -1.1 to +0.7%) and increased for IBD-related ED visits (+0.9%, 95% CI +0.3 to +1.6%) (Table 2.6). The

trend of increasing hazard of first ED visit for IBD-related reasons was also observed in children with CD, but in children with UC the hazard of first ED visit for IBD-related reasons remained stable over time.

The hazard of first ED visit for any reason within five years of diagnosis decreased slightly in children without IBD (-0.6%, 95% CI -0.9 to -0.3%) but remained stable in IBD patients (+0.4%, 95% CI -0.1 to +1.0%; interaction term p=0.003) (Table 2.7).

2.3.2.3 Outpatient Visits

In children diagnosed with IBD in 2005 or earlier, rates of IBD-specific and IBD-related outpatient visits within one year of diagnosis decreased by -1.3% (95% CI -1.9 to -0.6%) and -2.1% (95% CI -2.7 to -1.5%) per year, respectively (Table 2.4). IBD-related outpatient visits within three (-1.2%, 95% CI -1.7 to -0.6%) and five years (-0.9%, 95% CI -1.5 to -0.3%) from diagnosis also decreased in these children. The three- and five-year IBD-specific outpatient visit rates remained stable (three-year: +0.1%, 95% CI -0.5 to +0.1%; five-year: +0.6%, 95% CI 0.0 to +1.2%). These trends were also generally observed in children with CD and UC. However, UC children diagnosed in 2005 or earlier had increasing rates of IBD-specific outpatient visits within five years of diagnosis (+1.1%, 95% CI +0.1 to +2.1%), while rates of IBD-related outpatient visits within five years of diagnosis remained unchanged (-0.7%, 95% CI -1.7 to +0.3%).

Among children diagnosed with IBD after 2005, IBD-specific outpatient visit rates within one, three, and five years of diagnosis increased by +6.0% (95% CI +5.0 to +6.9%), +3.9% (95% CI +3.0 to +4.8%), and +4.0% (95% CI +3.1 to +4.9%) per year. IBD-related visits increased by

+3.7% (95% CI +2.7 to +4.6%), +2.2% (95% CI +1.4 to +3.1%), and +2.8% (95% CI +1.9 to +3.7%) per year. A similar trend was observed in the CD and UC subgroups.

In both children with and without IBD with a diagnosis or index date in or before 2005, there were similar decreases in rates of any type of outpatient visit within one year of diagnosis (children with IBD: -1.2%, 95% CI -2.0 to +0.4%; children without IBD: -1.8, 95% CI -2.2 to -1.4%; interaction term p=0.19) (Figure 2.1; Table 2.5). The frequency of outpatient visits within three and five years decreased for children without IBD (three-year: -1.8%, 95% CI -2.1 to -1.4%, and five-year: -1.6%, 95% CI -1.9 to -1.2%), but not in children with IBD (three-year: -0.6%, 95% CI -1.3 to +0.2%; five-year: -0.7%, 95% CI -1.5 to +0.1%). The differences in these rates between children with and without IBD were statistically significant (three-year interaction term p=0.003; five-year interaction term p=0.03).

In children diagnosed with IBD after 2005, there were annual increases of +3.2% (95% CI +1.9 to +4.4%), +1.5% (95% CI +0.4 to +2.7%), and +2.1% (95% CI +1.0 to +3.2%) in the rates of any type of outpatient visits within one, three, and five years of diagnosis. The frequency of outpatient visits among children without IBD with an index date after 2005 remained stable for visits within three and five years of the index date (one-year: -0.3%, 95% CI -0.9 to +0.4%; three-year: -0.4%, 95% CI -1.0 to +0.1%) but decreased for visits within five years of the index date (-0.7%, 95% CI -1.2 to -0.2%). However, the time trends in the frequency of outpatient visits were only statistically different between children with and without IBD within one year of diagnosis (one-year interaction term: p=0.005; three-year interaction term: p=0.32; five-year interaction term: p=0.71).

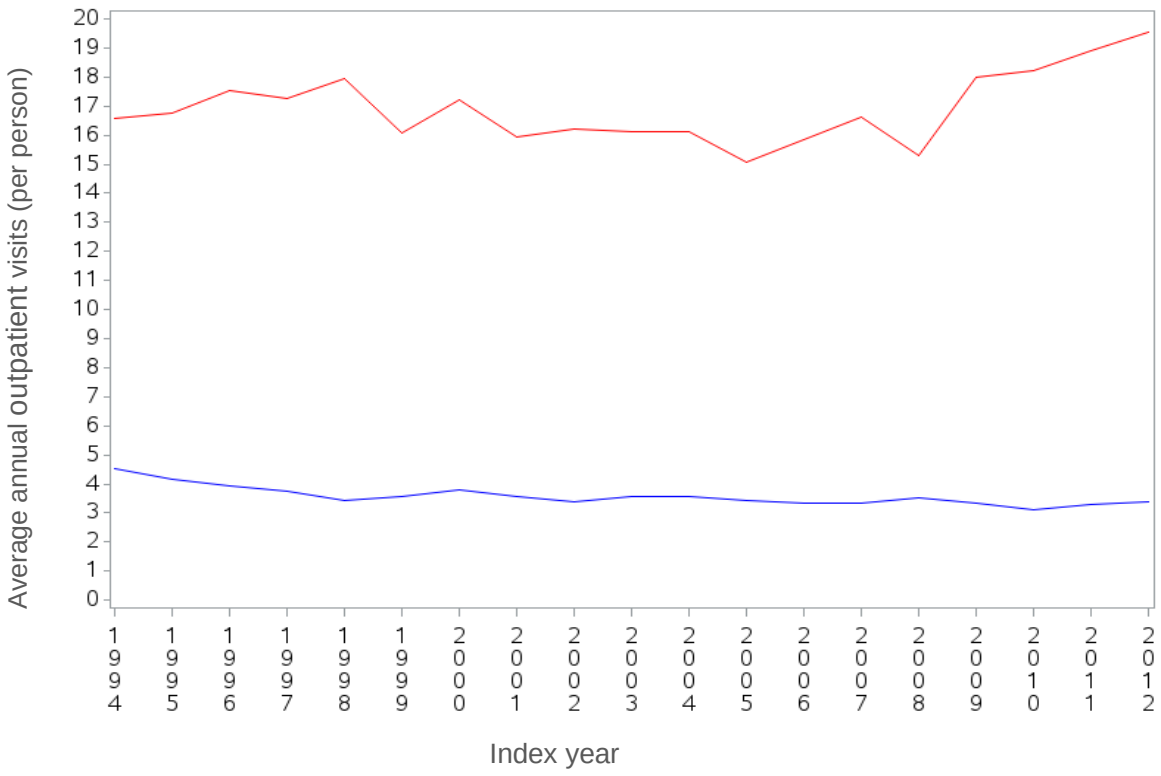


Figure 2.1 The plot of average all-cause outpatient visit counts among children with (red) and without (blue) IBD within one year of diagnosis per person per year for each fiscal year of diagnosis or index.

Table 2.4 The adjusted incidence rate ratios (95% confidence intervals) of IBD-specific and IBD-related health services use for a one year increase in year of diagnosis from adjusted negative binomial regression models for children with inflammatory bowel disease, overall and stratified by disease subtype.

Outcome	**Follow up from diagnosis (years)**	**Spline**†	**IBD** (*n*=5506)		**CD** (*n*=3205)		**UC** (*n*=1940)	
			IBD-specific	IBD-related	IBD-specific	IBD-related	IBD-specific	IBD-related
Hospitalizations	1	N/A	**0.981 (0.973-0.990)**	**0.981 (0.973-0.990)**	**0.982 (0.972-0.992)**	**0.982 (0.972-0.992)**	0.986 (0.970-1.002)	0.984 (0.969-1.000)
	3	N/A	**0.974 (0.967-0.982)**	**0.974 (0.966-0.981)**	**0.971 (0.962-0.980)**	**0.971 (0.962-0.980)**	**0.985 (0.971-0.9999)**	**0.982 (0.968-0.997)**
	5	N/A	**0.975 (0.968-0.982)**	**0.974 (0.967-0.982)**	**0.970 (0.962-0.979)**	**0.970 (0.962-0.979)**	0.989 (0.975-1.003)	**0.986 (0.972-0.9996)**
ED visits	1	N/A	1.003 (0.990-1.016)	**1.018 (1.008-1.028)**	1.010 (0.994-1.027)	**1.020 (1.007-1.034)**	0.986 (0.964-1.009)	1.012 (0.995-1.030)
	3	N/A	1.000 (0.990-1.011)	**1.014 (1.006-1.022)**	1.003 (0.989-1.016)	**1.015 (1.004-1.026)**	0.995 (0.977-1.014)	1.013 (0.999-1.027)
	5	N/A	1.002 (0.993-1.012)	**1.015 (1.007-1.023)**	1.002 (0.990-1.014)	**1.013 (1.003-1.023)**	1.003 (0.985-1.021)	**1.020 (1.007-1.033)**
Outpatient visits	1	Before 2005	**0.987 (0.981-0.994)**	**0.979 (0.973-0.985)**	**0.989 (0.982-0.997)**	**0.982 (0.974- 0.990)**	**0.983 (0.973-0.994)**	**0.977 (0.966-0.987)**
		After 2005	**1.060 (1.050-1.069)**	**1.037 (1.027-1.046)**	**1.056 (1.044-1.068)**	**1.038 (1.026-1.050)**	**1.069 (1.053-1.086)**	**1.030 (1.014-1.046)**

Outcome	Follow up from diagnosis (years)	Spline†	**IBD** (*n*=5506)		**CD** (*n*=3205)		**UC** (*n*=1940)	
			IBD-specific	IBD-related	IBD-specific	IBD-related	IBD-specific	IBD-related
	3	Before 2005	1.001 (0.995-1.001)	**0.988 (0.983-0.994)**	0.999 (0.992-1.006)	**0.990 (0.983-0.997)**	1.004 (0.993-1.014)	**0.988 (0.978-0.998)**
		After 2005	**1.039 (1.030-1.048)**	**1.022 (1.014-1.031)**	**1.034 (1.023-1.046)**	**1.021 (1.010-1.032)**	**1.053 (1.038-1.069)**	**1.026 (1.011-1.041)**
	5	Before 2005	1.006 (1.000-1.012)	**0.991 (0.985-0.997)**	1.004 (0.996-1.011)	**0.991 (0.984-0.998)**	**1.011 (1.001-1.021)**	0.993 (0.983-1.003)
		After 2005	**1.040 (1.031-1.049)**	**1.028 (1.019-1.037)**	**1.033 (1.022-1.045)**	**1.024 (1.013-1.035)**	**1.057 (1.042-1.073)**	**1.035 (1.021-1.050)**

†Before 2005 inclusive of the 2005 fiscal year.

Incidence rate ratios were obtained using negative binomial regression models.

Abbreviations: CD, Crohn's Disease; ED, emergency department; IBD, inflammatory bowel disease; N/A, not applicable; UC, ulcerative colitis.

Significant findings are indicated in bold font.

Table 2.5 The incidence rate ratios (95% confidence intervals) of all-cause health services use for a one year increase in year of diagnosis, or index, for children with and without inflammatory bowel disease.

Outcome	**Follow up from diagnosis (years)**	**Spline**†	**IBD** (*n*=5495)‡	**Without IBD** (*n*=26,677)	**Difference in rate changes between patients with and without IBD**
Hospitalizations	1*	N/A	**0.982 (0.976-0.988)**	**0.972 (0.954-0.991)**	p=0.35
	3	N/A	**0.974 (0.967-0.982)**	**0.966 (0.956-0.977)**	p=0.23
	5	N/A	**0.974 (0.967-0.982)**	**0.957 (0.949-0.965)**	**p=0.0028**
ED visits	1	N/A	1.008 (0.9997-1.017)	**0.993 (0.988-0.998)**	**p=0.0026**
	3	N/A	**1.008 (1.001-1.016)**	0.997 (0.993-1.0002)	**p=0.0034**
	5	N/A	**1.010 (1.003-1.016)**	0.998 (0.995-1.001)	**p=0.0013**
Outpatient visits	1	Before 2005	**0.988 (0.980-0.996)**	**0.982 (0.978-0.986)**	p=0.19
		After 2005	**1.032 (1.019-1.044)**	0.997 (0.991-1.004)	**p=0.0046****
	3	Before 2005	0.994 (0.987-1.002)	**0.982 (0.979-0.986)**	**p=0.0034**

Outcome	Follow up from diagnosis (years)	Spline†	IBD (*n*=5495)‡	Without IBD (*n*=26,677)	Difference in rate changes between patients with and without IBD
		After 2005	**1.015**	0.996	p=0.32**
			(1.004-1.027)	(0.990-1.001)	
	5	Before 2005	0.993	**0.984**	**p=0.03**
			(0.985-1.0003)	**(0.981-0.988)**	
		After 2005	**1.021**	**0.993**	p=0.71**
			(1.010-1.032)	**(0.988-0.998)**	

†Before 2005 inclusive of the 2005 fiscal year.

‡ Excludes children with IBD who were unmatched to any children without IBD.

*Poisson regression model used instead of negative binomial regression due to failure in model convergence. Pearson χ_2=1.4.

**P-values from likelihood ratio test for any difference in rates between children with and without IBD.

Incidence rate ratios were obtained from negative binomial regression models.

Abbreviations: CD, Crohn's Disease; ED, emergency department; IBD, inflammatory bowel disease; N/A, not applicable; UC, ulcerative colitis.

Significant findings are indicated in bold font.

Table 2.6 The adjusted hazard ratios (95% confidence intervals) of first IBD-specific and -related health services use within five years of diagnosis for a one year increase in year of diagnosis for children with inflammatory bowel disease, overall and stratified by disease subtype.

Outcome	**IBD** (*n*=5506)		**CD** (*n*=3205)		**UC** (*n*=1940)	
	IBD-specific	IBD-related	IBD-specific	IBD-related	IBD-specific	IBD-related
Hospitalization	**0.982 (0.975-0.989)**	**0.983 (0.976-0.990)**	**0.982 (0.974-0.991)**	**0.982 (0.974-0.991)**	**0.987 (0.975-0.999)**	0.988 (0.976-1.000)
ED visit	0.998 (0.989-1.007)	**1.009 (1.003-1.016)**	0.997 (0.986-1.009)	**1.010 (1.002-1.019)**	0.999 (0.984-1.015)	1.010 (0.998-1.022)

Hazard ratios were obtained from Cox proportional hazards regression models.

Abbreviations: CD, Crohn's Disease; ED, emergency department; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Significant findings are indicated in bold font.

Table 2.7 The hazard ratios (95% confidence intervals) of all-cause health services use for a one year increase in year of diagnosis, or index, for children with and without inflammatory bowel disease.

Outcome	**IBD** (*n*=5495) ‡	**Without IBD** (*n*=26677)	**Difference in changes between patients with and without IBD**
Hospitalization	**0.984 (0.977-0.990)**	**0.960 (0.952-0.969)**	**p<0.0001**
ED visit	1.004 (0.999-1.010)	**0.994 (0.991-0.997)**	**p=0.0025**

Hazard ratios were obtained from Cox proportional hazards regression models.

‡ Excludes children with IBD who were unmatched to any children without IBD.

Abbreviations: CD, Crohn's Disease; ED, emergency department; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Significant findings are indicated in bold font.

2.3.3 Time Trends in Surgical Outcomes

2.3.3.1 Intestinal resection

In CD patients, the odds of intestinal resection within one, three, and five years of diagnosis decreased by -5.8% (95% CI -8.0 to -3.5%), -6.1% (95% CI -7.7 to -4.4%), and -6.4% (95% CI -8.2 to -4.7%) per year, respectively (Table 2.8). The hazard of first intestinal resection within five years of diagnosis decreased by -6.0% (95% CI -7.3 to -4.6%) per year.

2.3.3.2 Colectomy

The odds of colectomy within one and three years of diagnosis in UC patients decreased by -3.8% (95% CI -7.2 to -0.2%) and -3.4% (95% CI -6.0 to -0.7%) per year, respectively, but the five-year colectomy odds remained stable (-2.2%, 95% CI -5.0 to +0.7%). The hazard of colectomy within five years of diagnosis decreased by -3.0% (95% CI -5.2 to -0.7%) per year.

Table 2.8 The adjusted odds ratios (OR), adjusted hazard ratios (HR), and 95% confidence intervals (CI) for intestinal resection in Crohn's disease and colectomy in ulcerative colitis patients for a one year increase in year of diagnosis.

Outcome	**Follow up from diagnosis date (years)**	**CD**	**UC**
OR (95% CI)	1	*n*=3204 **0.942 (0.920-0.965)**	*n*=1940 **0.962 (0.928-0.998)**
	3	*n*=3195 **0.939 (0.923-0.956)**	*n*=1931 **0.966 (0.940-0.993)**
	5	*n*=2742 **0.936 (0.918-0.953)**	*n*=1653 0.978 (0.950-1.007)
HR (95% CI)	5	*n*=3205 **0.940 (0.927-0.954)**	*n*=1940 **0.970 (0.948-0.993)**

Odds ratios were obtained from logistic regression models.

Hazard ratios were obtained from Cox proportional hazards regression models.

Abbreviations: CD, Crohn's Disease; CI, confidence interval; OR, odds ratio; HR, hazard ratio; UC, ulcerative colitis.

Significant findings are indicated in bold.

2.4 Discussion

2.4.1 The Importance of Assessing Temporal Trends in Inflammatory Bowel Disease Health Services Use

Over a period of time that has seen changes in the management of pediatric IBD, I observed decreasing trends in hospitalizations and surgeries. These decreases were accompanied by increasing outpatient and ED visits. These changes in health services utilization provide vital information for policy makers and care providers to plan for future health care demands for children with IBD as the landscape of IBD in Canada continues to evolve.

It is estimated that 10-20% of new IBD diagnoses occur among children, and the incidence of IBD is rising faster among children than any other age group.[149] There are currently 3000 Canadian children living with IBD – expected to rise to 7000 by 2030.[10,150] A greater number of children diagnosed with IBD will likely translate to more health care resources required to meet the needs of IBD patients. Patients with IBD use more health care services than healthy individuals, resulting in significantly higher costs to the health care system.[75] In 2018, the economic burden of IBD in Canada was estimated to be over $1.28 and $1.29 billion in direct and indirect costs, respectively.[2,3] Further, the differences between children with and without IBD have increased over time, with increasing outpatient visits and slower declines in hospitalization rates in children with IBD compared to children without IBD. Children with IBD will require ongoing care, and the costs of caring for these patients over the course of their lifetime are substantial. Understanding trends in health care utilization among children with IBD will ensure that our health care system is adequately prepared to care for the increasing number of children with IBD.

2.4.2 Study Findings on Temporal Trends of Health Services Use in Ontario Children Diagnosed with Inflammatory Bowel Disease

2.4.2.1 Hospitalizations

The number of hospitalizations per person per year, or rate, for IBD-specific, IBD-related, and for any (all-cause) reason decreased in children diagnosed with IBD between fiscal years 1994 and 2012. The change in the rate of time to first hospitalization (*i.e.*, hazard of hospitalization) for IBD-specific, IBD-related, and all-cause hospitalizations also decreased in children with IBD. These findings are consistent with previous Canadian studies reporting decreasing trends in hospitalization among children with IBD in Manitoba and with CD in Ontario[74,115] and adults with IBD in Ontario.[113,115] However, a previous Ontario study found overall rates of hospitalization had not changed between 1994 and 2004 and children diagnosed between 2001-2004 had higher odds of being hospitalized compared to those diagnosed at earlier times.[78] The present study was able to capture more recent trends and show that hospitalization rates among pediatric IBD patients have, in fact, declined over time.

Importantly, declines in all-cause hospitalizations were also observed in children without IBD, leaving it unclear whether the findings in IBD patients are related to IBD-specific interventions or other factors, such as general health care reforms, changing health care resources, or changing patient behaviour, but it does suggest systemic factors may be in part driving this decline – beyond changes to IBD care alone. Possible systemic factors include changes in pediatric-specific health care or government policy changes to the health system resulting in a reduced number of hospital beds and increased pressure to lower costs. In addition, the rates and hazards of hospitalization differed between children with and without IBD. Specifically, the magnitude of the decrease was larger in children without IBD after five years from diagnosis/index date, which suggests children with IBD may be less susceptible to secular

trends and pressures from policy-makers to reduce hospitalizations in Ontario during this time period.

Decreasing hospitalizations in Ontario have been reported since the 1980s. Between 1984 and 1994, the Ontario Ministry of Health increased its total funding for health services but reduced its funding for acute and chronic hospitals from 47% of total funding to 41%; 7,500 fewer hospital beds were filled during this time.[151] CIHI reported a 1.3% decrease in acute hospitalizations per year in Ontario between 1994 and 2010 compared with a national average of a 0.9% decrease.[152] Hospitalizations have also decreased for medical events requiring acute care[153–155] and chronic diseases such as multiple sclerosis[156,157] and rheumatoid arthritis.[158] In children, similar decreases have been reported in overall rates of hospitalizations in Ontario.[159] There was a 50% decrease in pediatric asthma hospitalization rates between fiscal years 2006 and 2015 across Canada;[160] hospitalizations among children with asthma and diabetes have also decreased in Ontario.[161,162] However, trends in the need for hospitalization among Ontario children with multiple sclerosis have been stable.[163] Decreasing trends in both adult and pediatric hospitalizations across diverse patient populations suggests that these decreases may result from initiatives aimed at reducing cost-intensive health services in Canada.

2.4.2.2 Emergency Department Visits

The rate of IBD-specific ED visits in children with IBD remained stable, but IBD-related visits became more frequent over time. In contrast to increasing rates of all-cause ED visits in children with IBD, ED visit rates decreased in children without IBD. The hazard of an ED visit within five years of diagnosis followed a similar pattern to the rates, except the hazard of all-cause ED visits, which was stable in children with IBD and decreased slightly in children

without IBD. These findings help fill a knowledge gap because temporal trends in ED visits among children with IBD in Canada are not well established. Internationally, increases in ED visits have been observed among children and adults with IBD;[101,104,164] however, the studies either reported absolute numbers of visits[164] or were cross-sectional in nature,[101,104] where patients could not be followed after visiting the ED. Therefore, trends in ED visits seen in these studies may reflect either true changes in health services use or changes in disease prevalence. In a previous study in Ontario, ED visit rates in CD patients decreased in both adults and children, which contrasts the findings in the present study, in which ED visit rates generally increased among children with CD.[115] This difference in findings may be a result of the use of different cohorts. My study used incident IBD patients because health service use is expected to be highest soon after the date of diagnosis.[77] However, Rahman, *et al.*[115], used prevalent cohorts, and it is possible that, while ED use is increasing in incident IBD patients diagnosed more recently, the ED use rates in prevalent IBD patients overall has been decreasing.

The rise in ED visits among children with IBD and divergent trends in ED visit use between children with IBD and without IBD may indicate ambulatory care needs among children with IBD are not being met. In children without IBD, sufficient outpatient and preventative care may have reduced the need for ED visit use over time.

In children with other chronic illnesses, ED visits have either remained stable or decreased. Specifically, ED visits in Ontario children with diabetes decreased,[165,166] while trends of ED visits in asthmatic children in the US remained stable.[167] Both these trends in children with other chronic diseases and the decreasing ED visit rates in children without IBD suggest the increasing ED visit use in children with IBD may be due to reasons related to their IBD. Children have presented to the ED for IBD care when their disease was severe, they needed care outside

of regular clinic hours, or were instructed to go to the ED by their care provider.[168] Furthermore, specific medications, namely corticosteroids and opioids, have been associated with ED use either because of side effects and complications or as indicators for patients with more severe disease.[103] However, care-takers may also influence the frequency at which children are seen at the ED. IBD-related ED visit use in children may have increased due to improved parental awareness of signs and symptoms associated with IBD or, alternatively, due to insufficient education among parents of children with IBD to understand when their child needs urgent care.

Increased IBD-related ED visits in children with IBD could also result from changes in physician practises, in which primary care providers send their patients with IBD to the ED more often because of a reluctance to care for patients with a disease where management strategies are rapidly evolving and increasing in complexity. The growing prevalence of IBD among children and increases in rates of outpatient visits may be outpacing the number of pediatric gastroenterologists, and families may believe that the ED provides the best opportunity for their child to access specialist care. Insufficient specialist care in outpatient settings has been associated with higher ED visit use in Ontario patients with IBD.[83,103] Observed ED visit frequencies, coupled with decreased hospitalizations, may reflect patients presenting to the ED without subsequent hospital admission. A US study found increases in the absolute numbers of ED visits but decreases in the proportion of children admitted to hospital.[104] The motivators for increased IBD-related ED visits in children is not clear and could result from one or a combination of the potential reasons described above.

2.4.2.3 Outpatient Visits

Our analysis of trends suggested an inflection point in 2005, meaning that trends in outpatient visits were different before and after this year. This coincided with the time in which infliximab first began being used in pediatric CD.[148] In children diagnosed between fiscal years 1994 and 2005, the rate of IBD-specific outpatient visits generally remained stable while IBD-related visit rates decreased. In this same time period, the rates of all-cause outpatient visits also remained stable in children with and without IBD. In children diagnosed with IBD since 2006, IBD-specific, IBD-related, and all-cause outpatient visit rates have increased; rates of all-cause outpatient visits were either stable (within one and three years of index) or decreasing (within five years of index) in children without IBD. The stable outpatient visit rates observed in children diagnosed between 1994-2005 in the present study are consistent with the stable outpatient visit rates in children diagnosed between 1994-2004 in the previous Ontario study.[78] However, my study provides new insights on the increasing trend in outpatient visit rates in children diagnosed with IBD more recently (after 2005).

The differences in increasing outpatient trends observed children with IBD but not in children without IBD suggest shifting patterns in health services use in IBD patients. These changing behaviours may indicate children with IBD may be monitored more frequently with the recent changes to IBD care, while children without IBD may have declining needs of frequent care by their health care provider.

Outpatient visits have been decreasing among all Ontario children.[102] The increasing trends in outpatient visits in children with IBD have also not been observed in children of other chronic diseases, such as multiple sclerosis[163] or asthma,[167,169] which suggests the increases in outpatient visits are unique to children with IBD. The increasing outpatient trends after 2005

could have been precipitated by changes in IBD care. One example of this change is a greater number of specialized care physicians available to IBD children.[78] Children diagnosed in or before 2005 may also have been more likely to be seen by an adult gastroenterologist in the later years of their care, who may be less available to see their patients than pediatric gastroenterologists. This could have resulted in the decreasing outpatient visits for IBD-related reasons before 2005. Following patients until 18 years of age, before the transition to adult care, may have provided further insight on the impact of transition in care. In addition, the more recent trend toward a treat-to-target approach in IBD,[148] and an increased proportion of patients on biologics may result in more frequent outpatient visits for monitoring of response to therapy and adverse effects. Increased monitoring of children with IBD in outpatient settings may be, in part, responsible for the decreasing need for hospitalization. Conversely, the decreasing hospitalizations could have resulted in increased compensatory outpatient visits after 2005 and IBD-related ED visits in IBD children. As with ED visits, it is possible the observed increased outpatient visits are due to a combination of reasons that were discussed above.

2.4.3 Study Findings on Temporal Trends of Surgical Outcomes in Ontario Children Diagnosed with Inflammatory Bowel Disease

The need for surgery has steadily decreased among children with both CD and UC, with substantial decreases in the need for intestinal resection among children with CD. These findings are consistent with previous studies demonstrating decreased need for surgery among children with CD[78] and adults with CD[170] and UC.[91,118] The need for colectomy in children with UC was previously shown to be stable in Ontario[78] but decreasing in Manitoba.[74] Though I did not identify an inflection point—indicating that the annual decrease in the need for colectomy

changed steadily over time—subtle differences in slope may have been missed in the preliminary plots of colectomy trends. Specifically, the decreases in UC may have been driven by more recent decreases in the need for colectomy. This could have been further explored by examining the differences in slopes between UC children diagnosed earlier versus children diagnosed more recently.

Health services use patterns can reflect the patients' behaviours of seeking care and may not represent medically necessary visits. Since surgical outcomes are believed to be less influenced by these behaviours compared to hospitalizations, ED visits, and outpatient visits, decreases in the need for surgery may be associated with improvement in the quality of IBD care and better disease control resulting from increased availability of effective therapies.

Randomized controlled trials and meta-analyses have demonstrated a lower need for surgery in patients on biologic therapy.[8,110,171,172] This has been further supported by previous studies that found decreased surgery rates in the post-biologic era.[107,173] However, this decrease may not be directly attributable to the use of anti-tumor necrosis factor (anti-TNF) therapies. In an Ontario study, the introduction of infliximab did not result in lower health services utilization or surgeries among adults with IBD over what would have been expected based on trends in these outcomes before the introduction of infliximab.[113] However, this study did not directly evaluate the effects of other therapies or changes to IBD care, which have also been associated with decreasing rates of IBD-related surgeries.[174,175] This study also did not include children, who have higher response rates to biologic therapy due a more predominant inflammatory disease behaviour, as opposed to greater stricturing rates in adult IBD.[148,176] The authors also noted that suboptimal use of biologics may have been one reason why expected decreases were not observed.

The notion that risk of surgery has been decreasing independently of biologic therapy is not new. A systematic review found that surgical rates have been decreasing over the last 60 years, long before biologic therapy was a treatment option for IBD.[8] Furthermore, the gradually changing trends seen in pediatric IBD surgery in my study suggest these trends have been gradually shifting since the beginning of the study (1994), before the introduction of biologics for the management of pediatric IBD. It is, therefore, likely that other factors have been gradually driving these trends. These factors could include improved outpatient care in children, such as a shorter time from symptom onset to diagnosis and increasing specialist care. The number of pediatric gastroenterologists has increased between 1994 and 2006 from 0.38 to 0.90 per 100,000 children, and IBD children have been increasingly treated by pediatric specialists instead of adult specialists.[78] Furthermore, an earlier visit to a gastroenterologist has been associated with a 17% (95% CI 0.2 to 29%) decrease in the risk of surgery.[108] In addition to the availability of specialists, a number of available pharmaceutical therapies and improved awareness and diagnostic equipment (*e.g.*, colonoscopies, MR/CT enterography) over time may have resulted in earlier diagnosis and treatment (before disease progression), averting the need for surgery. When IBD is diagnosed earlier in its course and treated effectively, surgery can be avoided. Improvements in access to care and better therapies may be making this possible.

2.4.4 Strengths and Limitations

This study had large sample size, was population-based, and included children without IBD. Using a population-based approach, I included all children in Ontario with IBD, reducing selection bias. Population-based data also ensured I included sufficient numbers of children without IBD and that they were selected at random (after matching). By comparing trends in

children with and without IBD, I distinguished between trends specific to IBD children and trends universal to all Ontario children.

Limitations of this study stemmed from my inability to identify reasons for changing trends, lack of subgroup analyses, issues with conducting health research using administrative data, the lack of control marker for surgeries, the inability to distinguish between medically necessary and not medically necessary ED visits or elective and non-elective hospital admissions or procedures, low power in children with UC, and the potential for increased Type I error due to testing multiple comparisons.

I did not look for direct associations between IBD care and time trends on health services use. Data on use of IBD medications are not universally available in Ontario health administrative data for individuals <65 years. I also did not have information on disease severity. As a result, I could not draw conclusions on the reasons the trends were observed. In addition, the identification of trend motivators was beyond the scope of my study.

I also did not include subgroup analyses that have been previously reported to be influential on health services use in pediatric IBD. For example, health services use in IBD children has been shown to differ by age group and sex.[76,77] However, when I tested for effect measure modification, the only interaction consistently observed across outcomes and models was between age and rurality. When further investigated, this interaction was found to be driven by small cells rather than true effect measure modification.

As with most routinely collected health administrative data, the study was susceptible to the consequences of conducting research using data that was not collected for research purposes. I lacked data on clinical characteristics (such as disease phenotype or severity), serum markers of

inflammation, characteristics of the intestinal microbiome, diet, or other factors that may have affected the outcomes. While I controlled for the confounding effects of sex, age, rurality, and mean neighbourhood income quintile, and these variables may have partially adjusted for some of the missing variables, it is very likely residual confounding persisted. Furthermore, administrative data are prone to misclassification bias. The algorithm used to identify IBD may have introduced some misclassification bias due to the imperfect nature of all algorithms. However, the algorithm has a high accuracy, and so it was assumed the misclassification bias originating from IBD identification errors was relatively low. In addition, while codes for surgery were validated,[114,142] they were validated in adults and outside of Ontario, though using the same CIHI-DAD database as my study. The accuracy of these codes may have performed differently among children in Ontario. Further, the codes used to identify IBD-related visits and hospitalizations were not validated. However, a panel of IBD experts chose and agreed upon these codes, and these codes have been used in previous studies.[76–78]

Initially, I included orthopedic surgeries to serve as a control for IBD-related surgeries. Orthopedic surgeries were selected because they are not related to gastrointestinal symptoms or complications of IBD and there had been no changes specific to orthopedic care that would have affected trends. However, orthopedic surgeries were rare, and I could not derive meaningful results. Therefore, I decided to forego a contextual control for surgical trends. Since surgeries are presumably performed only when there is a need (*i.e.*, medical treatment has failed or complications arise), changes in surgery trends likely reflect changes in IBD care.

ED visit patterns can reflect patient habits in seeking care rather than what care providers would consider to be medically necessary. One way to determine if EDs were medically necessary could have been determining what proportion of visits resulted in a hospitalization. As

a result, I am unable to conclude whether ED visits trends reflect an actual need in IBD patients, or are due to other reasons, such as poor patient education of when to seek care.

I also did not categorize hospital admissions or surgeries as elective or non-elective, and it is possible that the trends for these categories may differ.[114] However, the primary aim of our evaluation of health services use and surgeries over time was to determine overall trends. Future studies may choose to investigate these differences further.

While changing trends were commonly observed in CD and all IBD patients, these trends were sometimes diminished or not replicated in UC. There are fewer children in Ontario with UC and I may have been underpowered to detect significant trends. For example, the one- and three-year odds of colectomy decreased among children with UC, but the five-year odds (analyzed with a smaller sample size due to required follow-up time) remained stable. Alternatively, newer therapies may not work as well in children with UC. Children with severe UC often require higher doses of anti-TNF biologics to maintain therapeutic serum levels because of excretion of drug from the serum into feces through the heavily inflamed colonic mucosa.[177] Furthermore, some medications used for CD were approved later for use in UC; trends of decreasing health services utilization may not yet be apparent. Future studies assessing differences in disease treatment and management strategies between CD and UC children are needed.

Finally, I conducted a large number of analyses in this study, resulting in a risk of Type I error due to multiple comparisons. I did not correct p-values for multiple comparisons since each analysis was separate and independent, with only one major independent variable assessed (time). Where appropriate, statistically significant p-values were investigated with visual plots in order to determine if the significant p-values appeared credible or driven by small cells.

2.4.5 Future Directions

Although studies have reported decreases in the use of the costlier health services (*i.e.,* hospitalizations and surgeries) in the post-biologic era compared to the pre-biologic era, and these trends are consistent with clinical trials, Murthy, *et al.,*[113] demonstrated these decreases in Ontario may not be as strongly related to biologic use as was originally believed. The authors postulated that the lack of significant impact through biologic use may be a result of inefficient use of the therapy. Further research on the impact of appropriately (*e.g.,* proper dose and frequency) used biologic therapy on health services use trends is needed. In addition, since biologic therapy was not the only change to pediatric IBD care over recent years, future studies exploring the impact of other changes on health services use trends are warranted.

IBD affects all areas of patients' lives, and health services use is just one of those areas. While trends in health services use are informative in health care planning, so are trends in patients' quality of life, including absenteeism from school and educational attainment. These are particularly important in light of the high indirect costs of IBD in Canada. Health care policy makers need to plan for the evolving health care needs of children with IBD, ensuring that children receive the best possible care so that they can go on to lead healthy and productive lives.

While I primarily discussed the changes to pediatric IBD care, I did not discuss changes to quality of care, which may be important in determining how patients use available health services. For example, there has been a documented transition where the care of children with IBD is being increasingly provided by pediatric gastroenterologists. Children with IBD have unique needs and benefit from the specialized care that pediatric gastroenterologists can provide.[78,178] Furthermore, it is possible that improving or increasing transition programs that aid for adolescents smoothly move from pediatric to adult gastroenterologist care may over time lead

to better outcomes.[179] Future research should address whether we have seen changes to the quality of care, and whether these changes have impacted outcomes in children with IBD.

Since health services and surgical outcomes place a heavy financial burden on the Canadian health care system,[2] it is important for health care management and policy makers to understand the shifting care needs. Cost-effective health care, without foregoing the needs of the patients, is necessary. In addition, it is important for health care providers to understand the needs of their patients so that they receive best possible care and outcomes – with the goal of reducing the need for expensive hospitalizations and surgeries. It would, therefore, be important for future studies to identify reasons for these observed trends. Future studies should also evaluate trends in important subgroups, such as age and sex groups. Furthermore, since Ontario is geographically large and home to a diverse population, it would be beneficial for health care planners to be informed of whether the trends are province-wide or differ between specific sub-regions.

2.5 Conclusions

Trends of health services use in Ontario children diagnosed with IBD between fiscal years 1994 and 2012 were changing. Hospitalizations decreased in both children with and without IBD, which suggests the presence of a health system effect. In addition, ED visits for IBD-related reasons increased in IBD children, as did both IBD-specific and IBD-related outpatient visits in children diagnosed after 2005. These increases were not seen in children without IBD, suggesting a higher need for health services in the IBD population over time. Surgeries decreased in Ontario IBD children, and this decrease was seen in both the CD and UC subgroups. Understanding why these trends are occurring will help health care planners better prepare for the expected increasing burden of pediatric IBD.

Chapter 3. Comparison of distributed network meta-analysis to individual-level multivariable regression analysis using health administrative data

3.1 Introduction

In an age of "big data," there are large amounts of health administrative data available for epidemiology and health services research. However, with the use of health data comes important privacy concerns. Patient privacy is a strict ethical standard, and legislation prohibits the sharing of individual-level data across political borders.[180] For example, in Canada, health administrative data are collected at the provincial level on all legal residents of the province. However, privacy laws prohibit the sharing of individual-level records across provincial borders. Privacy-preserving methods are needed for multi-jurisdictional studies that do not compromise patient confidentiality. One such method is the distributed network analysis – a method which employs identical study methodology on individual-level data to obtain jurisdiction-specific effect estimates, and this approach can be followed by meta-analysis to obtain a pooled national estimate.[126] Studies have previously compared the use of this method to the results from individual-level analysis, but under limited conditions.[128,137]

Ontario health data provide an opportunity to explore the validity of the distributed network analysis because of the province's large population and pre-defined Local Health Integration Networks (LHIN). LHINs are involved in the local delivery of health care and can be

used as proxies for provinces. Because data are from a single province, LHIN-specific analyses can be compared with analyses using individual-level data.

I aimed to validate distributed network meta-analysis results against individual-level analysis results under a variety of conditions (different regression models and types of data, event rates, sample sizes, number of regions, and heterogeneity) in order to provide a tested, privacy-preserving tool to analyze aggregate health administrative data.

3.2 Methods

3.2.1 Study Design

I conducted a retrospective validation study based on the cohort developed in Chapter 2 to compare the results of analyses conducted using individual-level data and distributed network analyses. To simulate a distributed network analysis within the province of Ontario, I replicated the analyses described in Chapter 2 among children with and without inflammatory bowel disease (IBD) living in each Ontario LHIN, then pooled and meta-analyzed the results to obtain the provincial estimate (hereafter referred to as the "LHIN-based analysis"). The beta estimates of the regression models quantified the association between year of diagnosis (or index date) and health services use and surgery outcomes in pediatric IBD. I compared the results of the LHIN-based analysis to the results reported in Chapter 2 (hereafter referred to as the "individual-level analysis").

3.2.2 Data Sources

A comprehensive overview of data sources used to extract variables for the participants, exposures, and outcomes is supplied in the methods section of Chapter 2.

3.2.3 Study Setting, Participants, Exposures, and Outcomes

The patients, exposures, and outcomes from the first aim were used to conduct Aim 2, and are, therefore, summarized in the methods section of Chapter 2.

3.2.4 Local Health Integration Networks

LHINs are administrative units who have the ability to plan and regulate some level of local health care practices within its borders (Figure 3.1).[181] The postal code of residence at diagnosis for each patient with and without IBD was extracted from the RPDB and linked to the Local Health Integration Network (LHIN) database to assign each study participant the LHIN of residence on the date of their diagnosis. Residents of LHIN 10 (Kingston region) were excluded due to inconsistency in completeness of data based on shadow billings. Due to the small number of children with IBD in some LHINs, I combined LHIN 9 with LHIN 12, and LHIN 13 with LHIN 14. This combination was chosen based on assumed similarities in population characteristics of LHINs within close geographic proximity of each other. In addition, statistical models in LHINs 6 and 7 were not adjusted for rural/urban status since there were few (LHIN 6) or no (LHIN 7) rural patients in these LHINs. A total of 11 combined LHINs were included.

Figure 3.1 Map of the 14 Ontario Local Health Integration Networks (LHINs) from http://www.lhins.on.ca (accessed June 15, 2018).

3.2.5 Statistical Analysis

3.2.5.1 Participant Characteristics

The characteristics of the children with IBD and matched children without IBD in each LHIN are described as means (SD) or medians (IQR) for continuous characteristics or proportions for categorical characteristics.

3.2.5.2 Distributed Network (LHIN-Based) Analysis

Identical regression models (negative binomial, Poisson, logistic, and Cox proportional hazards) from Chapter 2 were applied to each LHIN to quantify LHIN-specific changes in pediatric IBD health service use and surgical outcomes over time. Exact logistic regression using the network Monte Carlo method[182] was used when conventional logistic regression models did not converge due to sparse data within a LHIN. For outcomes where regression models did not converge in three or fewer LHINs, those LHINs were excluded from the meta-analysis. Where greater than three LHINs did not converge, the outcome was not analyzed because it was assumed the exclusion of four or more LHINs may compromise the ability of the analysis to appropriately answer the research question. A summary of the study outcomes and models that did not converge in the LHINs is included in Appendix H. Both the exact and maximum-likelihood logistic regression model estimates from the LHIN-based analysis were compared to the estimates from the individual-level analysis, which were derived from maximum-likelihood logistic regression models.

3.2.5.3 Meta-Analysis

The meta-analysis of regression model beta estimates across LHINs was conducted using both fixed and random effects models. LHINs were weighted in accordance with the generic inverse variance weighting method. Heterogeneity was quantified using the I^2 statistic. The I^2 was calculated using τ^2 for random effects models and using Cochran's Q for fixed effects models.[183,184] The τ^2 was estimated using Restricted Estimates Maximum Likelihood (REML) for random effects models.[185,186] Heterogeneity across LHINs was tested using the Cochran's Q test at α=10%.

3.2.5.4 Comparison of Results From LHIN-Based Analyses and Individual-Level Analyses

The provincial beta estimates resulting from the distributed network and meta-analyses (*i.e.*, the LHIN-based analysis) were compared to the individual-level analysis (Chapter 2) using three methods. The first was a crude approach of calculating percent error between the two beta estimates (Equation 1). It was assumed that beta estimates from the meta-analyses that differed by ≥10% compared with individual analyses were not the same. This approach was extrapolated from the Mickey & Greenland (1989) study on confounder selection criteria, which stated that a 10% change in a regression model beta estimate after adjustment indicated a confounding effect.[187] The second method of comparison was a formal *z*-statistic test of the null hypothesis that the beta estimates were the same at α=5% (Equation 2).[188] Third, the provincial effect summaries (odds ratios, hazard ratios, and incidence rate ratios) and their corresponding 95% confidence intervals (CIs) were visually assessed for consistency.

Equation 1. $$Percent\ Error\ (\%) = 100 * \frac{\widehat{\beta_1} - \widehat{\beta_2}}{\widehat{\beta_1}}$$

Equation 2.[188] $$z = \frac{\widehat{\beta_1} - \widehat{\beta_2}}{\sqrt{SE\left(\widehat{\beta_1}\right)^2 + SE\left(\widehat{\beta_2}\right)^2}}$$

All regression model analyses were performed in SAS Enterprise Guide version 7.1 (SAS Institute, Cary, North Carolina, USA). Meta-analyses were conducted in R Version 3.5.3 using the Metafor package.[184,189]

3.2.6 Sensitivity Analyses

I conducted four sensitivity analyses. In the first, I combined the individual-level data for children living in LHINs with pediatric care centres (LHINs 2, 4, 7, and 11) and children living in LHINs without pediatric care centres (LHINs 1, 3, 5, 6, 8, 9 and 12, and 13 and 14). The beta estimates for these two groups were meta-analyzed then compared to the individual-level analyses. This sensitivity analysis was important because I expected children who received treatment at pediatric care centres to have received different care than children who were not seen at these centres. For example, they were likely to receive more specialized care and may have been seen more frequently than children who are not seen at these centres.

Secondly, I pooled LHIN-specific estimates for LHINs with pediatric centres and LHINs without pediatric centres separately. These pooled estimates were compared to estimates obtained from the individual-level analyses, stratified by the presence/absence of a pediatric centre. Large amounts of heterogeneity in this analysis were not expected compared to the first sensitivity analysis. However, this analysis allowed us to explore the impact of varying numbers of regions on the meta-analysis.

Since LHIN 14 is close to the Ontario-Manitoba provincial border, children from that LHIN may access care in Manitoba. Therefore, their health administrative data may not be contained within Ontario databases. I therefore ran a sensitivity analysis excluding children in LHIN 14 to determine if the results would be impacted by children receiving care out of province. I compared hospitalization rates and the need for surgery across LHINs 11, 12, 13, and 14 to determine if these outcomes were systematically different in LHIN 14 compared with other LHINs in Northern Ontario.

Lastly, when the three (or fewer) LHINs were excluded from the LHIN-based analysis due to non-convergence, I also excluded these LHINs from the individual-level analysis. This sensitivity analysis determined if the individual-level analysis effect estimates were robust to the exclusion of these LHINs. This sensitivity analysis was important to confirm that the exclusion of LHINs in which models did not converge in the LHIN-based analysis would not compromise the comparison of the effect estimates between the LHIN-based analysis and the individual-level analysis.

3.3 Results

3.3.1 Participant Characteristics

The overall cohort consisted of 5,518 children with IBD matched to 26,677 children without IBD. The descriptive characteristics of IBD and non-IBD patients included in the study, stratified by LHIN, are presented in Tables 3.1 and 3.2, respectively.

3.3.2 Comparison of LHIN-based Analyses and Individual-Level Analyses

In the LHIN-based analyses, the beta estimates for the models describing incidence rate ratios (IRR), hazard ratios (HR), and odds ratios (OR) from both fixed and random effects models were comparable (*z*-statistic $p>0.05$) to the beta estimates of the individual-level analyses (Appendices I & J). The beta and effect estimates from the fixed and random effects models were also comparable to the individual-level analysis estimates despite low event rates and small sample sizes. This was exemplified in the ORs of surgery within five years of diagnosis in UC

patients (OR for fixed and random effects models: 0.982, 95% CI 0.950 to 1.015; individual-level analysis: 0.978, 95% CI 0.950 to 1.007) (Figure 3.2). In addition, the estimates from exact logistic regression models in the LHIN-based analysis were comparable to the estimates from the individual-level analysis modelled using maximum likelihood logistic regression ($p>0.05$ in all cases).

3.3.3 Sensitivity Analyses

3.3.3.1 LHINs with and without Pediatric Inflammatory Bowel Disease Centres

The observed heterogeneity between LHINs with and without pediatric IBD centres varied across outcomes (Appendices K and L). In the first sensitivity analysis, which compared LHINs with pediatric care centres with LHINs without pediatric care centres, considerable heterogeneity ($I^2 > 75\%$)[190] was seen among analyses comparing emergency department (ED) visit and surgical outcomes. Moderate to considerable heterogeneity was seen across hospitalization and outpatient visit outcomes within LHINs with pediatric care centres and within LHINs without the centres. However, in each of the LHIN-based analyses, the fixed and random effects models were similar to the results from individual-level analyses across all levels of heterogeneity observed (z-statistic $p>0.05$).

3.3.3.2 Pooling of LHINs with Presence or Absence of Pediatric Inflammatory Bowel Disease Care Centres Separately

In the second sensitivity analysis pooling LHIN-specific estimates for LHINs with and without pediatric IBD centres separately, the observed heterogeneity varied among outcomes

(Appendices K and L). However, in all LHIN-based, the fixed and random effects models were similar to the results from individual-level analysis across all numbers of regions (4 LHINs with pediatric IBD centres and 7 combined LHINs without the centres) included in the meta-analysis (*z*-statistic $p>0.05$).

3.3.3.3 Including Versus Excluding LHIN 14

Provincial effect estimates were consistent when including and excluding LHIN 14 from the individual-level effect estimates (Appendix M). Hospitalization and surgery rates were similar in LHIN 14 compared with LHINs 11, 12, and 13.

3.3.3.4 The Impact of Model Non-Convergence

In the sensitivity analysis exploring whether effect estimates from the individual-level analysis were robust to the exclusion of LHINs that did not converge, the estimates were no different in the individual-level analysis after the exclusion of LHINs that did not converge (Appendix N).

3.3.4 The Effect of Heterogeneity

Overall, both fixed and random effects models were comparable to the results of the individual-level analysis across varying degrees of heterogeneity. In the presence of considerable heterogeneity, the 95% CIs for the fixed effects models were closer to the 95% CIs from the individual-level analyses than were the random effects models. Random effects models resulted in wider 95% CIs. This is exemplified in the IRRs of all-cause hospitalizations within one year

of diagnosis in IBD patients (I_2 = 81%, Cochran's Q test p <0.01; IRR for random effects model: 0.979, 95% CI 0.965 to 0.993, *z*-statistic p=0.75; fixed effects model: 0.982, 95% CI 0.976 to 0.988, *z*-statistic p=0.89; individual-level analysis: 0.982, 95% CI 0.976 to 0.988) (Figure 3.3).

In the presence of very low heterogeneity, both the fixed and random effects model 95% CIs were visually similar and approximated the CIs from the individual-level analysis. For example, low heterogeneity was observed in IRRs of IBD-specific ED visits within three years of diagnosis in CD children (I_2=1.9%, Cochran's Q p=0.50), and the fixed and random effects models resulted in identical beta estimates and 95% CIs (IRR: 1.006, 95% CI 0.993 to 1.020), which were comparable to the estimates from individual-level analysis (IRR: 1.002, 95% CI 0.989 to 1.016, *z*-statistic p=0.69).

3.3.5 Risk of Type I and Type II Error

In some cases, the presence of high heterogeneity led to Type II error in random effects models – the 95% CIs crossed the null in the LHIN-based analysis but not the individual-level analysis. This was the case when comparing the hazard ratios of IBD-related ED visits for IBD patients (HR for random effects model: 1.008, 95% CI 0.996 to 1.019; fixed effects model: 1.009, 95% CI 1.002 to 1.016; individual-level analysis: 1.009, 95% CI 1.003 to 1.016) (Figure 3.4).

Fixed effects models were also susceptible to Type II error. This was exemplified in the LHIN-based analysis of hazard of IBD-specific hospitalization in UC patients (HR for random effects model: 0.987, 95% CI 0.971 to 1.002; fixed effects model: 0.987, 95% CI 0.976 to 1.000; individual-level analysis: 0.987, 95% CI 0.975 to 0.999).

In the LHIN-based analysis there were 12 instances (10.5% of all LHIN-based analyses conducted) of Type II error in random effects models and 3 instances (0.26% of all LHIN-based analyses) in both fixed and random effects models. In all three sensitivity analyses concerning LHINs with and without pediatric care centres, Type II error was common for random effects models, though there were also instances when both fixed and random effects models were prone to this error.

Fixed effects models were also susceptible to Type I error, and an example of this error was seen in the meta-analysis of IRRs of all-cause ED visit within one year of diagnosis in IBD patients (IRR for random effects model: 1.009, 95% CI 1.000 to 1.018; fixed effects model: 1.009, 95% CI 1.001 to 1.017; individual-level analysis: 1.008, 95% CI 1.000 to 1.017). An instance of Type I error was also seen in random effects models, as well as the fixed effects model, in the sensitivity analysis comparing incidence rate ratios of IBD-related ED visits within one year of diagnosis in CD patients in LHINs without IBD centres (IRR for random effects model: 1.018, 95% CI 1.001 to 1.035; fixed effects model: 1.018, 95% CI 1.001 to 1.035; individual-level analysis: 1.015, 95% CI 0.999 to 1.032) (Figure 3.5).

In the LHIN-based analysis there were two occurrences in which fixed effects models produced a Type I error, and one occurrence where both fixed and random effects models produced this error. Type I error was rare but observed in the sensitivity analysis comparing LHINs with pediatric care centres and the sensitivity analysis comparing LHINs without pediatric care centres.

Table 3.1 Descriptive characteristics of patients with inflammatory bowel disease, stratified by Local Health Integration Network.

Characteristic		LHIN 1 (*n*=330)	2 (*n*=393)	3 (*n*=326)	4 (*n*=602)	5 (*n*=357)	6 (*n*=514)	7 (*n*=343)	8 (*n*=839)	11 (*n*=591)	9 & 12 (*n*=823)	13 & 14 (*n*=400)
Sex	Females	147 (44.6%)	175 (44.5%)	148 (45.4%)	263 (43.7%)	153 (42.9%)	220 (42.8%)	134 (39.1%)	347 (41.4%)	269 (45.5%)	365 (44.4%)	175 (43.8%)
	Males	183 (55.5%)	218 (55.5%)	178 (54.6%)	339 (56.3%)	204 (57.1%)	294 (57.2%)	209 (60.9%)	492 (58.6%)	322 (54.5%)	458 (55.7%)	225 (56.3%)
Age at Diagnosis (years)	Mean (SD)	13.7 (3.3)	13.2 (3.6)	13.3 (3.5)	13.2 (3.5)	12.5 (3.9)	13.1 (3.6)	12.7 (3.9)	12.9 (3.5)	13.0 (3.6)	13.1 (3.6)	13.6 (3.3)
	Median (IQR)	14.0 (4.0)	14.0 (5.0)	14.0 (4.0)	14.0 (5.0)	13.0 (5.0)	14.0 (5.0)	14.0 (6.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	15.0 (4.0)
Diagnosis	CD	167 (50.6%)	226 (57.5%)	216 (66.3%)	380 (63.1%)	189 (52.9%)	283 (55.1%)	191 (55.7%)	469 (55.9%)	384 (65.0%)	481 (58.4%)	226 (56.5%)
	UC	141 (42.7%)	147 (37.4%)	88 (27.0%)	185 (30.7%)	141 (39.5%)	198 (38.5%)	124 (36.2%)	311 (37.1%)	183 (31.0%)	289 (35.1%)	138 (34.5%)
	IBD-U	22 (6.7%)	20 (5.1%)	22 (6.8%)	37 (6.2%)	27 (7.6%)	33 (6.4%)	28 (8.2%)	59 (7.0%)	24 (4.1%)	53 (6.4%)	36 (9.0%)
Rural residence at diagnosis	Urban	298 (90.3%)	261 (66.4%)	284 (87.1%)	565 (93.9%)	347 (97.2%)	508-514 (98.8-99.9%)	343 (100.0%)	828 (98.7%)	515 (87.1%)	701 (85.2%)	274 (68.5%)
	Rural	32 (9.7%)	120 (33.1%)	42 (12.9%)	37 (6.2%)	10 (2.8%)	<6	0 (0.0%)	9 (1.1%)	75 (12.7%)	121 (14.7%)	126 (31.5%)

Characteristic		LHIN 1 (*n*=330)	2 (*n*=393)	3 (*n*=326)	4 (*n*=602)	5 (*n*=357)	6 (*n*=514)	7 (*n*=343)	8 (*n*=839)	11 (*n*=591)	9 & 12 (*n*=823)	13 & 14 (*n*=400)
	Unknown	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.2%)	1 (0.1%)	0 (0.0%)
Neighbourhood income Quintile at diagnosis	First (lowest)	46 (13.9%)	49 (12.5%)	29 (8.9%)	74 (12.3%)	36 (10.1%)	43 (8.4%)	86 (25.1%)	91 (10.9%)	58 (9.8%)	121 (14.7%)	81 (20.3%)
	Second	64 (19.4%)	73 (18.6%)	48 (14.7%)	112 (18.6%)	88 (24.7%)	53 (10.3%)	48 (14.0%)	111 (13.2%)	97 (16.4%)	161 (19.6%)	73 (18.3%)
	Third	59 (17.9%)	95 (24.2%)	54 (16.6%)	112 (18.6%)	134 (37.5%)	82 (16.0%)	42 (12.2%)	152 (18.1%)	120 (20.3%)	167 (20.3%)	75 (18.8%)
	Fourth	71 (21.6%)	89 (22.7%)	81 (24.9%)	155 (25.8%)	62 (17.4%)	155 (30.2%)	26 (7.6%)	223 (26.6%)	143 (24.2%)	199 (24.2%)	81 (20.3%)
	Fifth (Highest)	89 (27.0%)	85 (21.6%)	114 (25.0%)	148 (24.6%)	37 (10.4%)	181 (35.2%)	141 (41.1%)	260 (31.0%)	172 (29.1%)	174 (21.1%)	86 (21.5%)
	Unknown	1 (0.3%)	2 (0.5%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.2%)	1 (0.1%)	4 (1.0%)
Length of follow up (years)	Mean (SD)	10.5 (5.2)	10.5 (5.3)	11.0 (5.1)	11.8 (5.4)	9.9 (5.1)	10.6 (5.3)	11.0 (5.7)	11.2 (5.5)	10.7 (5.1)	11.2 (5.4)	11.6 (5.5)
	Median (IQR)	9.8 (8.8)	9.7 (8.3)	10.1 (8.3)	11.0 (9.3)	8.7 (8.0)	9.6 (8.2)	10.1 (9.7)	10.1 (9.2)	9.9 (8.4)	10.6 (9.1)	10.5 (9.6)
	Min	1.8	1.9	1.4	1.2	1.7	1.1	1.6	2.3	1.4	0.4	1.2
	Max	21.9	22.0	21.8	22.0	21.8	22.0	22.0	22.0	21.9	22.0	22.0

Abbreviations: CD, Crohn's Disease; IBD, inflammatory bowel disease; IBD-U, IBD type unclassifiable; IQR, interquartile range; LHIN, Local Health Integration Network; SD, standard deviation; UC, ulcerative colitis.

Table 3.2 Descriptive statistics of patients without inflammatory bowel disease stratified by Local Health Integration Network .

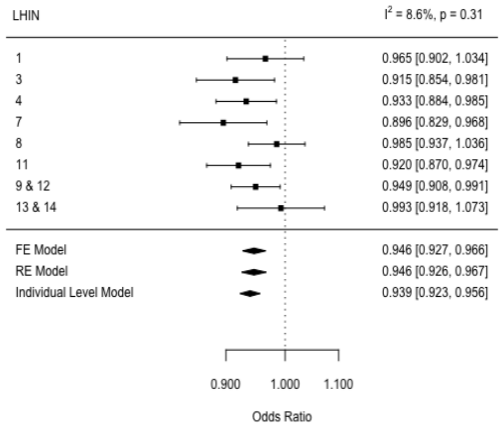
Characteristic		LHIN										
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**9 & 12**	**13 & 14**
		(*n*=1606)	(*n*=2018)	(*n*=1667)	(*n*=3363)	(*n*=1871)	(*n*=2581)	(*n*=1800)	(*n*=3366)	(*n*=2324)	(*n*=4227)	(*n*=1847)
Sex	Females	693 (43.2%)	842 (41.7%)	717 (43.0%)	1435 (42.7%)	816 (43.6%)	1093 (42.4%)	787 (43.7%)	1511 (44.9%)	1017 (43.8%)	1846 (43.7%)	813 (44.0%)
	Males	913 (56.9%)	1176 (58.3%)	950 (57.0%)	1928 (57.3%)	1055 (56.9%)	1488 (57.7%)	1013 (56.3%)	1855 (55.1%)	1307 (56.2%)	2381 (56.3%)	1034 (56.0%)
Age at diagnosis (years)	Mean (SD)	13.1 (2.5)	13.2 (3.6)	13.1 (2.5)	13.3 (3.4)	122.8 (3.7)	12.9 (3.6)	12.9 (3.7)	13.0 (3.6)	13.0 (3.6)	13.1 (3.6)	13.4 (3.4)
	Median (IQR)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (5.0)	14.0 (4.0)
Rural residence at diagnosis	Urban	1490 (92.8%)	1491 (73.9%)	1529 (91.7%)	3224 (95.9%)	1840 (98.3%)	2576-2580 (99.8%-99.96%)	1800 (100.0%)	3342 (99.3%)	2042 (87.9%)	3837 (90.8%)	1455 (78.8%)
	Rural	116 (7.2%)	527 (26.1%)	138 (8.3%)	139 (4.1%)	31 (1.7%)	<6	0 (0.0%)	24 (0.7%)	282 (12.1%)	390 (9.2%)	392 (21.2%)
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neighbourhood income quintile at diagnosis	First (lowest)	241 (15.0%)	264 (13.1%)	212 (12.7%)	414 (12.3%)	212 (11.3%)	147 (5.7%)	430 (23.9%)	349 (10.4%)	239 (10.3%)	584 (13.8%)	310 (17.3%)
	Second	267 (16.6%)	348 (17.2%)	267 (16.0%)	573 (17.0%)	429 (22.9%)	274 (10.6%)	318 (17.7%)	475 (14.1%)	368 (15.8%)	835 (19.8%)	313 (17.0%)
	Third	300 (18.7%)	433 (21.5%)	343 (20.6%)	625 (18.6%)	609 (32.6%)	453 (17.6%)	195 (10.8%)	644 (19.1%)	403 (17.3%)	898 (21.2%)	353 (19.1%)
	Fourth	357 (22.2%)	477 (23.6%)	368 (22.1%)	825 (24.5%)	389 (20.8%)	778 (30.1%)	221 (12.3%)	930 (27.6%)	592 (25.5%)	935 (22.1%)	403 (21.8%)

Characteristic		LHIN										
		1 (*n*=1606)	**2** (*n*=2018)	**3** (*n*=1667)	**4** (*n*=3363)	**5** (*n*=1871)	**6** (*n*=2581)	**7** (*n*=1800)	**8** (*n*=3366)	**11** (*n*=2324)	**9 & 12** (*n*=4227)	**13 & 14** (*n*=1847)
	Fifth (Highest)	441 (27.5%)	496 (24.6%)	477 (28.6%)	926 (27.5%)	232 (12.4%)	929 (36.0%)	636 (35.3%)	968 (28.8%)	722 (31.1%)	974 (23.0%)	457 (24.7%)
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.02%)	1 (0.05%)
Length of follow up (years)	Mean (SD)	11.5 (5.5)	11.6 (5.5)	11.4 (5.4)	11.5 (5.4)	10.4 (5.3)	11.0 (5.3)	11.3 (5.4)	11.1 (5.5)	11.2 (5.4)	11.1 (5.3)	11.8 (9.7)
	Median (IQR)	10.9 (9.5)	11.0 (9.5)	10.4 (8.9)	10.9 (9.3)	9.3 (8.5)	10.1 (8.7)	10.4 (9.1)	10.3 (9.3)	10.3 (9.0)	10.2 (8.9)	11.4 (9.7)
	Min	3.0	3.0	3.0	3.0	3.0	3.0	2.1	3.0	3.0	3.0	3.0
	Max	22.0	22.0	22.0	22.0	22.0	22.0	22.0	22.0	22.0	22.0	22.0

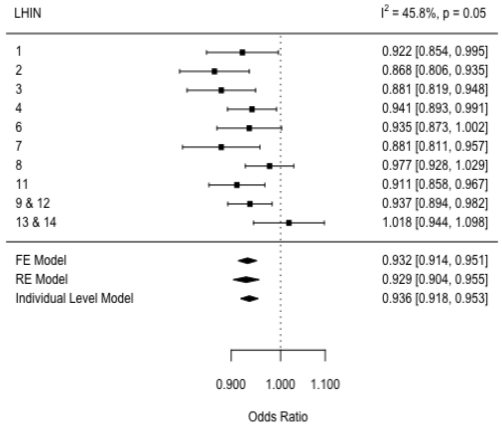
Abbreviations: CD, Crohn's Disease; IQR, interquartile range; LHIN, Local Health Integration Network; SD, standard deviation; UC, ulcerative colitis.

Crohn's disease Ulcerative colitis

3



5



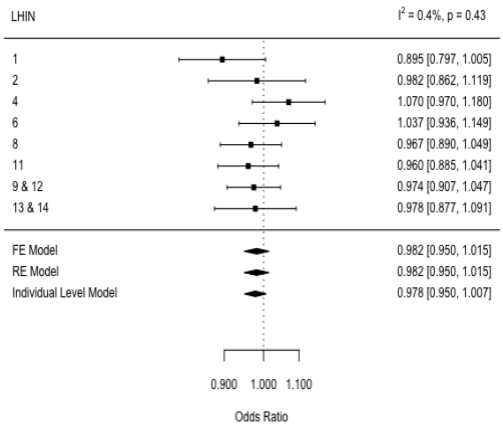


Figure 3.2 Forest plots for depicting the odds ratios [95% confidence intervals] from fixed and random effects meta-analyses compared with individual-level analyses for intestinal resection (Crohn's disease) and colectomy (ulcerative colitis) within three and five years of diagnosis in children with inflammatory bowel disease.

*The LHIN-based analysis was not performed for the one-year follow up in children with Crohn's disease and ulcerative colitis and the three-year follow up in children with ulcerative colitis because models did not converge in >3 Local Health Integration Networks.

Abbreviations: FE, fixed effects; LHIN, Local Health Integration Network; RE, random effects.

Children with IBD Children without IBD

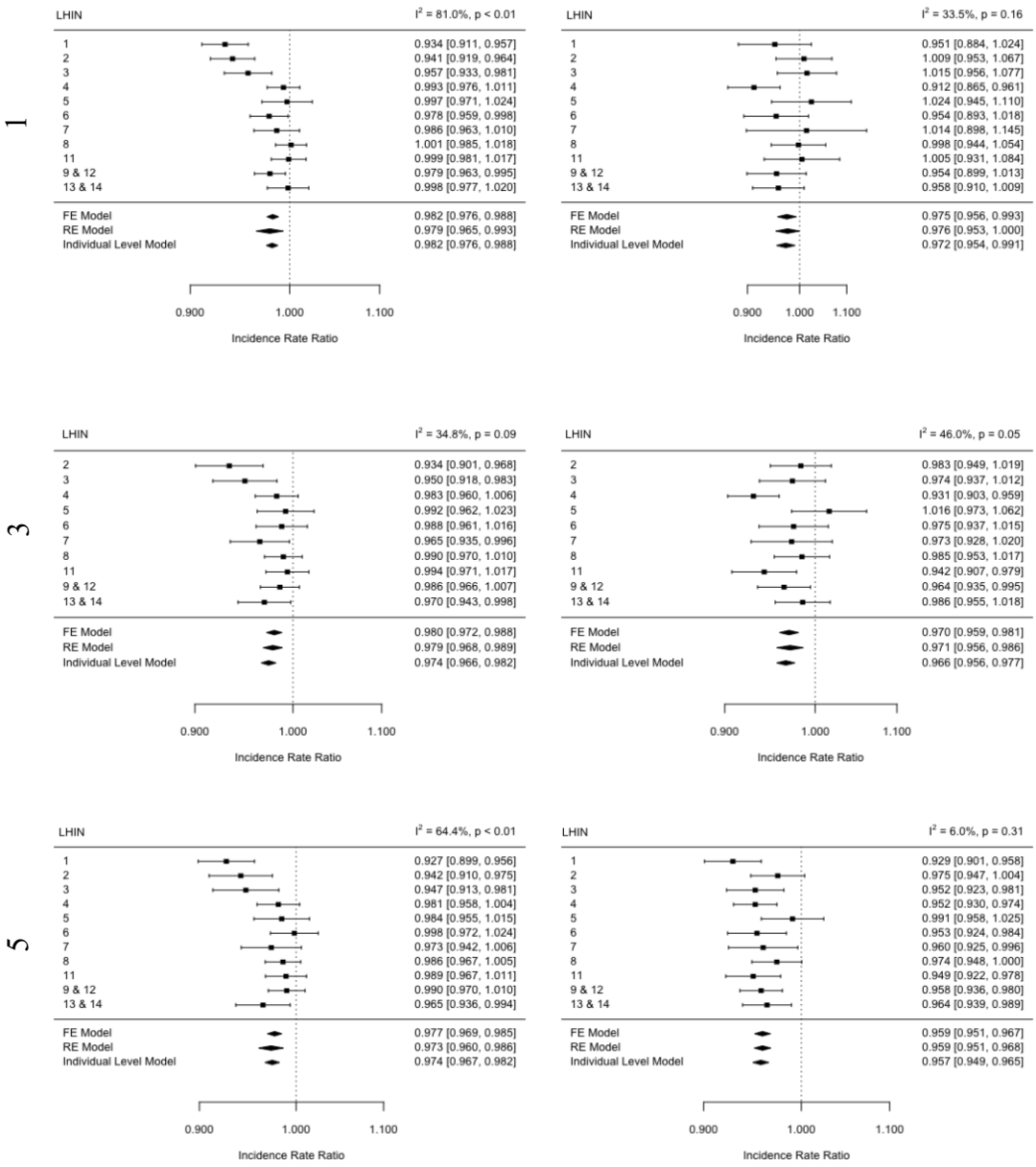


Figure 3.3 Forest plots for depicting the incidence rate ratios [95% confidence intervals] from fixed and random effects meta-analyses compared with individual-level analyses for all-cause hospitalizations within one, three, and five years of diagnosis in children with and without inflammatory bowel disease.

Abbreviations: IBD, inflammatory bowel disease; FE, fixed effects; LHIN, Local Health Integration Network; RE, random effects.

IBD-specific IBD-related

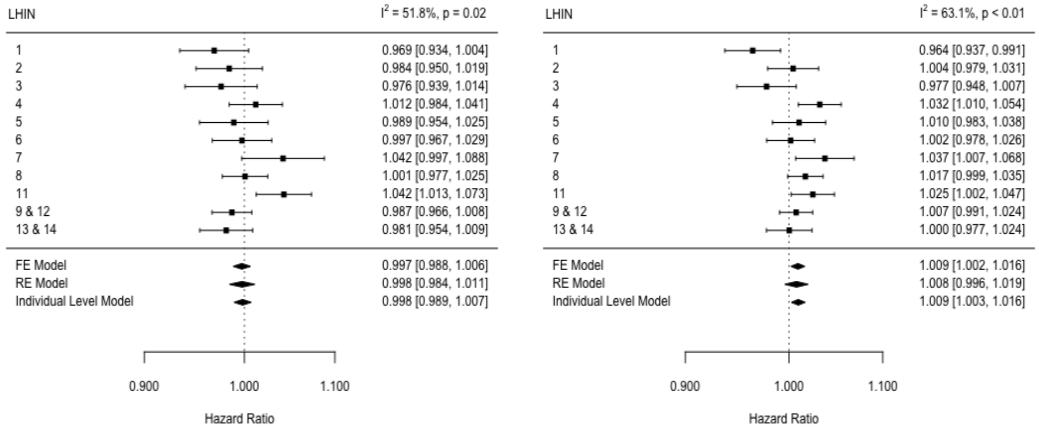


Figure 3.4 Forest plots for depicting the hazard ratios [95% confidence intervals] from fixed and random effects meta-analyses compared with individual-level analyses for IBD-specific and IBD-related emergency department visits within five years of diagnosis in children with inflammatory bowel disease.

Abbreviations: FE, fixed effects; LHIN, Local Health Integration Network; RE, random effects.

IBD-specific IBD-related

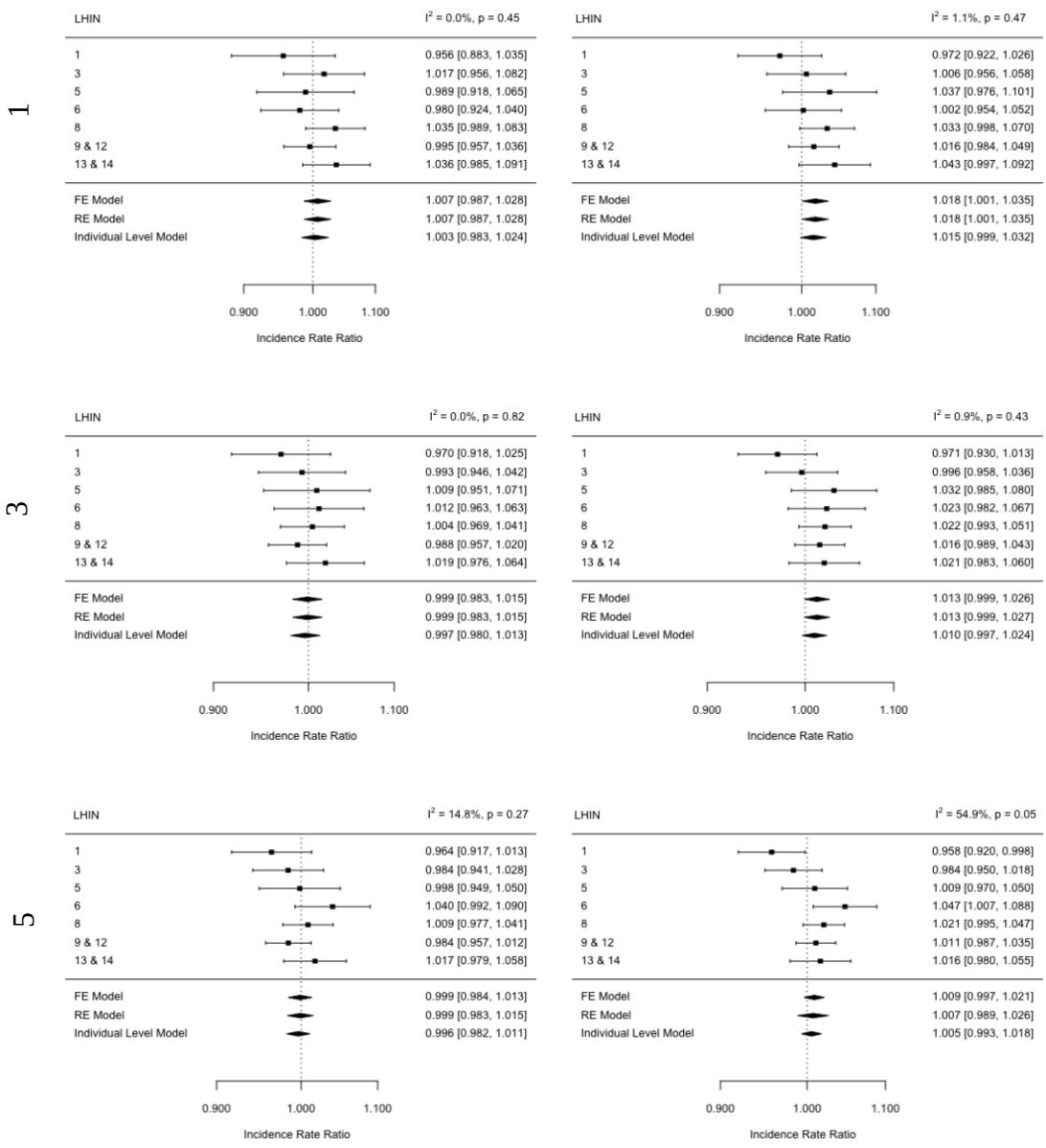


Figure 3.5 Forest plots for depicting the incidence rate ratios [95% confidence intervals] from fixed and random effects meta-analyses compared with individual-level analyses in the sensitivity analysis comparing Local Health Integration Networks without pediatric inflammatory bowel disease centres for IBD-specific and IBD-related emergency department visits within one, three, and five years of diagnosis in children with Crohn's disease.

Abbreviations: IBD, inflammatory bowel disease; FE, fixed effects; LHIN, Local Health Integration Network; RE, random effects.

3.4 Discussion

3.4.1 Study Findings

In this study, I demonstrated the results of individual-level multivariable regression analysis were similar to the results of the meta-analysis of regional results from distributed network (LHIN-based) analysis when assessing time trends in health services utilization in children with IBD using population-based health administrative data. This was true for both fixed and random effects meta-analysis models, all outcomes, follow-up periods, levels of heterogeneity, model types, event rates, number of regions, and sample sizes used in this study ($p>0.05$ for all comparisons). The study findings were robust to substituting maximum likelihood-based with exact logistic regression models when models failed to converge due to rare events. This study validates a privacy-preserving method when conducting inter-jurisdictional multi-database studies using health administrative data.

3.4.2 Heterogeneity and the Choice of Fixed or Random Effects Models

3.4.2.1 Results of Meta-Analysis

In the presence of low heterogeneity, fixed and random effects meta-analysis models were visually the same and statistically comparable to the individual-level analysis. In addition, the fixed and random effects meta-analyses produced comparable beta estimates ($p>0.05$) in the presence of high heterogeneity ($I^2>75\%$, Cochran's Q $p<0.10$, *e.g.,* Appendix K Table K.2) but the random effects models had wider 95% confidence intervals.

3.4.2.2 Addressing Heterogeneity in Meta-Analysis

There are three types of heterogeneity. The first is clinical heterogeneity, which refers to differences in populations, exposures, and outcomes. The second is methodological heterogeneity, which is introduced by differences in methods such as the regional study design and analysis. Statistical heterogeneity refers to differences between the regions that are not due to chance and can be a result of clinical and/or methodological heterogeneity. Statistical heterogeneity is often referred to as simply "heterogeneity." The heterogeneity in meta-analyses are caused by characteristics of regions that differentiate the regions from each other. Meta-analyses are effective when combining regions that are comparable. When regions are too different from each other (*i.e.*, there is high heterogeneity), the regions may not be comparable and should not be pooled with meta-analysis.

In distributed network analyses, methodological heterogeneity is theoretically reduced by using identical study design, methods, and statistical code in each region. High heterogeneity in could suggest differences in health services utilization and the need for surgery across LHINs due to availability of specialist care or demographic, socio-economic, or other environmental exposures.

3.4.2.3 Estimation and Quantification of Heterogeneity

I chose the restricted estimates maximum likelihood (REML) method to estimate variation between LHINs (τ^2). There are at least 16 known estimators of τ,[185] and there is an insufficient body of literature to compare and assess the use of each one. The DerSimonian-Laird method has historically been the most widely used estimator of τ, likely because it is easy to calculate and was one of the first methods described. Improved technological capacities have

given researchers access to more computationally demanding methods. I chose REML based on recent literature recommendations.[185,186] REML is less likely to falsely inflate the homogeneity when both τ^2 and number of regions are low compared to the DerSimonian-Laird estimator[185] and provides a reasonable compromise between bias and efficiency.[186] REML may perform better with continuous, rather than dichotomous, data.[185] However, REML is recommended when researchers are uncertain of the best estimator to use.[186] Thus, this tau estimator was used as it can perform well under the numerous conditions of this study. I applied the same estimator to each outcome and analysis for consistency because the study goal was to assess the validity of the distributed network approach, and not to compare the different methods of estimation.

Heterogeneity can be quantified in many ways: the H^2 statistic describes how many times larger the total variance is from the within-region variance; the R^2 statistic describes the inflation of the random effects model confidence intervals relative to the confidence intervals from the fixed effects model; and the I^2 statistic represents the proportion of heterogeneity that is not due to chance.[191] H^2 and R^2 have no upper bound, which makes it difficult to assign cut-off values to indicate the degree of heterogeneity. In contrast, the I^2 statistic has an upper bound of 100% and is intuitively meaningful, which is likely the reason for its frequent use. It has traditionally been calculated using Cochran's Q, but is being increasingly calculated using τ^2 so that the I^2 is more consistent with the τ^2. I used I^2 to quantify heterogeneity with these advantages in mind and tested for the presence of heterogeneity using Cochran's Q test. Cochran's Q test is a χ^2 distribution-based hypothesis test which assumes in the null hypothesis that there is one true effect measure across all LHINs, and the variation between the LHINs are due to chance. In a meta-analysis of a small number of regions, this test is low-powered and a higher p-value cut off is recommended.[190]

3.4.2.4 Properties of Fixed Versus Random Effects Models

In general, random effects models were more conservative in the presence of heterogeneity, meaning that their confidence intervals tended to be wider than the confidence intervals of fixed effects models. This is consistent with what was expected based on differences in how effect estimates in fixed and random effects meta-analyses are calculated. A fixed effects meta-analysis assumes that there is one true effect estimate; each LHIN provides an estimate of that true effect. In fixed effects models, the generic inverse variance method weights the estimate from each LHIN according to the inverse of its variance. Larger LHINs with smaller variances are weighted higher in the meta-analysis because larger LHINs would provide estimates closer to the true estimate. In contrast, random effects meta-analyses assume that effect estimates of each LHIN contribute to a distribution of true effect measures, and the combined effect measure is the average of that distribution. Random effects models are weighted based on the inverse of the variance of the LHIN-specific estimate (the within-region error variance) and the variance of the distribution of effect estimates (the between-region variance, or τ_2). This gives a more equal weight to all LHINs.

Since random effects meta-analyses incorporate an additional parameter in the estimation of a pooled effect estimate, they typically have wider confidence intervals than fixed effects meta-analyses. This is especially true when heterogeneity is high. Wider confidence intervals are more likely to cross the null compared to the narrower fixed effects model confidence intervals, which results in the notion that random effect models are more conservative than fixed effects models.

Wide confidence intervals are only one definition of "conservative." Conservative could alternatively be defined as an estimate that is shifted towards the null. Even if 95% confidence

intervals are wider in random effects models, fixed effects models may result in pooled estimates that are closer to the null.[192] This typically occurs when analysis of small regions produces estimates that are farther from the null. Random effects meta-analyses will assign a greater weight to these regions than fixed effects models. This results in the meta-analyzed estimate being further from the null when using random effects meta-analysis compared with fixed effects meta-analysis. In such scenarios, the fixed effects meta-analysis model estimate would be more conservative since it would be closer to the null.

In this study, both fixed and random effects models produced similar effect estimates. Therefore, I have limited discussion of whether random effects models were more conservative than fixed effects models based on the width of confidence intervals. Random effects meta-analyses were more conservative in the presence of heterogeneity and sometimes failed to detect an association that was statistically significant in the individual-level analysis (Type II error). There were also situations where the confidence intervals from fixed effects models were wider than seen in the individual-level analysis and significant associations were missed (Type II error). This occurred much less frequently in fixed effects than random effects model meta-analyses. Both models were also prone to Type I error - where the meta-analysis models detected a statistically significant association that was not observed in the individual-level analysis. This was infrequent but may have been the result of the large number of analyses that were conducted. Both types of errors typically occurred when the 95% confidence intervals were close to the null.

While random effects models incorporate heterogeneity into the meta-analysis, there may be cases where random effects models should not be used as a method of accommodating heterogeneity. In theory, methodological heterogeneity should be greatly reduced in distributed

network analysis (compared with traditional meta-analyses) because of the standardization of study design, analysis, and programming code across regions. However, between-region variation may also arise because of differences in data, characteristics of regions, and clinical heterogeneity. Where there is high heterogeneity expected from methodologic or clinical differences, it may be more appropriate to report regional estimates separately.

3.4.3 Findings of the Sensitivity Analyses

Children living in LHINs with pediatric care centres are most likely treated at those centres and receive specialized care. These children may, therefore, have been treated differently than children who did not reside in LHINs with pediatric centres. This difference could affect health service utilization and need for surgery. I, therefore, compared trends in LHINs with and without pediatric care centres. I expected the sensitivity analysis comparing LHINs with the centres to LHINs without the centres to introduce heterogeneity – a condition I wanted to explore when testing the validity of the distributed network meta-analysis. Even in the presence of high heterogeneity the distributed network meta-analysis was found to approximate results from individual-level analysis.

I compared pooled estimates of the 4 LHINs with pediatric care centres to estimates from the individual-level analysis stratified by LHINs with the centres to determine the impact of the number of pooled regions on the validity of the distributed network meta-analysis. The same comparison was done for the 7 (combined) LHINs without the centres. In both scenarios the distributed network analysis approximated results from the individual-level analysis in the presence of a small number of pooled regions.

LHIN 14 is a large northern region of Ontario bordering Manitoba with a highly rural and sparse population. Rural patients usually have to travel long distances to access medical care, especially larger health centres, such as hospitals, which are usually situated in more densely populated regions. It may, therefore, be easier for people living in this region to access health care in neighbouring Manitoba. This is of less concern in LHINs that neighbour Quebec or the US due to the accessibility of health care within Ontario. To investigate potential bias introduced into my study by LHIN 14 patients seeking care from Manitoba, I excluded patients residing in LHIN 14 at diagnosis from the individual-level analysis as a sensitivity analysis. Trends in health care utilization did not differ when excluding patients in LHIN 14. In addition, individuals living in other Canadian provinces near provincial borders may similarly travel to neighbouring provinces for health care, making this an important issue for consideration in national studies. For these reasons I found it appropriate to include LHIN 14 in this study.

In the sensitivity analysis exploring whether effect estimates from the individual-level analysis were robust to the exclusion of LHINs that did not converge in the LHIN-based analysis, the estimates were no different in the individual-level analysis after the exclusion of LHINs that did not converge. This sensitivity analysis indicated it was appropriate to compare the effect estimates from LHIN-based analysis (with non-converging LHINs excluded) to the effect estimates from the individual-level analysis (without excluding the non-converging LHINs).

3.4.4 Privacy-Preserving Analysis Methods

In Ontario, ICES is a prescribed entity recognized by the Information and Privacy Commissioner of Ontario. It allows ICES to collect, use, and analyze patient health administrative data within the regulatory boundaries defined in the Personal Health Information Protection Act (PHIPA).[193] Privacy regulations fall under provincial jurisdictions. The privacy of health data is under provincial jurisdiction and laws prevent the sharing of identifiable patient information across provincial borders to uphold patient confidentiality. In light of these laws, and to protect patients, methods of analyzing health administrative data while maintaining patient privacy are needed.

Privacy-preserving multi-regional analysis methods other than distributed network analysis have been described in literature. For example, individual patient data (IPD) meta-analysis is similar to distributed network analysis because it requires that individual-level data be separately analyzed then meta-analyzed to obtain an aggregate estimate. Unlike a distributed network analysis (which conducts the same primary data analysis in each region and meta-analyzes the results), IPD meta-analyses can use data from published literature that has to be recollected and re-analyzed using methods tailored to each dataset to answer their research question, or use statistical analysis methods most appropriate for each region.[194,195] This approach may require researchers to request access to raw data from the original literature, which is usually not feasible since this data usually involves sensitive, identifying patient information, or may introduce methodological heterogeneity if the analysis differs by region.

Another example of privacy-preserving methods of analyzing multi-jurisdictional research involves the use of Jerboa© software. This software was designed to extract data from regional databases, producing individual-level, regional, and aggregated data such as person-time

and number of events per age group in a common format, which is then used for analysis.[196] This approach is different from the distributed network approach used by the US Food and Drug Administration's Sentinel Initiative (and pilot program Mini-Sentinel),[125,197] the Canadian Network for Observational Drug Effect Studies (CNODES),[126] and the Observational Medical Outcomes Partnership (OMOP).[198,199] These approaches to multi-database studies were initially designed for pharmacoepidemiologic studies. The distributed network analysis approach uses individual-level data to produce regional effect estimates, which can then be pooled in a meta-analysis yielding an overall estimate.

Both the Sentinel Initiative and OMOP use a common data model.[198,199] A common data model involves not only a shared protocol and analysis code, but also requires each local database to standardize files into a common format across all the databases.[126,197,199] This framework requires an initial time investment of data extraction tools to create the standardized files, but is more efficient and decreases the time required to conduct a distributed network analysis.[126,199] This approach may be more challenging to integrate in Canadian networks, such as CNODES and CanGIEC, due to different structures of health administrative data across provinces.

3.4.5 Comparison of Privacy-Preserving Analysis Methods Across Jurisdictions to Individual-Level Analysis

Since the creation of the Sentinel network and CNODES, studies have explored alternative methods of combining aggregate data. One study used weighted regression on stratum-specific means, but it only explored a continuous outcome and the author noted the analysis could not accommodate a continuous predictor.[136] A simulation study compared the hazard ratios and corresponding 95% confidence intervals from case-centered logistic regression

analysis to those from meta-analysis.[131] In case-centered logistic regression of risk-set data,[130,200] each site contributes risk-sets containing a patient with the outcome and comparable individuals who are at risk of the outcome at the time the person with the outcome had the event. A variable indicating whether or not the person with the outcome was exposed is modelled as the dependent variable and the log odds of the proportion of exposed individuals in the risk-set is modelled as the independent variable as the offset. This approach provides comparable results to Cox regression.[200] The meta-analysis was susceptible to bias and lower-powered than case-centered regression in some circumstances, such as low sample size or event rate.[131] Similar to my study, fixed and random effects models gave comparable results. However, this study lacked an ideal reference standard.[131] More recent simulation studies addressed this limitation.[133] One study compared the results of site-specific Cox regression summary table data, risk-set data, and site-specific estimate meta-analysis to pooled individual-level data. Summary table data analysis uses data pooled on event counts and person-time by strata of exposure groups, and risk-set data uses the composition of the risk set at each time of event within each strata. All three of the data sharing methods were comparable to individual-level data. Inconsistencies were again noted for small sample sizes (<1000 patients per site) and rare events, particularly in the meta-analysis method.[133] The studies differed from mine in that they used propensity and disease risk scores for confounding adjustment and are simulations. However, other studies, which evaluated confounding adjustment methods in distributed network analysis[129] and conducted real-world distributed network analysis,[132,134,135] have also looked at the validity of meta-analysis, in addition to other methods of combining aggregate data.

Other studies have also compared results from distributed network analysis to individual-level data. One such study was done in Nordic countries.[128] However, the authors compared logistic regression and fixed effects meta-analysis. Fixed effects models were specifically

selected because the study used standardized analysis and participating countries have similar health care systems. A random effects meta-analysis was only performed if heterogeneity was statistically significant. The authors of the study concluded that the results from the fixed effects models visually appeared similar to the results from the individual-level data. The random effects models were found to have wider 95% confidence intervals in the presence of heterogeneity.

Researchers used the Canadian Longitudinal Study on Aging to visually compare results from individual-level analysis using a binary outcome (odds ratio) with results from distributed network analysis (with both fixed and random effects models). They also compared findings to micro-aggregation,[137] a method in which data is aggregated into a defined number of groups for each of the covariates, with each group containing a specific number of observations, rather than directly using individual-level data. They reported the fixed effects model and micro-aggregation produce results most similar to the individual-level analysis. This study likely captured more regional differences (heterogeneity) than I was able to in my study because it used data from seven provinces while my study only examined the Ontario population. However, this comparison of individual-level and distributed network analyses did not use population-based health administrative data.

My findings are consistent with those of previous validation studies. However, my validation study differed from previous work because it explored a number of conditions (regression model types, event rates, sample sizes, number of pooled regions, and heterogeneity), compared the use of fixed effects to random effects meta-analysis model for all analyses, and tested the beta coefficients of the statistical models from the different methods in addition to visual assessment. Validated tools for cross-regional analyses are needed as researchers increasingly rely on distributed network analyses to conduct multijurisdictional research. This

includes established (including CNODES, CanGIEC, Sentinel, and OMOP) and developing initiatives (including the Canadian Data Platform of the Health Data Research Network [HDRN]).[201]

3.4.6 Strengths and Limitations

My study tested distributed network meta-analysis under varied conditions, allowed for replicate analyses, and used population-based data.

I demonstrated that distributed network meta-analysis accurately estimates the results of individual-level multivariable regression models under numerous circumstances. The method worked for negative binomial/Poisson, logistic, and Cox proportional hazards regression models. This study had a wide range of sample sizes, event rates, and number of regions. Although provinces can dramatically vary in sample size and event rates, my analysis also included small sample sizes and rare event rates, and I found the distributed network analysis delivered accurate estimates nonetheless. In addition, since inverse-variance weighted meta-analysis models tend to give more weight to more populous regions, it is possible that larger provinces may be given more weight in the meta-analysis. However, despite different sample sizes between LHINs, the meta-analysis was successful. I also substituted maximum-likelihood logistic regression models for exact logistic regression models when sparse data resulted in models not converging. In these cases, distributed network analysis still approximated maximum-likelihood logistic regression models from individual-level analysis. Meta-analyses performed well in situations with both low and high heterogeneity and with differing numbers of pooled regions. Under all conditions, both fixed and random effects models from the distributed network analysis were able to estimate the results from individual-level analyses. Furthermore, since a large number of conditions were

tested, it allowed for the replication of the analyses to assess the accuracy of the results. I demonstrated the results to be consistent.

This study used population-based health administrative data, which minimized the risk of selection bias in this study. I used all children with IBD in Ontario and up to five children without IBD for every child with IBD. This allowed for the simulation of a distributed network analysis with LHINs serving as proxies for multiple jurisdictions. By including all children with IBD in Ontario, this study had sufficient sample sizes in each LHIN to conduct meaningful analyses.

My study had several limitations. Only children in Ontario were included. However, I expected to see heterogeneity across LHINs because Ontario is home to a large, diverse, and geographically dispersed population. Further, LHINs are independent administrative units involved in the local delivery of health care, leading to differences in care, physician practises, access to care, geographic variation, environmental exposures, underlying risk, or demographics across LHINs. Nevertheless, there are differences in the health care system across provinces (*e.g.*, coverage of prescription medications; economic, social and political landscapes) and Ontario residents may have different characteristics and environmental exposures making them systematically different for residents of other provinces. As a result, distributed network analyses evaluating health services utilization in multiple provinces may have greater heterogeneity than was seen within Ontario. These differences may lead to higher heterogeneity across provinces than was observed within a single province.

There may be methodological heterogeneity in how health administrative data is collected and made available to researchers across regions. These differences may be more pronounced for provincial datasets (*e.g.*, physician claims used to identify outpatient visits) than

national databases (*e.g.*, CIHI-DAD used to identify hospitalizations). One example of how these databases may differ is through slightly different code lists used across provinces (Ontario uses an abbreviated version of ICD-9 codes for outpatient physician billing). Despite shared analytic code, methodological differences may persist due to these nuanced differences across provincial health administrative databases.

Validated algorithms used to identify people with IBD vary between provinces.[13,202,203] In this study, I was able to use the same algorithm to identify patients in all of Ontario because the algorithm was validated using Ontario health administrative data.[13] However, other provinces will use algorithms that perform better in their population to reduce misclassification bias.[204] However, not all provinces have validated algorithms and multiprovince studies may rely on externally-validated algorithms. These differences in the accuracy of identifying cases may contribute to between-province heterogeneity in a way that I could not describe in this study.

Multivariable regression models did not converge in some LHINs due to the small number of patients and low event rates in these LHINs. I took three approaches to counteract issues of model convergence: (1) pooling LHIN 9 with 12 and 13 with 14; (2) running exact logistic regression models instead of maximum-likelihood logistic regression models; and (3) excluding non-converging LHINs from the meta-analysis. Similar problems may arise when meta-analyzing data from small provinces. In such situations, it may not be feasible to combine data from small regions, and exact methods are not always available as an alternative to likelihood-based regression models. Pooled analyses may not always be possible, and researchers may need to choose between eliminating jurisdictions or removing outcomes.

I did not evaluate all possible conditions in which distributed network analyses may be conducted. For example, I only compared individual-level and distributed network analyses for

small effects since the annual change in health services utilization and risk of surgery was relatively small. Thus, I am uncertain about the validity of distributed network analysis when larger effect estimates are expected. However, one rationale for conducting distributed network analyses is to obtain a larger sample size to increase the power of detecting small, but important, effect estimates on drug safety and effectiveness.[126] The comparability of distributed network analyses and meta-analyses may differ across study design (*e.g.*, case-control study instead of a cohort study) or analytic approach (*e.g.*, multi-level regression models) or when very low event rates or very small sample sizes are expected.

In the analysis using all-cause events in the cohort of matched children with and without IBD, children without IBD were selected from a provincial pool of children, which resulted in children with IBD being matched to children without IBD at a provincial level, but not within each LHIN. Patients were not matched on LHIN of residence because I expected that would lead to a higher number of unmatched children with IBD, which would result in a loss of power. In a real-world distributed network analysis, patients would be matched within the region of residence. In addition, the covariates the IBD and non-IBD children were matched on were not included in the models of all-cause health services use in children with and without IBD. However, these concerns did not apply to the analysis of trends in IBD-specific and IBD-related events since those trends were only examined in children with IBD and used multivariate regression models to adjust for confounding.

There is no definitive method available for comparing the results from the distributed network analysis and individual-level data analysis. I used a visual assessment and two mathematical approaches to compare findings: (1) percent error between the results from the distributed network analysis and individual-level analysis and (2) the *z*-statistic. Calculated

percent errors for some outcomes were well above the 10% cut-off value deemed appropriate *a priori*. I expect these high percent errors were a consequence of the small effect sizes seen in this study. These effect estimates and 95% confidence intervals appeared to be visually no different from each other, frequently only differing at the second or third decimal place. The *z*-statistic tested the null hypothesis that the beta estimates were equal between the individual-level analysis and the distributed network analysis. The test assumes independence and a normal distribution.[188] While these assumptions were not likely met, they were assumed in order to compare regression coefficients. The results from the *z*-statistic were consistent with the visual assessments of the odds, hazard, and rate ratios and their respective 95% confidence intervals. I therefore relied on the results of the *z*-statistic to test the difference between the beta estimates and visual assessment of the effect summaries and 95% confidence intervals.

3.4.7 Methodological Advice for Future Studies Using Distributed Network Analysis

I found that the use of a distributed network approach coupled with a meta-analysis successfully reproduced results from individual-level analyses. This approach can be used when privacy regulations prevent individual-level analyses. However, there are scenarios in which researchers should exercise caution before conducting distributed network analysis. This may be the case when researchers are not confident in their ability to reduce methodological bias, such as when regional databases do not share a similar structure (*e.g.*, missing important variables, different code lists or different coding systems). Furthermore, studies of very rare event rates or populations may lack sufficient power to conduct meaningful analyses even after combining multiple jurisdictions.

The general advice on using fixed versus random effects models in meta-analysis has been to consider a fixed effects model if the studies are "identical" and the results do not need to be generalizable beyond the population included in the study.[140] A random effects model is recommended if the studies included are not identical but are similar enough to pool and there is a need to generalize beyond the population included in the study.[140] In the distributed network analysis in my study, both the fixed and random effects models provided estimates comparable to results from individual-level data analysis, with random effects models having slightly wider 95% confidence intervals.

The choice between fixed or random effects meta-analysis model in a distributed network analysis depends on the research goal, implications of the research, and knowledge of included regions. Random effects models are sometimes preferred by researchers due to their wider confidence intervals and greater likelihood of avoiding Type I error.[205] The observation of a statistically significant effect in a random effects model is believed to be more reassuring of its significance than if it was found in a fixed effects model. Based on the results of this study, it is reasonable to use random effects meta-analyses, especially since greater heterogeneity is expected in distributed network analyses involving multiple provinces. The generalizability of findings beyond the study population also warrants consideration since health administrative data are not always available in regions of interest.

There are scenarios in which it would be preferable to commit a Type I error over a Type II error. An example of this is when investigating a potential rare but harmful side effect of a medication. In these situations, it may be preferable or more ethical to report a statistically significant effect that may not be true instead of being underpowered to detect a significant association. If a dangerous drug side effect is left unreported, it can pose a serious risk to the

patients who were administered the drug. However, in an observational study on health services, such as the data analyzed in my study, it may be preferable to commit a Type II error and not detect true changes in health services use trends. Underreporting of such trends would not lead to detrimental effects on the patients, and a Type I error in health services research may prompt unnecessary, ineffective, difficult, and costly changes to the health care system.

Knowledge of the regions, such as understanding the database structure, the health care system, or the data collection methods included in the distributed network meta-analysis may also influence the choice of a random or fixed effects meta-analysis. When data collection and structure are identical across regions, heterogeneity due to methodological differences are reduced. If there are no underlying differences in the populations of these regions that could influence the association of interest, then the assumption of fixed effects models that each region is estimating the true effect may be warranted. These models, therefore, give more weight to larger regions, which are expected to give a more precise estimate of the true effect than a smaller region.

Heterogeneity may arise where data collection and structure or underlying characteristics of the population are not constant across regions. These differences may contribute to slightly different associations being observed in each jurisdiction. To account for these differences, random effects models assume that there is a distribution of true effects. Between-region heterogeneity, or τ^2, is incorporated in the weights assigned to individual regions in the meta-analysis. This results in random effects models providing a more equal weight to all regions, regardless of their size.

Distributed network analyses will only be as good as the data from each included region. If researchers have reason to believe that data from a smaller region may be more accurate (*i.e.*,

less risk of bias) then it is advisable to present region-specific estimates without the meta-analysis since meta-analyzed estimates would be skewed in the direction of the bias. Meta-analysis is also not recommended when high heterogeneity is expected. This heterogeneity may result from fundamental differences in health care systems, populations among regions included in the study, or disease manifestation. In this study, I expected children residing in LHINs with pediatric care centres to have different health services and surgical outcomes compared to children residing in LHINs without these centres because of differences in care provision. While I did see considerable heterogeneity in some outcomes (*e.g.,* surgeries), I proceeded with the meta-analysis to test the distributed network meta-analysis method against individual-level analysis in the presence of high heterogeneity. Although I found that the meta-analyzed results were similar to the individual-level analyses, investigators may decide to forego the meta-analysis if their research question involves comparison of regions that are systematically different from each other.

When deciding upon the best approach to presenting findings from distributed network analyses, researchers should understand the advantages and consequences of fixed and random effects meta-analysis models. Researchers will need to decide which error (Type I or Type II) is most acceptable given their study goals and implications. In addition, researchers should inspect, and agree with, the weighting assigned to each region by each model based on their knowledge of the regions. If particular regions are suspected to introduce undue influence, or if regions are expected to have drastic differences between each other, then a meta-analysis is not recommended, and the results of the regions are best reported separately.

3.4.8 Impact and Future Directions

I specifically explored the validity of the distributed network analytic approach as described and used by Canadian networks such as CNODES and CanGIEC.[12,126] I found this approach to be a valid alternative to analyzing individual-level data when privacy regulations prevent sharing of individual-level records. Future studies should also explore the validity of the distributed network analysis on both a larger scale (*e.g.*, inter-provincial data from national databases) and smaller scale (*e.g.*, multicentre data from multiple electronic medical records). Further validation will help us understand the impact of heterogeneity from sources of variation that were uncaptured in my study.

Studies exploring the accuracy of privacy-preserving health administrative data analysis methods are becoming more relevant in the era of big data. Access to a wealth of administrative data allows for more efficient epidemiologic and health services research, including evaluation of drug effectiveness and safety, disease surveillance, and research evaluating health care practices and changes in health care policy. Increasing capacity for pan-Canadian research would allow us to identify and evaluate differences in health care practices and subsequent outcomes across provinces, informing evidence-based policy changes to ensure all Canadians have access to the best possible health care while ensuring efficient use of limited health care resources. Multi-jurisdictional research also improves the generalizability of findings and increases power to detect clinically meaningful associations for rare outcomes.

We are currently seeing a significant growth in initiatives conducting multi-jurisdictional research. Building off the success of existing platforms (*e.g.*, CNODES, CanGIEC, and Sentinel), the stage is being set for the Health Data Research Network (HDRN).[201] The HDRN, funded by the Canadian Institutes of Health Research, is working with the Strategy for Patient-

Oriented Research (SPOR) and centres with data holdings in all Canadian provinces. This Network aims to tackle some of the challenges facing pan-Canadian research, including developing a common data model and creating the infrastructure to support national studies. Data will become more accessible through this initiative, while also maintaining provincial privacy laws. Thus, validated privacy preserving methods will be a necessary component of the pan-Canadian research conducted through the HDRN.

3.5 Conclusions

Distributed network analysis is a satisfactory privacy-preserving alternative to individual-level analysis under the conditions used in this study. While the random effects models gave slighter wider 95% confidence intervals than fixed effects models in the presence of heterogeneity, both meta-analysis models were able to estimate the results from individual-level analysis. I recommend the choice of meta-analysis model be made based on the combination of study goals and an understanding of the regional analyses and the weighting assigned to regions under the meta-analysis model of choice. Future studies should aim to validate this method using pan-Canadian data from national databases.

Chapter 4. Concluding Remarks

Annual changes to health services use in Ontario children diagnosed with IBD between fiscal years 1994 and 2012 were assessed using population-based multivariate regression models. Hospitalization rates have decreased in both IBD children and their non-IBD counterparts, which suggest the influence of an underlying health system effect. ED visits, and outpatient visits in children diagnosed after 2005, have increased only in children with IBD. These shifting trends are important factors for health care planners to consider as they prepare for the increasing burden of pediatric IBD. Further research on the drivers of these trends is warranted.

In my evaluation of distributed network analysis, I found that meta-analysis of aggregate data from individual-level multivariable regression analyses is a valid alternative to using primary analysis of individual-level data. This method can be used for multi-province Canadian initiatives as well as multi-regional international studies when individual-level data cannot be shared for privacy or other reasons. The choice between fixed and random effects meta-analysis models should take into consideration regional study design, heterogeneity, and knowledge of regional analyses.

"Big data" in the form of health administrative data and electronic health records provide unprecedented opportunities for health-related research. Multi-jurisdictional population-based studies improve study generalizability and statistical power. However, researchers using health administrative data to conduct these studies will face challenges due to the increasing complexity of the data and the lack of tested methods available to meet the analysis demands of this relatively new but rapidly evolving field. In addition, researchers will likely face more

challenges with heterogeneity resulting from differing data collection, coding, analysis, and synthesis across independent regions or institutions, and understanding the role and impact of heterogeneity in the analyses and interpretations will become increasingly valuable. Established and future initiatives aimed at employing health administrative data to conduct multi-jurisdictional research will continue to need the development of methodological capacity to support the challenges that will arise in this field, and methodology validation will be central to the integrity of such studies.

Chapter 5. References

1. Rocchi A, Benchimol EI, Bernstein CN, et al. Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol*. 2012;26(11):811-817.

2. Kuenzig ME, Benchimol EI, Lee L, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: Direct Costs and Health Services Utilization. *J Can Assoc Gastroenterol*. 2019;2(S1):S17-S33. doi:10.1093/jcag/gwy055

3. Kuenzig ME, Lee L, El-Matary W, et al. The impact of inflammatory bowel disease in Canada 2018: Indirect costs of IBD care. *J Can Assoc Gastroenterol*. 2019;2(S1):S34-S41. doi:10.1093/jcag/gwy050

4. Benchimol EI, Bernstein CN, Bitton A, et al. The impact of inflammatory bowel disease in Canada 2018: A scientific report from the Canadian Gastro-Intestinal Epidemiology Consortium to Crohn's and Colitis Canada. *J Can Assoc Gastroenterol*. 2019;2(S1):1-5. doi:10.1093/jcag/gwy052

5. Melesse DY, Lix LM, Nugent Z, et al. Estimates of disease course in Inflammatory bowel disease using administrative data: A population-level study. *J Crohn's Colitis*. 2017;11(5):562-570. doi:10.1093/ecco-jcc/jjw201

6. Chen W, Lu C, Hirota C, Iacucci M, Ghosh S, Gui X. Smooth Muscle Hyperplasia/Hypertrophy is the Most Prominent Histological Change in Crohn's Fibrostenosing Bowel Strictures: A Semiquantitative Analysis by Using a Novel Histological Grading Scheme. *J Crohn's Colitis*. 2017;11(1):92-104. doi:10.1093/ecco-

jcc/jjw126

7. Crohn's and Colitis Canada. http://www.crohnsandcolitis.ca. Published 2016. Accessed May 28, 2018.

8. Frolkis AD, Dykeman J, Negrón ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013;145(5):996-1006. doi:10.1053/j.gastro.2013.07.041

9. Coward S, Clement F, Benchimol EI, et al. The rising prevalence of inflammatory bowel disease in Canada: Analyzing the past to predict the future. *J Can Assoc Gastroenterol*. 2018;1(S2):47-48. doi:10.1093/jcag/gwy009.029

10. Coward S, Clement F, Benchimol EI, et al. Past and Future Burden of Inflammatory Bowel Diseases Based on Modeling of Population-Based Data. *Gastroenterology*. 2019;156:1345-1353.e4. doi:10.1053/j.gastro.2019.01.002

11. Benchimol EI, Fortinsky KJ, Gozdyra P, Van Den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflamm Bowel Dis*. 2011;17(1):423-439. doi:10.1002/ibd.21349

12. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. *Am J Gastroenterol*. 2017;112(7):1120-1134. doi:10.1038/ajg.2017.97

13. Benchimol EI, Guttmann A, Griffiths AM, et al. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: Evidence from health administrative

data. *Gut*. 2009;58(11):1490-1497. doi:10.1136/gut.2009.188383

14. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology*. 2008;135(6):1907-1913. doi:https://dx.doi.org/10.1053/j.gastro.2008.09.012

15. Herzer M, Denson LA, Baldassano RN, Hommel KA. Patient and parent psychosocial factors associated with health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2011;52(3):295-299. doi:10.1097/MPG.0b013e3181f5714e

16. Loftus E V, Guérin A, Yu AP, et al. Increased Risks of Developing Anxiety and Depression in Young Patients With Crohn's Disease. *Am J Gastroenterol*. 2011;106(9):1670-1677. doi:10.1038/ajg.2011.142

17. Marrie RA, Walld R, Bolton JM, et al. Psychiatric comorbidity increases mortality in immune-mediated inflammatory diseases. *Gen Hosp Psychiatry*. 2018;53:65-72. doi:10.1016/J.GENHOSPPSYCH.2018.06.001

18. El-Matary W, Dufault B, Moroz SP, Schellenberg J, Bernstein CN. Education, Employment, Income, and Marital Status Among Adults Diagnosed With Inflammatory Bowel Diseases During Childhood or Adolescence. *Clin Gastroenterol Hepatol*. 2017;15(4):518-524. doi:10.1016/j.cgh.2016.09.146

19. Malmborg P, Mouratidou N, Sachs MC, et al. Effects of Childhood-onset Inflammatory Bowel Disease on School Performance: A Nationwide Population-based Cohort Study Using Swedish Health and Educational Registers. *Inflamm Bowel Dis*. 2019;25(10):1663-1673. doi:10.1093/ibd/izz040

20. Mayberry MK, Probert C, Srivastava E, Rhodes J, Mayberry JF. Perceived discrimination in education and employment by people with Crohn's disease: a case control study of educational achievement and employment. *Gut*. 1992;33:312-314. doi:10.1136/gut.33.3.312

21. Adler J, Raju S, Beveridge AS, Wang S, Zhu J, Zimmermann EM. College adjustment in University of Michigan students with Crohn's and colitis. *Inflamm Bowel Dis*. 2008;14(9):1281-1286. doi:10.1002/ibd.20484

22. Ferguson A, Sedgwick DM. Morbidity of juvenile-onset inflammatory bowel disease: predictors of morbidity and health status in early adult life. *J R Coll Physicians Lond*. 1994;28(3):220-227.

23. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol*. 2009;6(9):513-523. doi:10.1038/nrgastro.2009.124

24. Peneau A, Savoye G, Turck D, et al. Mortality and Cancer in Pediatric-Onset Inflammatory Bowel Disease: A Population-Based Study. *Am J Gastroenterol*. 2013;108(10):1647-1653. doi:10.1038/ajg.2013.242

25. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology*. 2008;135(4):1114-1122. doi:https://dx.doi.org/10.1053/j.gastro.2008.06.081

26. Szigethy EM, Youk AO, Benhayon D, et al. Depression Subtypes in Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):574-581. doi:10.1097/MPG.0000000000000262

27. Clark JG, Srinath AI, Youk AO, et al. Predictors of Depression in Youth With Crohn Disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):569-573. doi:10.1097/MPG.0000000000000277

28. Reigada LC, Bruzzese JM, Benkov KJ, et al. Illness-specific anxiety: Implications for functioning and utilization of medical services in adolescents with inflammatory bowel disease. *J Spec Pediatr Nurs*. 2011;16(3):207-215. doi:10.1111/j.1744-6155.2011.00292.x

29. Benchimol EI, Kaplan GG, Otley AR, et al. Rural and Urban Residence During Early Life is Associated with a Lower Risk of Inflammatory Bowel Disease: A Population-Based Inception and Birth Cohort Study. *Am J Gastroenterol*. 2017;112:1412-1422. doi:10.1038/ajg.2017.208

30. Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. *Gut*. 2013;62(10):1505-1510. doi:10.1136/gutjnl-2012-303954

31. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and Inflammatory Bowel Disease: A Meta-analysis. *Mayo Clin Proc*. 2006;81(11):1462-1471. doi:10.4065/81.11.1462

32. Kuenzig ME, Yim J, Coward S, et al. The NOD2-Smoking Interaction in Crohn's Disease is likely Specific to the 1007fs Mutation and may be Explained by Age at Diagnosis: A Meta-Analysis and Case-Only Study. *EBioMedicine*. 2017;21:188-196. doi:10.1016/j.ebiom.2017.06.012

33. Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet*. 2016;387:156-167.

doi:10.1016/S0140-6736(15)00465-1

34. Economou M, Trikalinos TA, Loizou KT, Tsianos E V., Ioannidis JPA. Differential Effects of NOD2 Variants on Crohn's Disease Risk and Phenotype in Diverse Populations: A Metaanalysis. *Am J Gastroenterol*. 2004;99(12):2393-2404. doi:10.1111/j.1572-0241.2004.40304.x

35. Verstockt B, Smith KG, Lee JC. Genome-wide association studies in Crohn's disease: Past, present and future: Past. *Clin Transl Immunol*. 2018;7(1):e1001. doi:10.1002/cti2.1001

36. Roth MP, Petersen GM, McElree C, Vadheim CM, Panish JF, Rotter JI. Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews. *Gastroenterology*. 1989;96(4):1016-1020. doi:10.1016/0016-5085(89)91618-1

37. Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD. *Am J Gastroenterol*. 2006;101(5):993-1002. doi:10.1111/j.1572-0241.2006.00381.x

38. Weterman IT, Peña AS. Familial Incidence of Crohn's Disease in The Netherlands and a Review of the Literature. *Gastroenterology*. 1984;86(3):449-452. doi:10.1016/S0016-5085(84)80014-1

39. Yang SK, Hong M, Zhao W, et al. Genome-wide association study of Crohn's disease in Koreans revealed three new susceptibility loci and common attributes of genetic susceptibility across ethnic populations. *Gut*. 2014;63(1):80-87. doi:10.1136/gutjnl-2013-305193

40. El-Tawil AM. Jews and Inflammatory Bowel Diseases. *J Gastrointestin Liver Dis*. 2009;18(2):137-138.

41. Chuang LS, Villaverde N, Hui KY, et al. A Frameshift in CSF2RB Predominant Among Ashkenazi Jews Increases Risk for Crohn's Disease and Reduces Monocyte Signaling via GM-CSF. *Gastroenterology*. 2016;151(4):710-723.e2. doi:10.1053/j.gastro.2016.06.045

42. Kenny EE, Pe'er I, Karban A, et al. A genome-wide scan of ashkenazi jewish crohn's disease suggests novel susceptibility loci. Abecasis GR, ed. *PLoS Genet*. 2012;8(3):e1002559. doi:10.1371/journal.pgen.1002559

43. Niv Y, Abuksis G, Fraser GM. Epidemiology of ulcerative colitis in Israel: A survey of Israeli kibbutz settlements. *Am J Gastroenterol*. 2000;95(3):693-698. doi:10.1016/S0002-9270(99)00908-9

44. Loftus E V. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126(6):1504-1517. doi:10.1053/J.GASTRO.2004.01.063

45. Molodecky NA, Soon IS, Rabi DM, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. *Gastroenterology*. 2012;142(1):46-54.e42. doi:10.1053/j.gastro.2011.10.001

46. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778. doi:10.1016/S0140-6736(17)32448-0

47. Probert CS, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. Epidemiological study of

ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. *Gut*. 1992;33(5):687-693. doi:10.1136/gut.33.5.687

48. Benchimol EI, Guttmann A, Nguyen GC, et al. Inflammatory Bowel Disease in Immigrants to Canada And Their Children: A Population-Based Cohort Study. *Am J Gastroenterol*. 2015;110(4):553-563. doi:10.1038/ajg.2015.52

49. Benchimol EI, Manuel DG, To T, et al. Asthma, Type 1 and Type 2 Diabetes Mellitus, and Inflammatory Bowel Disease amongst South Asian Immigrants to Canada and Their Children: A Population-Based Cohort Study. *PLoS One*. 2015;10(4). doi:10.1371/journal.pone.0123599

50. Virta L, Auvinen A, Helenius H, Huovinen P, Kolho K-L. Association of Repeated Exposure to Antibiotics With the Development of Pediatric Crohn's Disease--A Nationwide, Register-based Finnish Case-Control Study. *Am J Epidemiol*. 2012;175(8):775-784. doi:10.1093/aje/kwr400

51. Kaplan GG, Hubbard J, Korzenik J, et al. The inflammatory bowel diseases and ambient air pollution: A novel association. *Am J Gastroenterol*. 2010;105(11):2412-2419. doi:10.1038/ajg.2010.252

52. Radon K, Windstetter D, Poluda AL, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. *Pediatrics*. 2007;120(2):354-361. doi:10.1542/peds.2006-3624

53. Bernstein CN, Kraut A, Blanchard JF, Rawsthorne P, Yu N, Walld R. The relationship between inflammatory bowel disease and socioeconomic variables. *Am J Gastroenterol*. 2001;96(7):2117-2125. doi:10.1111/j.1572-0241.2001.03946.x

54. Sonnenberg A. Disability from inflammatory bowel disease among employees in West Germany. *Gut*. 1989;30(3):367-370. doi:10.1136/gut.30.3.367

55. Dhaliwal J, Walters T, Mack D, et al. Phenotypic variation in paediatric IBD by age: a multi-centre prospective inception cohort study of the Canadian Children IBD Network. 2019. doi:10.1093/ecco-jcc/jjz106

56. Shah SC, Khalili H, Gower-Rousseau C, et al. Sex-Based Differences in Incidence of Inflammatory Bowel Diseases-Pooled Analysis of Population-Based Studies From Western Countries. 2018. doi:10.1053/j.gastro.2018.06.043

57. Shah SC, Khalili H, Chen CY, et al. Sex-based differences in the incidence of inflammatory bowel diseases—pooled analysis of population-based studies from the Asia-Pacific region. *Aliment Pharmacol Ther*. 2019;49(7):904-911. doi:10.1111/apt.15178

58. Gupta N, Bostrom AG, Kirschner BS, et al. Gender differences in presentation and course of disease in pediatric patients with Crohn disease. *Pediatrics*. 2007;120(6):1418-1425. doi:10.1542/peds.2007-0905

59. Kennedy NA, Lamb CA, Berry SH, et al. The Impact of NOD2 Variants on Fecal Microbiota in Crohn's Disease and Controls Without Gastrointestinal Disease. *Inflamm Bowel Dis*. 2018;24(3):583-592. doi:10.1093/ibd/izx061

60. Frank DN, Robertson CE, Hamm CM, et al. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2011;17(1):179-184. doi:10.1002/ibd.21339

61. Li J, Butcher J, Mack D, Stintzi A. Functional Impacts of the Intestinal Microbiome in the

Pathogenesis of Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2015;21(1):139-153. doi:10.1097/MIB.0000000000000215

62. Kleessen B, Kroesen AJ, Buhr HJ, Blaut M. Mucosal and invading bacteria in patients with inflammatory bowel disease compared with controls. *Scand J Gastroenterol*. 2002;37(9):1034-1041. doi:10.1080/003655202320378220

63. Pascal V, Pozuelo M, Borruel N, et al. A microbial signature for Crohn's disease. *Gut*. 2017;66(5):813-822. doi:10.1136/gutjnl-2016-313235

64. Lepage P, Häsler R, Spehlmann ME, et al. Twin Study Indicates Loss of Interaction Between Microbiota and Mucosa of Patients With Ulcerative Colitis. *Gastroenterology*. 2011;141(1):227-236. doi:10.1053/j.gastro.2011.04.011

65. Zitomersky NL, Atkinson BJ, Franklin SW, et al. Characterization of Adherent Bacteroidales from Intestinal Biopsies of Children and Young Adults with Inflammatory Bowel Disease. *PLoS One*. 2013;8(6):e63686. doi:10.1371/journal.pone.0063686

66. Schirmer M, Denson L, Vlamakis H, et al. Compositional and Temporal Changes in the Gut Microbiome of Pediatric Ulcerative Colitis Patients Are Linked to Disease Course. *Cell Host Microbe*. 2018;24(4):600-610. doi:10.1016/j.chom.2018.09.009

67. Ott SJ, Musfeldt M, Wenderoth DF, et al. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut*. 2004;53(5):685-693. doi:10.1136/gut.2003.025403

68. Hansen R, Russell RK, Reiff C, et al. Microbiota of De-Novo Pediatric IBD: Increased Faecalibacterium Prausnitzii and Reduced Bacterial Diversity in Crohn's But Not in

Ulcerative Colitis. *Am J Gastroenterol*. 2012;107(12):1913-1922. doi:10.1038/ajg.2012.335

69. Chinweije Nwosu F, Thorkildsen L-T, Avershina E, et al. Age-Dependent Fecal Bacterial Correlation to Inflammatory Bowel Disease for Newly Diagnosed Untreated Children. *Gastroenterol Res Pract*. 2013;2013. doi:10.1155/2013/302398

70. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of crohn's disease. *Gastroenterology*. 2012;142(3):482-489. doi:10.1053/j.gastro.2011.11.040

71. De Souza HSP, Fiocchi C, Iliopoulos D. The IBD interactome: An integrated view of aetiology, pathogenesis and therapy. *Nat Rev Gastroenterol Hepatol*. 2017;14(12):739-749. doi:10.1038/nrgastro.2017.110

72. Zhernakova A, van Diemen C, Wijmenga C. Detecting shared pathogenesis from the shared genetics of immune-related diseases. *Nat Rev*. 2009;10(1):43-55. doi:10.1038/nrg2489

73. Coward S, Heitman SJ, Clement F, et al. Ulcerative colitis-associated hospitalization costs: a population-based study. *Can J Gastroenterol Hepatol*. 2015;29(7):357-362. doi:10.1155/2015/627370

74. Singh H, Nugent Z, Targownik LE, El-Matary W, Brownell M, Bernstein CN. Health Care Use by a Population-Based Cohort of Children With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2015;13(7):1302-1309.e3. doi:10.1016/j.cgh.2015.01.022

75. Bernstein CN, Longobardi T, Finlayson G, Blanchard JF. Direct Medical Cost of

Managing IBD Patients: A Canadian Population-based Study. *Inflamm Bowel Dis*. 2012;18(8):1498-1508. doi:10.1002/ibd.21878

76. Benchimol EI, Mack DR, Nguyen GC, et al. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. *Gastroenterology*. 2014;147(4):803-805. doi:10.1053/j.gastro.2014.06.023

77. Benchimol EI, To T, Griffiths AM, Rabeneck L, Guttmann A. Outcomes of pediatric inflammatory bowel disease: socioeconomic status disparity in a universal-access healthcare system. *J Pediatr*. 2011;158(6):960-964. doi:10.1016/j.jpeds.2010.11.039

78. Benchimol EI, Guttmann A, To T, Rabeneck L, Griffiths AM. Changes to surgical and hospitalization rates of pediatric inflammatory bowel disease in Ontario, Canada (1994-2007). *Inflamm Bowel Dis*. 2011;17(10):2153-2161. doi:10.1002/ibd.21591

79. Schaefer ME, Machan JT, Kawatu D, et al. Factors that determine risk for surgery in pediatric patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2010;8(9):789-794. doi:10.1016/j.cgh.2010.05.021

80. Gupta N, Cohen SA, Bostrom AG, et al. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterology*. 2006;130(4):1069-1077. doi:10.1053/j.gastro.2006.02.003

81. Rinawi F, Assa A, Hartman C, et al. Incidence of Bowel Surgery and Associated Risk Factors in Pediatric-Onset Crohn's Disease. *Inflamm Bowel Dis*. 2016;22(12):2917-2923. doi:10.1097/MIB.0000000000000937

82. Aloi M, Lionetti P, Barabino A, et al. Phenotype and disease course of early-onset

pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20(4):597-605. doi:10.1097/01.MIB.0000442921.77945.09

83. Nguyen GC, Bouchard S, Diong C. Access to specialists and emergency department visits in inflammatory bowel disease: A population-based study. *J Crohn's Colitis*. 2019;13(3):330-336. doi:10.1093/ecco-jcc/jjy161

84. Kappelman MD, Porter CQ, Galanko JA, et al. Utilization of healthcare resources by U.S. children and adults with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(1):62-68. doi:10.1002/ibd.21371

85. Nguyen GC, Bayless TM, Powe NR, LaVeist TA, Brant SR. Race and health insurance are predictors of hospitalized Crohn's disease patients undergoing bowel resection. *Inflamm Bowel Dis*. 2007;13(11):1408-1416. doi:10.1002/ibd.20200

86. Nguyen GC, LaVeist TA, Gearhart S, Bayless TM, Brant SR. Racial and Geographic Variations in Colectomy Rates Among Hospitalized Ulcerative Colitis Patients. *Clin Gastroenterol Hepatol*. 2006;4(12):1507-1513. doi:10.1016/j.cgh.2006.09.026

87. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg*. 2000;231(1):38-45. doi:10.1097/00000658-200001000-00006

88. Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology*. 1993;105(6):1716-1723. doi:10.1016/0016-5085(93)91068-S

89. Nguyen GC, Bollegala N, Chong CA. Factors associated with readmissions and outcomes of patients hospitalized for inflammatory bowel disease. *Clin Gastroenterol Hepatol*.

2014;12(11):1897-1904. doi:10.1016/j.cgh.2014.02.042

90. Abou Khalil M, Boutros M, Nedjar H, et al. Incidence Rates and Predictors of Colectomy for Ulcerative Colitis in the Era of Biologics: Results from a Provincial Database. *J Gastrointest Surg*. 2018;22(1):124-132. doi:10.1007/s11605-017-3530-y

91. Targownik LE, Singh H, Nugent Z, Bernstein CN. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. *Am J Gastroenterol*. 2012;107(8):1228-1235. doi:10.1038/ajg.2012.127

92. Sedgwick DM, Barton JR, Hamer-Hodges DW, et al. Population-based study of surgery in juvenile onset Crohn's disease. *Br J Surg*. 1991;78(2):171-175. doi:10.1002/bjs.1800780212

93. Sedgwick DM, Barton JR, Hamer-Hodges DW, Nixon SJ, Ferguson A, Sedgwick MDM. Population-based study of surgery in juvenile onset ulcerative colitis. *Br J Surg*. 1991;78(2):176-178. doi:10.1002/bjs.1800780213

94. Nahon S, Lahmek P, Macaigne G, et al. Socioeconomic deprivation does not influence the severity of Crohn's Disease: Results of a Prospective Multicenter Study. *Inflamm Bowel Dis*. 2009;15(4):594-598. doi:10.1002/ibd.20794

95. Jackson JF, Dhere T, Sitaraman S, Repaka A, Shaukat A. Crohn's Disease in an African-American Population. *Am J Med Sci*. 2008;336(5):389-392. doi:10.1097/MAJ.0b013e31816a5c06

96. Walker DG, Williams HRTT, Kane SP, et al. Differences in inflammatory bowel disease phenotype between South Asians and Northern Europeans living in North West London,

UK. *Am J Gastroenterol*. 2011;106(7):1281-1289. doi:10.1038/ajg.2011.85

97. Nguyen GC, Chong CA, Chong RY. National estimates of the burden of inflammatory bowel disease among racial and ethnic groups in the United States. *J Crohn's Colitis*. 2014;8(4):288-295. doi:10.1016/j.crohns.2013.09.001

98. Benchimol E, Ellen Kuenzig M, Bernstein C, et al. Rural and urban disparities in the care of Canadian patients with inflammatory bowel disease: a population-based study. *Clin Epidemiol*. 2018;(10):1613-1626. doi:10.2147/CLEP.S178056

99. Benchimol E, Boualit M, Wong J, Colombel J-F, Gower-Rousseau C. Predictors of the need for second intestinal resection in children with Crohn's disease. *Inflamm Bowel Dis*. 2011;17:S6. doi:10.1097/00054725-201112002-00014

100. Benchimol EI, Manuel DG, Mojaverian N, et al. Health Services Utilization, Specialist Care, and Time to Diagnosis with Inflammatory Bowel Disease in Immigrants to Ontario, Canada: A Population-Based Cohort Study. *Inflamm Bowel Dis*. 2016;22(10):2482-2490. doi:10.1097/MIB.0000000000000905

101. Ma C, Smith M, Guizzetti L, et al. Assessing National Trends and Disparities in Ambulatory, Emergency Department, and Inpatient Visits for Inflammatory Bowel Disease in the United States (2005–2016). *Clin Gastroenterol Hepatol*. 2020. doi:10.1016/j.cgh.2020.01.023

102. Guttmann A, Lam K, Schultz S, Jaakkimainen L. *Primary Care for Children. In: Jaakkimainen L, Upshur REG, Klein-Geltink JE, et Al., Eds. Primary Care in Ontario: ICES Atlas.* Toronto: The Institiute for Clinical Evaluative Sciences; 2006.

103. Nugent Z, Singh H, Targownik LE, Strome T, Snider C, Bernstein CN. Predictors of Emergency Department Use by Persons with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2016;22(12):2907-2916. doi:10.1097/MIB.0000000000000965

104. Pant C, Deshpande A, Fraga-Lovejoy C, et al. Emergency Department Visits Related to Inflammatory Bowel Disease: Results From Nationwide Emergency Department Sample. *J Pediatr Gastroenterol Nutr*. 2015;61(3):282-284. doi:10.1097/MPG.0000000000000815

105. Pant C, Deshpande A, Sferra TJ, Gilroy R, Olyaee M. Emergency department visits for acute pancreatitis in children: Results from the nationwide emergency department sample 2006-2011. *J Investig Med*. 2015;63(4):646-648. doi:10.1097/JIM.0000000000000154

106. deBruyn JCC, Soon IS, Hubbard J, Wrobel I, Panaccione R, Kaplan GG. Nationwide temporal trends in incidence of hospitalization and surgical intestinal resection in pediatric inflammatory bowel diseases in the United States from 1997 to 2009. *Inflamm Bowel Dis*. 2013;19(11):2423-2432. doi:10.1097/MIB.0b013e3182a56148

107. Reich KM, Chang HH-J, Rezaie A, et al. The incidence rate of colectomy for medically refractory ulcerative colitis has declined in parallel with increasing anti-TNF use: a time-trend study. *Aliment Pharmacol Ther*. 2014;40(6):629-638. doi:10.1111/apt.12873

108. Nguyen GC, Nugent Z, Shaw S, Bernstein CN. Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. *Gastroenterology*. 2011;141(1):90-97. doi:10.1053/j.gastro.2011.03.050

109. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of Adalimumab Therapy on Incidence of Hospitalization and Surgery in Crohn's Disease: Results From the CHARM Study. *Gastroenterology*. 2008;135(5):1493-1499. doi:10.1053/j.gastro.2008.07.069

110. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology*. 2005;128(4):862-869. doi:10.1053/j.gastro.2005.01.048

111. Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. *Gastroenterology*. 2014;146(1):110-118. doi:10.1053/j.gastro.2013.09.032

112. Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther*. 2017;45(1):3-13. doi:10.1111/apt.13847

113. Murthy SK, Begum J, Benchimol EI, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: A population-based interrupted time series study. *Gut*. 2020;69(2):274-282. doi:10.1136/gutjnl-2019-318440

114. Ma C, Moran GW, Benchimol EI, et al. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *Am J Gastroenterol*. 2017;112(12):1840-1848. doi:10.1038/ajg.2017.394

115. Rahman A, Jairath V, Feagan BG, et al. Declining hospitalisation and surgical intervention rates in patients with Crohn's disease: a population-based cohort. *Aliment Pharmacol Ther*. 2019;50(10):1086-1093. doi:10.1111/apt.15511

116. Carroll MW, Kuenzig ME, Mack DR, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: Children and Adolescents with IBD. *J Can Assoc Gastroenterol*.

2019;2(S1):S49-S67. doi:10.1093/jcag/gwy056

117. Israeli E, Ryan JD, Shafer L-A, Bernstein CN. Younger age at diagnosis is associated with panenteric, but not more aggressive, Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12(1):72-79. doi:10.1016/j.cgh.2013.06.027

118. Kaplan GG, Seow CH, Ghosh S, et al. Decreasing Colectomy Rates for Ulcerative Colitis: A Population-Based Time Trend Study. *Am J Gastroenterol*. 2012;107(12):1879-1887. doi:10.1038/ajg.2012.333

119. Safran C. Using routinely collected data for clinical research. *Stat Med*. 1991;10(4):559-564. doi:10.1002/sim.4780100407

120. Hemkens LG, Benchimol EI, Ead S, et al. The reporting of studies using routinely collected health data was often insufficient. *J Clin Epidemiol*. 2016;79:104-111. doi:10.1016/j.jclinepi.2016.06.005

121. Muggah E, Graves E, Bennett C, Manuel DG. Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. *BMC Public Health*. 2013;13(1):16. doi:10.1186/1471-2458-13-16

122. ICES. https://www.ices.on.ca/. Published 2020. Accessed January 31, 2020.

123. Brown JS, Holmes JH, Shah K, Hall K. Distributed Health Data Networks: A Practical and Preferred Approach to Multi-Institutional Evaluations of Comparative Effectiveness, Safety, and Quality of Care. *Med Care*. 2010;48(6):45-51. doi:10.1097/MLR.0b013e3181d9919f

124. Maro JC, Platt R, Holmes JH, et al. Design of a national distributed health data network.

Ann Intern Med. 2009;151(5):341-344. doi:10.7326/0003-4819-151-5-200909010-00139

125. Platt R, Wilson M, Chan KA, Benner JS, Marchibroda J, McClellan M. The new sentinel network - Improving the evidence of medical-product safety. *N Engl J Med*. 2009;361(7):645-647. doi:10.1056/NEJMp0905338

126. Suissa S, Henry D, Caetano P, et al. Cnodes: The canadian network for observational drug effect studies. *Open Med*. 2012;6(4):134-140. doi:10.1002/pds.4936

127. Bazelier MT, Eriksson I, de Vries F, et al. Data management and data analysis techniques in pharmacoepidemiological studies using a pre-planned multi-database approach: A systematic literature review. *Pharmacoepidemiol Drug Saf*. 2015;24(9):897-905. doi:10.1002/pds.3828

128. Selmer R, Haglund B, Furu K, et al. Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy. *Pharmacoepidemiol Drug Saf*. 2016;25(10):1160-1169. doi:10.1002/pds.4033

129. Li X, Fireman BH, Curtis JR, et al. Validity of Privacy-Protecting Analytical Methods That Use only Aggregate-Level Information to Conduct Multivariable-Adjusted Analysis in Distributed Data Networks. *Am J Epidemiol*. 2019;188(4):709-723. doi:10.1093/aje/kwy265

130. Toh S, Gagne JJ, Rassen JA, Fireman BH, Kulldorff M, Brown JS. Confounding adjustment in comparative effectiveness research conducted within distributed research networks. *Med Care*. 2013;51:S4-S10. doi:10.1097/MLR.0b013e31829b1bb1

131. Toh S, Reichman ME, Houstoun M, et al. Multivariable confounding adjustment in distributed data networks without sharing of patient-level data. *Pharmacoepidemiol Drug Saf*. 2013;22(11):1171-1177. doi:10.1002/pds.3483

132. Toh S, Shetterly S, Powers JD, Arterburn D. Privacy-preserving analytic methods for multisite comparative effectiveness and patient-centered outcomes research. *Med Care*. 2014;52(7):664-668. doi:10.1097/MLR.0000000000000147

133. Yoshida K, Gruber S, Fireman BH, Toh S. Comparison of Privacy-Protecting Analytic and Data-sharing Methods: a Simulation Study. *Pharmacoepidemiol Drug Saf*. 2018;27(9):1034-1041. doi:10.1002/pds.4615

134. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med*. 2012;172(20):1582-1589. doi:10.1001/2013.jamainternmed.34

135. Rassen JA, Avorn J, Schneeweiss S. Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple health care utilization databases. *Pharmacoepidemiol Drug Saf*. 2010;19(8):848-857. doi:10.1002/pds.1867

136. Moineddin R, Urquia ML. Regression analysis of aggregate continuous data. *Epidemiology*. 2014;25(6):929-930. doi:10.1097/EDE.0000000000000172

137. Yang D, Zolfaghari S, Postuma R, Saha-Chaudhuri P. A comparison of privacy-preserving statistical methods for analyzing distributed data with binary outcome variables. In: *Canadian Society for Epidemiology and Biostatistics*. Ottawa, ON; :Abstract 174.

138. Hansen RA, Zeng P, Ryan P, et al. Exploration of heterogeneity in distributed research network drug safety analyses. *Res Synth Methods*. 2014;5(4):352-370. doi:10.1002/jrsm.1121

139. Platt RW, Dormuth CR, Chateau D, Filion K. Observational Studies of Drug Safety in Multi-Database Studies: Methodological Challenges and Opportunities. *eGEMs (Generating Evid Methods to Improv patient outcomes)*. 2016;4(1):9. doi:10.13063/2327-9214.1221

140. Borenstein M, Hedges L V, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97-111. doi:10.1002/jrsm.12

141. Statistics Canada. Population by year, by province and territory. Summary Table. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm. Published 2014. Accessed May 30, 2018.

142. Ma C, Crespin M, Proulx M-C, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. *BMC Gastroenterol*. 2012;12(1):39. doi:10.1186/1471-230X-12-39

143. Payne EH, Gebregziabher M, Hardin JW, Ramakrishnan V, Egede LE. An empirical approach to determine a threshold for assessing overdispersion in Poisson and negative binomial models for count data. *Commun Stat Simul Comput*. 2018;47(6):1722-1738. doi:10.1080/03610918.2017.1323223

144. Allison PD. *Logistic Regression Using SAS: Theory and Application, Second Edition ITPro Collection*. SAS Institute; 2012.

https://books.google.ca/books/about/Logistic_Regression_Using_SAS.html?id=NF9kwF1lOF4C&redir_esc=y. Accessed August 31, 2019.

145. Allison PD. Logistic Regression Using the SAS® System. *Technometrics*. 2000;42(3):323-324. doi:10.1080/00401706.2000.10486078

146. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(6):1314-1321. doi:10.1002/ibd.21493

147. Glazier RH, Creatore MI, Agha MM, et al. Socioeconomic misclassification in Ontario's health care registry. *Can J Public Heal*. 2003;94(2):140-143.

148. Hyams J, Crandall W, Kugathasan S, et al. Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children. *Gastroenterology*. 2007;132(3):863-873. doi:10.1053/j.gastro.2006.12.003

149. Benchimol EI, Manuel DG, Guttmann A, et al. Changing Age Demographics of Inflammatory Bowel Disease in Ontario, Canada. *Inflamm Bowel Dis*. 2014;20(10):1761-1769. doi:10.1097/MIB.0000000000000103

150. Kaplan GG, Bernstein CN, Coward S, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: Epidemiology. *J Can Assoc Gastroenterol*. 2019;2(S1):S6-S16. doi:10.1093/jcag/gwy054

151. Berger J. *Patterns of Health Care in Ontario. The ICES Practice Atlas, Volume 1, 1994*. Vol 151.; 1994.

152. Canadian Institute for Health Information. *Highlights of 2011–2012 Emergency*

Department Visits and Inpatient Hospitalizations.; 2013. https://secure.cihi.ca/free_products/DAD-NACRS_Quick Stats_Highlights_2011-2012_EN_web.pdf. Accessed November 30, 2019.

153. Colantonio A, Croxford R, Farooq S, Laporte A, Coyte PC. Trends in hospitalization associated with traumatic brain injury in a publicly insured population, 1992-2002. *J Trauma - Inj Infect Crit Care*. 2009;66(1):179-183. doi:10.1097/TA.0b013e3181715d66

154. Fu TS, Jing R, McFaull SR, Cusimano MD. Recent trends in hospitalization and in-hospital mortality associated with traumatic brain injury in Canada: A nationwide, population-based study. *J Trauma Acute Care Surg*. 2015;79(3):449-455. doi:10.1097/TA.0000000000000733

155. Checchin D, Freeman M, Terres JAR. Temporal Trends and Regional Variation in Hospitalization Rates for Stroke in Canada, 2002-2009 [Abstract 331]. In: *Canadian Journal of Cardiology*. Vol 28. ; :S220. doi:10.1016/j.cjca.2012.07.327

156. Evans C, Kingwell E, Zhu F, Oger J, Zhao Y, Tremlett H. Hospital admissions and MS: Temporal trends and patient characteristics. *Am J Manag Care*. 2012;18(11):735-742.

157. Marrie RA, Elliott L, Marriott J, et al. Dramatically changing rates and reasons for hospitalization in multiple sclerosis. *Neurology*. 2014;83(10):929-937. doi:10.1212/WNL.0000000000000753

158. Rai SK, Antonio J, Na-Zubieta A~, et al. Trends in Gout and Rheumatoid Arthritis Hospitalizations in Canada From 2000 to 2011. *Arthritis Care Res (Hoboken)*. 2017;69(5):758-762. doi:10.1002/acr.23012

159. To T, Guttmann A, Dick PT. *Inpatient and Day Surgery Use by Children in Ontario*.; 2001. https://www.ices.on.ca/Publications/Atlases-and-Reports/2001/Inpatient-and-day-surgery-use.

160. Canadian Institute for Health Information. *Asthma Hospitalizations Among Children and Youth in Canada: Trends and Inequalities Chartbook*. Ottawa, ON; 2018.

161. Crighton EJ, Mamdani MM, Upshur RE. A population based time series analysis of asthma hospitalisations in Ontario, Canada: 1988 to 2000. *BMC Health Serv Res*. 2001;1:1-6. doi:10.1186/1472-6963-1-1

162. Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent trends in hospitalization for diabetic ketoacidosis in Ontario children. *Diabetes Care*. 2002;25(9):1591-1596. doi:10.2337/diacare.25.9.1591

163. Marrie RA, O'Mahony J, Maxwell CJ, et al. High rates of health care utilization in pediatric multiple sclerosis: A Canadian population-based study. *PLoS One*. 2019;14(6):1-13. doi:10.1371/journal.pone.0218215

164. Huh G, Yoon H, Choi YJ, et al. Trends in emergency department visits and hospitalization rates for inflammatory bowel disease in the era of biologics. *PLoS One*. 2019;14(1):e0210703. doi:10.1371/journal.pone.0210703

165. Booth GL, Hux JE, Fang J, Chan BTB. Time trends and geographic disparities in acute complications of diabetes in Ontario, Canada. *Diabetes Care*. 2005;28(5):1045-1050. doi:10.2337/diacare.28.5.1045

166. Nakhla M, Rahme E, Simard M, Guttmann A. Outcomes associated with a pediatric

clinical diabetes network in Ontario: a population-based time-trend analysis. *C Open*. 2017;5(3):E586-E593. doi:10.9778/cmajo.20170022

167. Sullivan PW, Ghushchyan V, Kavati A, et al. Trends in Asthma Control, Treatment, Health Care Utilization, and Expenditures Among Children in the United States by Place of Residence: 2003-2014. *J Allergy Clin Immunol Pract*. 2019;7:1835-1842. doi:10.1016/j.jaip.2019.01.055

168. Hoffenberg EJ, Park KT, Dykes DM, et al. Appropriateness of Emergency Department Use in Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr*. 2014;59(3):324-326. doi:10.1097/MPG.0000000000000457

169. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: Prevalence, health care utilization, and mortality. *Pediatrics*. 2002;110(2 I):315-322. doi:10.1542/peds.110.2.315

170. Ma C, Moran GW, Benchimol EI, et al. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *Am J Gastroenterol*. 2017;112(12):1840-1848. doi:10.1038/ajg.2017.394

171. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy Rate Comparison After Treatment of Ulcerative Colitis With Placebo or Infliximab. *Gastroenterology*. 2009;137(4):1250-1260. doi:10.1053/j.gastro.2009.06.061

172. Costa J, Magro F, Caldeira D, Alarcão J, Sousa R, Vaz-Carneiro A. Infliximab reduces hospitalizations and surgery interventions in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Inflamm Bowel Dis*. 2013;19(10):2098-2110. doi:10.1097/MIB.0b013e31829936c2

173. Abou Khalil M, Boutros M, Nedjar H, et al. Incidence Rates and Predictors of Colectomy for Ulcerative Colitis in the Era of Biologics: Results from a Provincial Database. *J Gastrointest Surg*. 2018;22(1):124-132. doi:10.1007/s11605-017-3530-y

174. Ramadas A V, Gunesh S, Thomas GAO, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. *Gut*. 2010;59(9):1200-1206. doi:10.1136/gut.2009.202101

175. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12(3):414-422. doi:10.1016/j.cgh.2013.06.019

176. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549. doi:10.1016/S0140-6736(02)08512-4

177. Rosen MJ, Minar P, Vinks AA. Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis. *Aliment Pharmacol Ther*. 2015;41(11):1094-1103. doi:10.1111/apt.13175

178. Benchimol EI, Bernstein CN, Bitton A, et al. The impact of inflammatory bowel disease in Canada 2018: A scientific report from the Canadian Gastro-Intestinal Epidemiology Consortium to Crohn's and Colitis Canada. *J Can Assoc Gastroenterol*. 2019;2(S1):1-5. doi:10.1093/jcag/gwy052

179. Strohl M, Zhang X, Lévesque D, Bessissow T. Transition care in inflammatory bowel disease: A needs assessment survey of Quebec gastroenterologists and allied nurses.

World J Gastrointest Pharmacol Ther. 2017;8(3):186-192. doi:10.4292/wjgpt.v8.i3.186

180. Nicholls SG, Langan SM, Benchimol EI. Reporting and Transparency in Big Data: The Nexus of Ethics and Methodology. In: Mittelstadt B., Floridi L. (eds) The Ethics of Biomedical Big Data. Law, Governance and Technology Series. In: Vol 29. Springer, Cham; 2016:339-365. doi:10.1007/978-3-319-33525-4_15

181. Local Health Integration Network (LHIN). http://www.lhins.on.ca/. Published 2014. Accessed February 2, 2020.

182. Mehta CR, Patel NR, Senchaudhuri P. Efficient Monte Carlo Methods for Conditional Logistic Regression. *J Am Stat Assoc*. 2000;95(449):99-108. doi:10.1080/01621459.2000.10473906

183. Viechtbauer W. *Package "Metafor."*; 2019. https://cran.r-project.org/web/packages/metafor/metafor.pdf. Accessed September 8, 2019.

184. Viechtbauer W. Conducting meta-analyses in R with the metafor. *J Stat Softw*. 2010;36(3):1-48. doi:10.18637/jss.v036.i03

185. Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods*. 2016;7(1):55-79. doi:10.1002/jrsm.1164

186. Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat*. 2005;30(3):261-293. doi:10.3102/10769986030003261

187. Mickey RM, Greenland S. The Impact of Confounder Selection Criteria On Effect Estimation. *Am J Epidemiol*. 1989;130(5):125-137.

188. Clogg CC, Petkova E, Haritou A. Statistical Methods for Comparing Regression Coefficients Between Models. *Am Jouranl Sociol*. 1995;100(5):1261-1293. doi:10.1086/230638

189. R Core Team. R: A language and environment for statistical computing. 2019. https://www.r-project.org/.

190. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. www.handbook.cochrane.org. Published 2011. Accessed October 24, 2019.

191. Borenstein M, Higgins JPT, Hedges L V., Rothstein HR. Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Res Synth Methods*. 2017;8(1):5-18. doi:10.1002/jrsm.1230

192. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *Am J Epidemiol*. 1999;150(5):469-475. doi:10.1093/oxfordjournals.aje.a010035

193. ICES. Privacy at ICES. https://www.ices.on.ca/Data-and-Privacy/Privacy-at-ICES. Published 2020. Accessed February 2, 2020.

194. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: Rationale, conduct, and reporting. *BMJ*. 2010;340(7745):521-525. doi:10.1136/bmj.c221

195. Yamaguchi Y, Sakamoto W, Goto M, et al. Meta-analysis of a continuous outcome combining individual patient data and aggregate data: A method based on simulated individual patient data. *Res Synth Methods*. 2014;5(4):322-351. doi:10.1002/jrsm.1119

196. Coloma PM, Schuemie MJ, Trifirò G, et al. Combining electronic healthcare databases in

Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacoepidemiol Drug Saf*. 2011;20(1):1-11. doi:10.1002/pds.2053

197. Curtis LH, Weiner MG, Boudreau DM, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. *Pharmacoepidemiol Drug Saf*. 2012;21:23-31. doi:10.1002/pds.2336

198. Ryan PB, Madigan D, Stang PE, Marc Overhage J, Racoosin JA, Hartzema AG. Empirical assessment of methods for risk identification in healthcare data: Results from the experiments of the Observational Medical Outcomes Partnership. *Stat Med*. 2012;31(30):4401-4415. doi:10.1002/sim.5620

199. Trifir G, Coloma PM, Rijnbeek PR, et al. Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how? doi:10.1111/joim.12159

200. Fireman B, Lee J, Lewis N, Bembom O, Van Der Laan M, Baxter R. Influenza Vaccination and Mortality: Differentiating Vaccine Effects From Bias. *Am J Epidemiol*. 2009;170(5):650-656. doi:10.1093/aje/kwp173

201. Health Data Research Network Canada. Health Data Research Network Canada. https://www.hdrn.ca/. Published 2020. Accessed February 8, 2020.

202. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's Disease and Ulcerative Colitis in a Central Canadian Province: A Population-based Study. *Am J Epidemiol*. 1999;149(10):916-924. doi:10.1093/oxfordjournals.aje.a009735

203. Rezaie A, Quan H, Fedorak RN, Panaccione R, Hilsden RJ. Development and validation

of an administrative case definition for inflammatory bowel diseases. *Can J Gastroenterol*. 2012;26(10):711-717. doi:10.1155/2012/278495

204. Benchimol EI, Guttmann A, Mack DR, et al. Validation of international algorithms to identify adults with inflammatory bowel disease in health administrative data from Ontario, Canada. *J Clin Epidemiol*. 2014;67(8):887-896. doi:10.1016/j.jclinepi.2014.02.019

205. Deeks JJ, Higgins JPT AD (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). *Cochrane*. 2019.

Chapter 6. Appendices

Table of Contents

Appendix A. Summary of Matching Children with IBD to Children without Inflammatory Bowel Disease

Table A.1 The summary of the matching results of children with inflammatory bowel disease.

Number of matched children without IBD	Number of Children with IBD	Percentage of Children with IBD
0	23	0.42
1	48	0.87
2	93	1.69
3	112	2.03
4	103	1.87
5	5139	93.13

Abbreviations: IBD, Inflammatory bowel disease.

Table A.2 The descriptive statistics of the children with inflammatory bowel disease with no matched children without inflammatory bowel disease.

Characteristic		Number of unmatched children with IBD
Sex	Females	13 (56.5%)
	Males	10 (43.5%)
Rural residence at diagnosis	Urban	1 (4.4%)
	Rural	19 (82.6%)
	Unknown	3 (13.0%)
Neighbourhood income quintile at diagnosis	First (lowest)	6 (26.1%)
	Second	4 (17.4%)
	Third	1 (4.4%)
	Fourth	5 (21.7%)
	Fifth (Highest)	1 (4.4%)
	Unknown	6 (26.1%)

Abbreviations: IBD, inflammatory bowel disease.

Appendix B. IBD-Specific and IBD-Related Diagnosis Codes

Table B.1 IBD-specific and IBD-related diagnosis codes.

Description	ICD-9	OHIP diagnostic code	ICD-10
IBD-specific			
Crohn's disease	555.x	555	K50.x
Ulcerative colitis	556.x	556	K51.x
IBD-related			
Anorexia	7830	787	R63.0
Abnormal Weight Gain	783.1		R63.5
Abnormal Weight Loss	783.2		R63.4
Lack of expected normal physiological development	783.4		R62.8, R62.9
Symptoms involving digestive system, including: (787.0) Nausea and vomiting ; (787.1) Heartburn; (787.2) Dysphagia; (787.3) Gas/bloating; (787.6) Encopresis, fecal incontinence; (787.9) Other symptoms involving digestive system	787.x	787	R11.x, R12.x, R13.x, R14.x, R15.x, R19.x
Abdominal pain	7890	787	R10.x
Dyspepsia	536.8	536	K30
Cachexia	799.4		R64
Esophagitis	530.1	530	K20, K21.x
Ulcer of esophagus	5302		K22.1
Gastric ulcer	531.x	531	K25.x
Duodenal ulcer	532.x	532	K26.x
Peptic ulcer	533.x		K27.x
GJ ulcer	534.x	534	K28.x
Gastritis/duodenitis	535.x	535	K29.x

Description	ICD-9	OHIP diagnostic code	ICD-10
Intestinal obstruction	560.8 560.9	560	K31.5 K56.6
Rectal/anal hemorrhage	569.3	569	K62.5
Other disorder of rectum/anus, including: ulcer; pain, sphincter tear (healed); dysplasia; other specified, including proctitis, inflamm.	569.4	569	K62.6, K62.8
Abscess of the intestine	569.5	569	K63.0
Other disorders of intestine, including: fistula (excl rectum); ulcer of intestine; perforation; angiodysplasia, no hemorrhage; angiodysplasia, with hemorrhage; dieulafoy; and other (including enteroptosis, granuloma of intestine, prolapse of intestine, pericolitis, perisigmoiditis, visceroptosis)	569.8	569	K63.2, K63.3, K63.1, K552.x, K638.x
Malabsorption	262, 263.0, 263.1, 263.2, 263.9, 579.8, 579.9	579	E43, E44.0, E44.1, E45, E46, K90.8, K90.9
Anal Fistula	565.1	565	K60.3
Anal Abscess	566	566	K610, K611, K612, K613, K614
Ureteral Fistula	593.8		N288.1, N288.8
Urethral Fistula	599.1		N36.0
Fistula of stomach & duod	537.4		K31.6
Vesical fistula	596.2		N32.2
Fistula involving female GU	619.x		N82.x
Hemorrhoids, including: (455.9) Anal skin tags	455.x	455	I84.x

Description	ICD-9	OHIP diagnostic code	ICD-10
Rheumatoid arthritis	713.1, 714.x, 716.4, 716.5, 716.6, 716.7, 716.8, 716.9	714	M050, M052, M053, M058, M059, M060, M061 M062, M064, M068 M069, M070, M074, M075, M076, M080, M081, M082, M083, M084, M088, M089, M090, M091, M092, M098, M130, M131, M139
Arthropathy associated GI cause	713.3		M074 M076 M075
Inflammatory spondylopathies, including: (720.0) Ankylosing spondylitis; (720.1) Spinal enthesopathy; (720.2) Sacroiliitis; (720.8) Other inflammatory; (720.9) Other unspecified inflammatory	720.x	720	M45.x, M46.x
Scleritis & episcleritis	379.x	379	H15.x
Unspecified iridocyclitis (uveitis NOS)	364.3	364	H20.9
Chorioretinitis, unspecified (uveitis, posterior NOS)	363.2	363	H30.9
Acute and subacute iridocyclitis	364	364	H20.0
Erythema nodosum	695.2	695	L52
Pyoderma	6860	686	L08.0
Pyogenic granuloma of the skin and soft tissue	686.1	686	L98.0
Oral aphthae	528.2	528	K12.0
Short stature	783.4		E34.3

Description	ICD-9	OHIP diagnostic code	ICD-10
Osteoporosis	7330.x, 7331	733	M80.x, M81.x, M82.x, M83.x
Osteomyelitis	730, 730.1, 730.2	730	M86.x
Acute glomerulonephritis	580.x	580	N00.x
Nephrolithiasis	592.x	592	N20.x
Primary Sclerosing Cholangitis	576.1	576	K83.0
Venous embolism/thrombosis	453.x		I82.x

Abbreviations: IBD, inflammatory bowel disease; ICD-9, the 9th revision of the International Statistical Classification of Diseases and Related Health Problems; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; OHIP, Ontario Health Insurance Plan.

Appendix C. Summary of Excluded Outpatient Visits

Table C.1 Codes for infusions, telephone, or tele-medicine outpatient visits.

Code type	Code
Infusion	G376, G379
Telephone	K034, K730-K739
Tele-medicine	B100-B102, B200, B201

Table C.2 Outpatient Visits Excluded Due To Associated Tele-Medicine, Transfusion, Or Telephone Call Codes.

Type of outpatient visit	Population	Number of outpatient visits that were not physician clinic visits	Total number of outpatient visits	Proportion of outpatient visits that were not in clinic visits (%)
IBD-specific	IBD	3837	190765	2.01
	CD	2744	128852	2.13
	UC	931	53296	1.75
IBD-related	IBD	4559	243470	1.87
	CD	3204	162409	1.97
	UC	1132	69080	1.64
All-cause	IBD	6386	608783	1.05
	Non-IBD	5038	1216903	0.41

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Appendix D. Validated IBD-related Surgery Codes in CIHI-DAD

Table D.1 Validated Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) codes for resection and colectomy in CD and UC.

CCP Codes for Resection/Colectomy	
RESECTION/COLECTOMY FOR CD[1]	**COLECTOMY FOR UC[2]**
5741- multiple segmental resection of small intestine	
5742- Other partial resection of small intestine	
5743- Total removal of small intestine	
575- partial excision of large intestine	575- partial excision of large intestine
5751- multiple segmental resection of large intestine	5751- multiple segmental resection of large intestine
5753-right hemicolectomy	5753-right hemicolectomy
5755-left hemicolectomy	5755-left hemicolectomy
576-total colectomy	576-total colectomy
5752- cecectomy	5752- cecectomy
5754- resection of transverse colon	5754- resection of transverse colon
5756- sigmoidectomy	5756- sigmoidectomy
5759- other partial excision of large intestine	5759- other partial excision of large intestine

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

Table D.2 Validated Canadian Classification of Health Intervention (CCI) Codes for Resection and Colectomy in Crohn's Disease.[1]

Procedural codes	Definition
1.NK.87.xx	Excision partial, small intestine
1.NM.87.xx	Excision partial, large intestine
1.NM.89.xx	Excision total, large intestine
1.NQ.87.xx	Excision partial, rectum
1.NQ.89.xx	Excision total, rectum (including proctocolectomy)
1.NQ.90.xx*	Excision total with reconstruction, rectum
1.NM.91.xx**	Excision radical, large intestine

*Was not included in validation algorithm but was used prior to 2006 and was replaced by 1NQ89.

**Was not included in the Crohn's disease validation algorithm but was included in the ulcerative colitis validation algorithm.

Table D.3 Validated Canadian Classification of Health Intervention (CCI) codes for resection and colectomy in ulcerative colitis.[2]

Procedural codes	Definition
1.NM.87.xx	Excision partial, large intestine
1.NM.89.xx	Excision total, large intestine endoscopic
1.NM.91.xx	Excision radical, large intestine
1.NQ.89.xx or 1.NQ.90.xx	Excision total, rectum or excision total with reconstruction, rectum using open approach with ileum

References

1. Ma C, Moran GW, Benchimol EI, et al. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *Am J Gastroenterol*. 2017;112(12):1840-1848. doi:10.1038/ajg.2017.394
2. Ma C, Crespin M, Proulx M-C, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. *BMC Gastroenterol*. 2012;12(1):39. doi:10.1186/1471-230X-12-39

Appendix E. Visual Plots Assessing Statistically Significant Violations of Cox Proportional Hazards Assumption

Appendix E can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter2_E_F_G

Appendix F. Hypothesis Testing of the Cox Proportional Hazards Assumption

Appendix F can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter2_E_F_G

Appendix G. Plots of Each Outcome Against Time

Appendix G can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter2_E_F_G

Appendix H. Models Convergence Issues in LHINs

Table H.1 Summary of model convergence errors and decisions for the distributed network meta-analysis.

Regression Model	Outcome	Population	Outcome Type	Follow up from diagnosis (years)	Non-converging LHIN(s)	Decision
Negative binomial/ Poisson	Hospitalizations	Ulcerative colitis	IBD-specific	1	6	Drop LHIN from meta-analysis
		IBD and non-IBD	All-cause	3	1, 8	Drop LHINs from meta-analysis
Logistic	Surgery	Crohn's disease	Intestinal resection	1	2, 3, 5, 6, 7, 8, 11	Forego analysis
				3	2, 5, 6	Drop LHINs from meta-analysis
				5	5	Drop LHIN from meta-analysis
		Ulcerative colitis	Colectomy	1	2, 3, 4, 5, 6, 7, 8, 15, 16	Forego analysis
				3	3, 4, 5, 7, 8	Forego analysis
				5	3, 5, 7	Drop LHIN from meta-analysis
Exact Logistic (network Monte Carlo method)	Surgery	Crohn's disease		1	4, 6, 15	Drop LHINs from meta-analysis
				3	2, 3, 4, 11, 15	Forego analysis
				5	2, 3, 4, 8, 11, 15, 16	Forego analysis

Regression Model	Outcome	Population	Outcome Type	Follow up from diagnosis (years)	Non-converging LHIN(s)	Decision
		Ulcerative colitis		5	11, 15	Drop LHINs from meta-analysis

Abbreviations: IBD, inflammatory bowel disease; LHIN, local health integration network.

Appendix I. Results of LHIN-Based Analysis

Appendix I can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter3_I_J_K_L

Appendix J. Forest Plots of LHIN-Based Analysis

Appendix J can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter3_I_J_K_L

Appendix K. Results of Sensitivity Analyses to Assess Impact of Pediatric Care Centres

Appendix K can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter3_I_J_K_L

Appendix L. Forest Plots of Sensitivity Analyses to Assess Impact of Pediatric Care Centres

Appendix L can be found online at:
https://osf.io/53uxn/?view_only=377085e21a144db9aba5369aab879e71

File Name:

Appendices_Chapter3_I_J_K_L

Appendix M. Sensitivity Analysis Assessing the Robustness of the Individual-level Analysis Effect Estimates to the Exclusion of Residents from LHIN 14

Table M.1 The sensitivity analysis of the robustness of the individual level model provincial estimate after the removal of LHIN 14.

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
Poisson/Negative Binomial	Hospitalization	IBD	IBD-specific	1	N/A	0.981 (0.973-0.990)	0.980 (0.972-0.989)
				3	N/A	0.974 (0.967-0.982)	0.974 (0.966-0.982)
				5	N/A	0.975 (0.968-0.982)	0.975 (0.968-0.982)
			IBD-related	1	N/A	0.981 (0.973-0.990)	0.980 (0.972-0.989)
				3	N/A	0.974 (0.966-0.981)	0.974 (0.966-0.981)
				5	N/A	0.974 (0.967-0.981)	0.974 (0.967-0.981)
		CD	IBD-specific	1	N/A	0.982 (0.972-0.992)	0.982 (0.971-0.992)
				3	N/A	0.971 (0.962-0.980)	0.972 (0.962-0.981)
				5	N/A	0.970 (0.962-0.979)	0.971 (0.962-0.979)
			IBD-related	1	N/A	0.982 (0.972-0.992)	0.982 (0.972-0.992)
				3	N/A	0.971 (0.962-0.980)	0.971 (0.962-0.980)
				5	N/A	0.970 (0.962-0.979)	0.970 (0.962-0.979)
		UC	IBD-specific	1	N/A	0.986 (0.970-1.002)	0.984 (0.968-1.001)
				3	N/A	0.985 (0.971-1.000)	0.984 (0.969-0.999)
				5	N/A	0.989 (0.975-1.003)	0.988 (0.974-1.003)
			IBD-related	1	N/A	0.984 (0.969-1.000)	0.982 (0.966-0.999)

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
				3	N/A	0.982 (0.968-0.997)	0.981 (0.967-0.996)
				5	N/A	0.986 (0.972-1.000)	0.985 (0.971-0.999)
		IBD	All	1	N/A	0.982 (0.976-0.988)	0.981 (0.975-0.987)
				3	N/A	0.974 (0.966-0.982)	0.974 (0.966-0.982)
				5	N/A	0.974 (0.967-0.982)	0.974 (0.967-0.982)
		Non-IBD	All	1	N/A	0.972 (0.954-0.991)	0.976 (0.957-0.995)
				3	N/A	0.966 (0.956-0.977)	0.968 (0.957-0.978)
				5	N/A	0.957 (0.949-0.965)	0.958 (0.949-0.966)
	Emergency department visit	IBD	IBD-specific	1	N/A	1.003 (0.990-1.016)	1.001 (0.988-1.015)
				3	N/A	1.000 (0.990-1.011)	1.000 (0.989-1.010)
				5	N/A	1.002 (0.993-1.012)	1.002 (0.992-1.012)
			IBD-related	1	N/A	1.018 (1.008-1.028)	1.017 (1.007-1.027)
				3	N/A	1.014 (1.005-1.022)	1.013 (1.005-1.022)
				5	N/A	1.015 (1.007-1.023)	1.014 (1.007-1.022)
		CD	IBD-specific	1	N/A	1.010 (0.994-1.027)	1.009 (0.992-1.026)
				3	N/A	1.002 (0.989-1.016)	1.002 (0.988-1.015)
				5	N/A	1.002 (0.990-1.014)	1.001 (0.989-1.014)
			IBD-related	1	N/A	1.020 (1.007-1.033)	1.019 (1.006-1.032)
				3	N/A	1.015 (1.004-1.025)	1.014 (1.003-1.025)

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
				5	N/A	1.013 (1.003-1.023)	1.012 (1.002-1.022)
		UC	IBD-specific	1	N/A	0.986 (0.964-1.009)	0.985 (0.963-1.008)
				3	N/A	0.995 (0.977-1.014)	0.995 (0.976-1.014)
				5	N/A	1.003 (0.985-1.021)	1.003 (0.985-1.021)
			IBD-related	1	N/A	1.012 (0.995-1.030)	1.011 (0.994-1.028)
				3	N/A	1.013 (0.999-1.027)	1.012 (0.998-1.027)
				5	N/A	1.020 (1.006-1.033)	1.020 (1.006-1.033)
		IBD	All-cause	1	N/A	1.008 (1.000-1.017)	1.007 (0.999-1.016)
				3	N/A	1.008 (1.001-1.016)	1.008 (1.001-1.015)
				5	N/A	1.010 (1.003-1.016)	1.009 (1.002-1.016)
		Non-IBD	All-cause	1	N/A	0.993 (0.988-0.998)	0.993 (0.988-0.998)
				3	N/A	0.997 (0.993-1.000)	0.996 (0.993-1.000)
				5	N/A	0.998 (0.994-1.001)	0.997 (0.994-1.001)
	Outpatient visit	IBD	IBD-specific	1	Before 2005	0.987 (0.981-0.994)	0.989 (0.982-0.995)
				1	After 2005	1.060 (1.050-1.069)	1.058 (1.049-1.068)
				3	Before 2005	1.001 (0.995-1.006)	1.002 (0.996-1.008)
				3	After 2005	1.039 (1.030-1.048)	1.038 (1.029-1.047)
				5	Before 2005	1.006 (1.000-1.012)	1.006 (1.000-1.012)
				5	After 2005	1.040 (1.031-1.049)	1.040 (1.031-1.049)

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
			IBD-related	1	Before 2005	0.979 (0.973-0.985)	0.980 (0.973-0.986)
				1	After 2005	1.037 (1.027-1.046)	1.036 (1.026-1.045)
				3	Before 2005	0.988 (0.983-0.994)	0.989 (0.984-0.995)
				3	After 2005	1.022 (1.014-1.031)	1.022 (1.013-1.030)
				5	Before 2005	0.991 (0.985-0.997)	0.992 (0.986-0.997)
				5	After 2005	1.028 (1.019-1.037)	1.028 (1.019-1.037)
		CD	IBD-specific	1	Before 2005	0.989 (0.982-0.997)	0.990 (0.982-0.997)
				1	After 2005	1.056 (1.044-1.068)	1.055 (1.044-1.067)
				3	Before 2005	0.999 (0.992-1.006)	0.999 (0.992-1.006)
				3	After 2005	1.034 (1.023-1.046)	1.035 (1.024-1.046)
				5	Before 2005	1.004 (0.996-1.011)	1.003 (0.996-1.011)
				5	After 2005	1.033 (1.022-1.045)	1.034 (1.023-1.046)
			IBD-related	1	Before 2005	0.982 (0.974-0.990)	0.982 (0.974-0.990)
				1	After 2005	1.038 (1.026-1.050)	1.039 (1.027-1.051)
				3	Before 2005	0.990 (0.983-0.997)	0.990 (0.983-0.997)
				3	After 2005	1.021 (1.010-1.032)	1.021 (1.010-1.032)
				5	Before 2005	0.991 (0.984-0.998)	0.991 (0.984-0.998)
				5	After 2005	1.024 (1.013-1.035)	1.025 (1.014-1.037)
		UC	IBD-specific	1	Before 2005	0.983 (0.973-0.994)	0.986 (0.976-0.997)

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
				1	After 2005	1.069 (1.053-1.086)	1.066 (1.049-1.082)
				3	Before 2005	1.004 (0.993-1.014)	1.006 (0.996-1.017)
				3	After 2005	1.053 (1.038-1.069)	1.050 (1.034-1.066)
				5	Before 2005	1.011 (1.001-1.021)	1.014 (1.003-1.024)
				5	After 2005	1.057 (1.042-1.073)	1.054 (1.039-1.070)
			IBD-related	1	Before 2005	0.977 (0.966-0.987)	0.979 (0.969-0.990)
				1	After 2005	1.030 (1.014-1.046)	1.026 (1.010-1.042)
				3	Before 2005	0.988 (0.978-0.998)	0.990 (0.980-1.000)
				3	After 2005	1.026 (1.011-1.041)	1.023 (1.008-1.038)
				5	Before 2005	0.993 (0.983-1.003)	0.995 (0.985-1.005)
				5	After 2005	1.035 (1.021-1.050)	1.033 (1.018-1.048)
		IBD	All-cause	1	Before 2005	0.988 (0.980-0.996)	0.988 (0.980-0.996)
				1	After 2005	1.032 (1.019-1.044)	1.031 (1.019-1.044)
				3	Before 2005	0.994 (0.987-1.002)	0.994 (0.987-1.002)
				3	After 2005	1.015 (1.004-1.027)	1.015 (1.004-1.027)
				5	Before 2005	0.993 (0.985-1.000)	0.993 (0.985-1.000)
				5	After 2005	1.021 (1.010-1.032)	1.021 (1.010-1.033)
		Non-IBD	All-cause	1	Before 2005	0.982 (0.978-0.986)	0.982 (0.978-0.986)
				1	After 2005	0.997 (0.991-1.004)	0.997 (0.990-1.003)

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
				3	Before 2005	0.982 (0.979-0.986)	0.983 (0.979-0.986)
				3	After 2005	0.996 (0.990-1.001)	0.995 (0.990-1.001)
				5	Before 2005	0.984 (0.981-0.988)	0.985 (0.981-0.988)
				5	After 2005	0.993 (0.988-0.998)	0.993 (0.988-0.998)
Logistic	Surgery	CD	Intestinal Resection	1	N/A	0.942 (0.920-0.965)	0.939 (0.916-0.961)
				3	N/A	0.940 (0.923-0.956)	0.938 (0.921-0.955)
				5	N/A	0.936 (0.918-0.953)	0.934 (0.917-0.952)
		UC	Colectomy	1	N/A	0.962 (0.928-0.998)	0.960 (0.925-0.996)
				3	N/A	0.966 (0.940-0.993)	0.967 (0.941-0.994)
				5	N/A	0.978 (0.950-1.007)	0.981 (0.952-1.010)
Cox Proportional hazards	Hospitalization	IBD	IBD-specific	5	N/A	0.982 (0.975-0.989)	0.982 (0.975-0.989)
			IBD-related	5	N/A	0.983 (0.976-0.990)	0.983 (0.977-0.990)
		CD	IBD-specific	5	N/A	0.982 (0.974-0.991)	0.983 (0.974-0.991)
			IBD-related	5	N/A	0.982 (0.974-0.991)	0.983 (0.974-0.991)
		UC	IBD-specific	5	N/A	0.987 (0.976-0.999)	0.985 (0.973-0.998)
			IBD-related	5	N/A	0.988 (0.976-1.000)	0.987 (0.975-0.999)
		IBD	All-cause	5	N/A	0.984 (0.977-0.990)	0.984 (0.977-0.991)
		Non-IBD	All-cause	5	N/A	0.960 (0.952-0.969)	0.961 (0.952-0.970)
		IBD	IBD-specific	5	N/A	0.998 (0.989-1.007)	0.999 (0.990-1.008)

Regression Model	Outcome	Population	Outcome type	Follow up from diagnosis (years)	Spline	Provincial Effect Estimate (95% CI)	Provincial Effect Estimate (95% CI) after dropped LHIN 14
	Emergency department visit		IBD-related	5	N/A	1.009 (1.003-1.016)	1.010 (1.003-1.017)
		CD	IBD-specific	5	N/A	0.997 (0.986-1.009)	0.997 (0.986-1.009)
			IBD-related	5	N/A	1.010 (1.002-1.019)	1.010 (1.001-1.019)
		UC	IBD-specific	5	N/A	0.999 (0.984-1.015)	0.999 (0.984-1.016)
			IBD-related	5	N/A	1.010 (0.998-1.022)	1.010 (0.998-1.022)
		IBD	All-cause	5	N/A	1.004 (0.999-1.010)	1.003 (0.998-1.009)
		Non-IBD	All-cause	5	N/A	0.994 (0.991-0.997)	0.995 (0.991-0.998)
	Surgery	CD	Intestinal Resection	5	N/A	0.940 (0.927-0.954)	0.939 (0.926-0.953)
		UC	Colectomy	5	N/A	0.970 (0.948-0.993)	0.971 (0.948-0.994)

Abbreviations: CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; N/A, not applicable; UC, ulcerative colitis.

Appendix N. Sensitivity Analysis Excluding Non-Converging LHINs from Individual-level Analysis

Table N.1 Individual-level analysis effect estimates (from Chapter 2) before and after dropping the non-converging Local Health Integration Network(s) in Chapter 3.

Model	Outcome	Outcome Type	Population	Follow up from diagnosis (years)	Dropped LHIN(s)*	Individual Level Analysis Effect Estimate (95% CI) (all LHINs)	Individual Level Analysis Effect Estimate (95% CI) (Dropped LHINs)
Negative binomial/ Poisson regression	Hospitalizations	IBD-specific	UC	3	1	0.986 (0.970-1.002)	0.990 (0.973-1.008)
		All-cause	IBD	3	1	0.974 (0.966-0.982)	0.978 (0.970-0.986)
			Children without IBD	3	1	0.966 (0.956-0.977)	0.968 (0.958-0.979)
Logistic Regression	Surgery	Intestinal resection	CD	1	*>3 LHINs*	-	-
				3	2, 5, 6	0.940 (0.923-0.956)	0.949 (0.930-0.968)
				5	5	0.936 (0.918-0.953)	0.935 (0.917-0.953)
		Colectomy	UC	1	*>3 LHINs*	-	-
				3	*>3 LHINs*	-	-
				5	3, 5, 7	0.978 (0.950-1.007)	0.984 (0.954-1.015)
	Surgery	Intestinal resection	CD	1	4, 6, 15	0.942 (0.920-0.965)	0.944 (0.919-0.970)

Model	Outcome	Outcome Type	Population	Follow up from diagnosis (years)	Dropped LHIN(s)*	Individual Level Analysis Effect Estimate (95% CI) (all LHINs)	Individual Level Analysis Effect Estimate (95% CI) (Dropped LHINs)
Exact Logistic Regression (network Monte Carlo method)				3	*>3 LHINs*	-	-
				5	*>3 LHINs*	-	-
		Colectomy	UC	5	11, 15	0.978 (0.950-1.007)	0.977 (0.947-1.008)

Abbreviations: CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; LHIN, Local Health Integration Network; UC, ulcerative colitis.

*When >3 LHINs were dropped the LHIN-based analysis was not performed.